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New Chirality Recognizing Reagents for the Determination of Absolute Stereochemistry and Enantiomeric Purity by NMR

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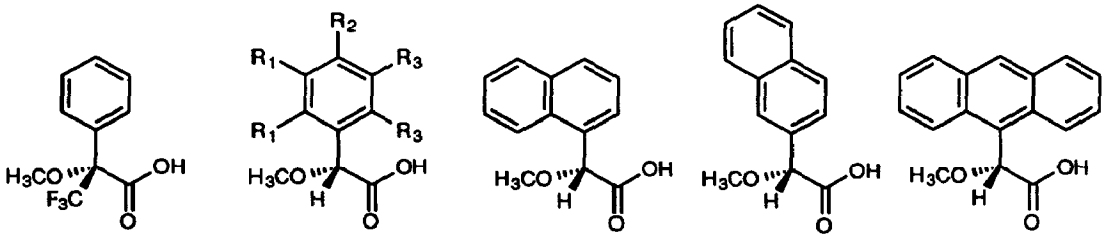
Abstract: The new chiral aryl methoxyacetic acids **3-8** were prepared and used as reagents for recognition of the chirality of alcohols and amines by ^{1}H-NMR and for analysis of enantiomeric purity. Separation of NMR signals by compounds **6-8** is two to three times greater than by the standard reagents MTPA (**1**) and MPA (**2**). The influence of conformational and magnetic factors in this effectiveness is discussed.

The NMR-based method introduced by Mosher and Trost[1] for the determination of the absolute stereochemistry of organic molecules is widely used[2]. It consists in the comparison of the ^{19}F and ^{1}H-NMR shifts of the two diastereoisomers obtained by derivatization of alcohols or amines with commercially available R and S methoxytrifluoromethylphenylacetic acid (MTPA, **1**) or its analogue methoxyphenylacetic acid (MPA, **2**). The chemical shifts of the diasteroisomers indicate whether the secondary asymmetric centre of the starting alcohol or amine is R or S based on an established conformational model.



(R)-**1**(MTPA) (R)-**2** R_1=R_2=R_3=H (MPA)
(R)-**3** R_1=R_2=R_3=F
(R)-**4** R_1=R_3=H; R_2=OMe
(R)-**5** R_1=R_2=OMe; R_3=H (R)-**6** (R)-**7** (R)-**8**

Figure 1

Quite frequently, however, these chemical shifts differ by 0.01 ppm or less, possibly within experimental error, making it difficult to judge which hydrogens in the parent substrate resonate upfield and which downfield, and thereby hindering identification of absolute configuration. The small chemical shift difference is also the major limitation to the use of MTPA (**1**) and MPA (**2**) for NMR determination of the enantiomeric purity of mixtures[3]. Surprisingly, however, there seems to have been no systematic search for new, more efficient reagents affording larger proton NMR shift differences than **1** and **2**.

In this paper we report that use of new arylmethoxyacetic acids[4] (AMAs, **3-8**, Figure 1), for chiral recognition by ^{1}H-NMR allows much better signal separation than use of **1** or **2**. The influence of electronic and conformational factors in the effectiveness of these reagents is discussed.

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The ability of acids **1-8** to separate the signals of steroisomers was first tested with i-propanol and (-)-menthol as substrates. Table 1 shows ^1H chemical shifts of the methyl groups of the i-propyl and (-)-menthyl esters of the new AMAs **3-8** and the known **1** and **2**, together with the differences ($\Delta\delta$) between corresponding signals of the R and S derivative. The introduction of strong acceptor substituents on the benzene ring, as in **3**, produces a less effective reagent than **1** or **2** with almost negligible $\Delta\delta$ values. Compound **4**, which has a donor substituent in a non hindered position, gives larger $\Delta\delta$ values than **3** but smaller values than **2**.

The introduction of a larger number of donor groups on the benzene ring, as in **5**, improves on the results of **4** but still gives $\Delta\delta$ values about the same as those obtained with **2**, even though a more electron-rich aromatic ring should produce a more intense anisotropic effect.

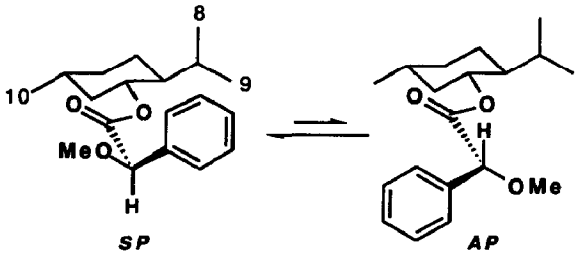

Figure 2. Main conformations of (-)-menthyl ester of (R)-MPA. SP: syn-periplanar (shielded i-propyl group) and AP: anti-periplanar (non-shielded).

The above apparently anomalous results are due to conformational changes that affect the relative population of conformers differing in the orientation of the aromatic ring with respect to the methyl groups under study. Molecular Mechanics and semiempirical AM1 calculations[5] showed that the R isomers of the (-)-menthyl esters of **2**, **3**, **4** and **5** exist in conformational equilibrium and that the shielding observed at room temperature is exchange averaged. The esters of (R)-**2**, **3** and **4** are constituted by almost the same two sets of conformers: In one the C_α-O bond nearly eclipses the C=O bond and the i-propyl group is shielded by the aryl ring (conformer SP in Figure 2) while in the other (AP), C_α-O lies anti to C=O, leaving the i-propyl in the non-shielded region. A similar equilibrium of ester array holds for the S isomers, but in this case the AP conformer is the one that causes the shielding of the i-propyl group by the aromatic ring. The reason why the R and S isomers have different chemical shifts is that the conformer in which the i-propyl is shielded by the aromatic ring predominates in the case of the R isomer (SP) but is the minor conformer of the S isomer (AP). Since the relative population of the SP form increases from **3** to **2** to **4**, the low $\Delta\delta$ value observed in the esters of **3** is due to both the weaker anisotropic effect of its electron-depleted aromatic ring and its unfavourable conformer distribution. Calculations for the shielded conformers of the esters of **4** reveal a distorted geometry with the aromatic ring in a less favourable position than in **2** for transmission of the anisotropic effect to the substrate.

The conformer distribution of the ester of **5** is more complex and better described as involving three sets of conformers: shielded, non-shielded and intermediate. Again, the orientation of the aromatic ring is less favourable than in **2** for effective shielding, and this neutralizes the increase of magnetic anisotropy due to the three donor groups.

From these results, we concluded that although the introduction of donor substituents on the aromatic ring might be