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Determination of the Absolute Configuration and Enantiomeric Purity of Chiral Primary Alcohols by ^{1}H NMR of 9-Anthrylmethoxyacetates.

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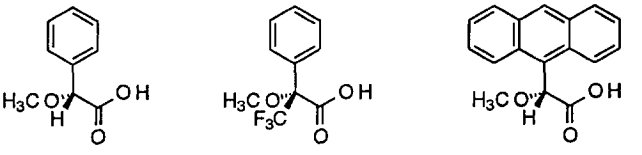
Abstract: The absolute configuration and e.e. of chiral primary alcohols with the asymmetric centre at the β carbon can be determined by comparison of the ^{1}H NMR spectra of their esters with (*R*)- and (*S*)-9-anthrylmethoxyacetic acids (9-AMA). Highly hindered primary alcohols or primary alcohols with the asymmetric centre at longer distance from the hydroxy group can hardly be determined by this method that is nevertheless highly useful for e.e. determination.

The interest on the use of NMR as a technique for the determination of the absolute stereochemistry and enantiomeric purity of organic compounds is obvious from the large number of papers recently published where this method is used.

It is based on the comparison of the ^{1}H NMR shifts of the two diastereoisomers obtained by derivatization of the chiral substrate (a secondary alcohol or primary amine attached to a stereogenic centre most frequently) with commercially available (*R*)- and (*S*)-methoxyphenylacetic acid (MPA, **1**)[1a,b] or its analogue methoxytrifluoromethylphenylacetic acid (MTPA, **2**)[1b,c,d] (Fig. 1). The chemical shifts of the derivatives indicate whether the secondary asymmetric centre of the starting alcohol or amine is *R* or *S* based on an established conformational model. In the last few years we have discussed the foundations of this methodology, its limitations and as a result, new AMAAs (arylmethoxyacetic acids), more effective and reliable reagents than **1** or **2**, have been introduced[2a,b,c]. Particularly interesting is the 9-anthrylmethoxyacetic acid (9-AMA, **3**), that generates diferences[3] ($\Delta\delta^{RS}$) in secondary alcohols several times greater than MPA or MTPA.



(*R*)-**1** (MPA) (*R*)-**2** (MTPA) (*R*)-**3** (9-AMA)

Figure 1

The usefulness of 9-AMA as auxiliary reagent derives from its high conformational preference around the Cα-CO bond, much higher than in MPA and MTPA esters, and from the favourable orientation adopted by the anthryl ring in the most stable conformer. Therefore, the 9-AMA part of a 9-AMA ester can be considered almost rigid, and so, if there were some conformational preference in the primary alcohol part of the ester, it should be transmitted to the NMR spectra *via* the aromatic shielding effect[4] generated by the ring.

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In this paper we wish to present preliminary results on the use of this auxiliary reagent to determine the e.e. and the absolute configuration of chiral primary alcohols. With that purpose, the optically active primary alcohols **4-10** with the asymmetric center at the β carbon, shown in Fig. 2, were derivatized with (*R*)- and (*S*)-9-AMA and the ^{1}H NMR spectra of the resulting diastereomeric esters compared[5, 6].

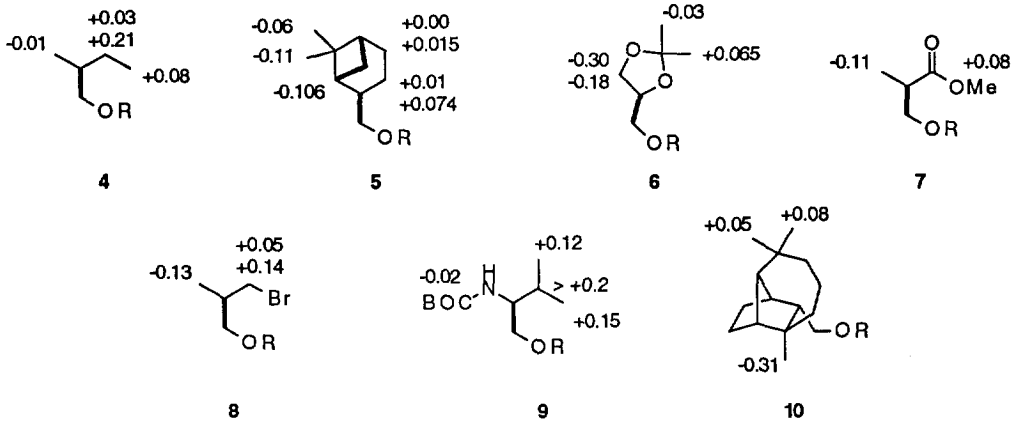


Figure 2

The utility of 9-AMA to determine the e.e. of those alcohols was judged from the $\Delta\delta^{RS}$ values. As we can see from Fig. 2, the figures obtained are good enough to calculate the peaks integrals that are useful for e.e. calculation.

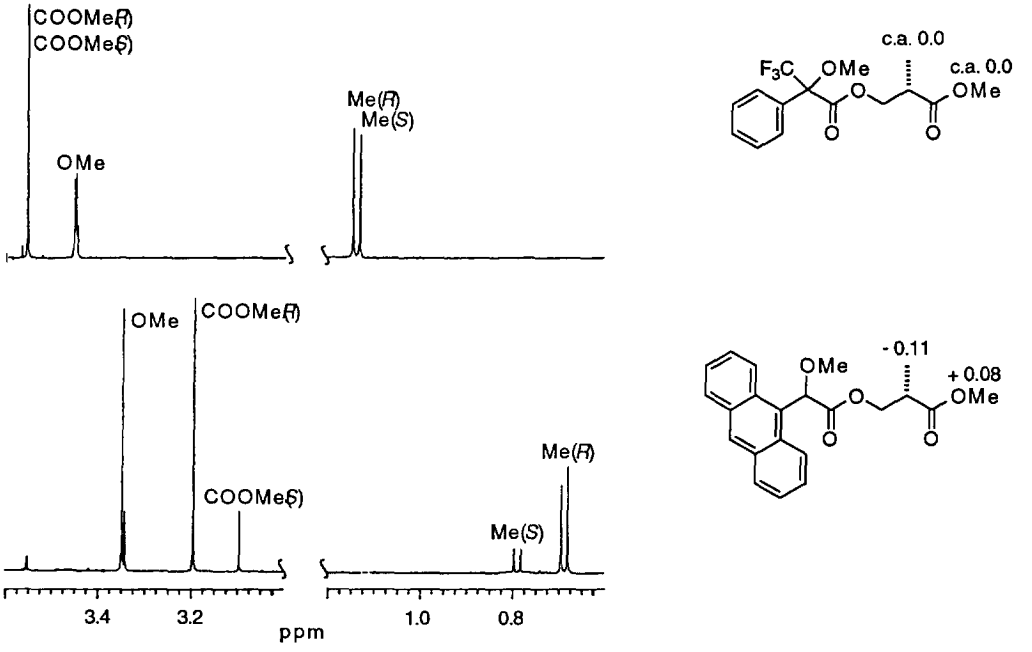


Figure 3. Partial ^{1}H NMR spectra of diastereomeric esters of **7** in $CDCl_3$ at 300 K. $\Delta\delta^{RS}$ are represented on the drawings. a) Mixture of (*R*)- and (*S*)-MTPA esters (94:6) b) Mixture of (*R*)- and (*S*)-9-AMA esters (83:17).

When the commercially available MPA **1** or MTPA **2** were used instead of 9-AMA **3**, practically identical NMR spectra were observed for the diasteromeric esters, with $\Delta\delta^{RS}$ values extremely small. Those values fall well within the experimental variation associated with solvent and concentration effects and therefore, this precludes their use for e.e. calculations. These results are illustrated in Fig. 3 by the ^{1}H NMR spectra of the esters of **7** with (*R*)- and (*S*)-MTPA and 9-AMA.

This difference between MPA **1** and MTPA **2** for one part and 9-AMA **3** for the other, must be surely related to the low efficiency of MPA and MTPA to transmit their aromatic shielding effects to the parent substrate. The effect is practically lost in primary alcohols due to the longer distance between the asymmetric centre and the auxiliary reagent and the associated increase of rotational freedom, while in the case of 9-AMA esters, we still obtain a measurable shift due to the larger magnetic cone and the lack of rotational freedom characteristic of this reagent.

Particularly important in Fig. 2 is the sign of the $\Delta\delta^{RS}$ parameter. As can be seen, it is homogeneously distributed in all the compounds tested: positive for all the protons located at one side of the asymmetric centre and negative for those in the other side. This constant behaviour is maintained in flexible (i.e. **4**), and rigid compounds (i.e. **5**), in the presence of polar groups (i. e. **6**, **7**, **8**) and also when a different steric enviroment is involved (i.e. **9**).

This means that the (*R*)- and (*S*)-9-AMA esters of a single enantiomer of a chiral primary alcohol (i.e. (*R*)-**7**), have a prefered conformation —the same for both diasteroisomers— and, in the average, the anthryl system of i.e. the (*R*)-9-AMA ester of **7** selectively shifts the protons placed on one side of the substrate (i.e.the methyl group of **7**) to higher field, while in the (*S*)-9-AMA ester the group affected is the MeO. As a consequence, the absolute configuration of a primary alcohol with an asymmetric centre at the β carbon can be easily determined by ^{1}H NMR comparison of its esters with (*R*)- and (*S*)-9-AMA and identification of the signals that move upfield in each ester.

Fig. 4 represents the conformation that accounts for those experimental results and that can be used as a model to predict the absolute configuration in a very simple way: substituent L_2 is the one shifted to higher field in the (*R*) ester and substituent L_1 is the one shifted to higher field in the (*S*) ester. The spatial distribution of L_1 and L_2 around the asymmetric centre is then deduced from the chemical shifts of L_1 and L_2 (or $\Delta\delta^{RS}$) in both derivatives.

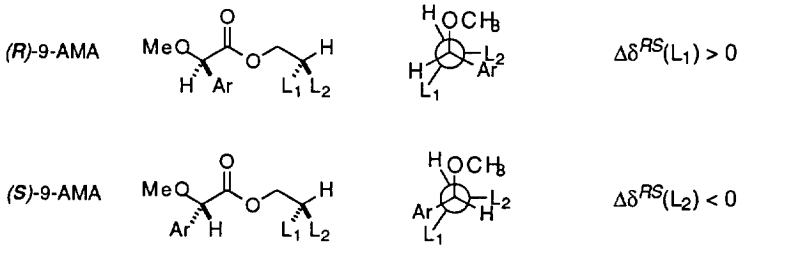


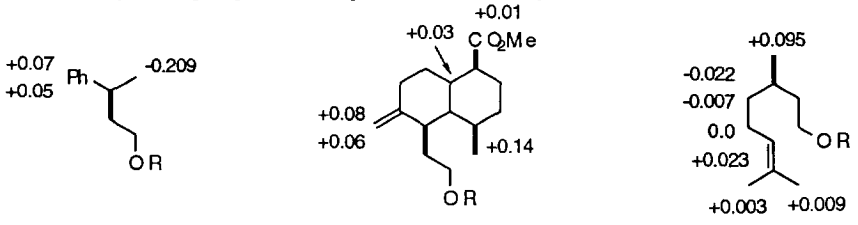
Figure 4

In order to evaluate the limitations of this model, we searched for alcohols whose structural characteristics would prevent the adoption of that conformation. According to calculations[7], alcohol **10** is one of such compounds and in fact, the chemical shifts and the signs of $\Delta\delta^{RS}$ observed do not agree with the absolute configuration of the compound neither can this be predicted by the model. This result can be known in advance by the calculations that emerge as a powerful tool to secure the fiability of the method.

We also considered the influence of the distance from the stereogenic centre to the OH group in the

molecule. The longer the distance gets, the lower should be the efficacy of the reagent to transmit the aromatic shielding effect to the substrate due to the new degrees of rotational freedom, and therefore the lower conformational preference involved.

To investigate the influence of this factor, we studied the possibility of extending this methodology to primary alcohols with the asymmetric centre placed at carbon γ (i.e. **11**, **12** and **13**) and found that the $\Delta\delta^{RS}$ values were, as expected, smaller than before (Fig. 5). In addition, not a regular pattern for the signs of $\Delta\delta^{RS}$ is observed in the esters of the hindered alcohol **12** and those of the more flexible **11** and **13**. Thus, we conclude that the absolute configuration of primary alcohols with the asymmetric centre placed more than 3 bonds away from the hydroxy group cannot be predicted in this way.



11 **12** **13**

Figure 5

In conclusion, we have shown that the absolute configuration (and e.e.) of a primary alcohol with an asymmetric centre at position β can be determined by comparison of the ^{1}H NMR of the corresponding 9-AMA esters to an empirical conformational model. The absolute configurations of highly hindered alcohols (i.e. **10**) that cannot adopt the adequate conformation, or primary alcohols with the asymmetric centre at longer distance (i.e **11-13**), can hardly be deduced by this method although it works highly well for e.e. calculation.

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3. $\Delta\delta^{RS}$ represents the difference between the chemical shift of the same group of the alcohol in the (*R*)- and (*S*)-derivative ($\Delta\delta^{RS} = \delta R - \delta S$).
4. Haigh, C. W.; Mallion, R. B. *Progress in NMR spectroscopy* ; Pergamon Press Ltd, 1980; *13*, 303-344.
5. ^{1}H NMR spectra were measured at 500.13 MHz in a Bruker AMX-500 spectrometer at T=300 K and in $CDCl_3$ containing TMS as internal standard. The esters were prepared by the standard method without racemization and purified by HPLC. All compounds gave satisfactory analysis and spectroscopic data. The absolute stereochemistry was confirmed by CD.
6. This procedure is equivalent to the comparison between the esters of both enantiomers of the parent alcohol and one enantiomer of the auxiliary reagent (9-AMA).
7. MM calculations were carried out using the Insight II program running on a Silicon Graphics Iris Computer and performed with the CVFF force field. For more details, see ref 2b.

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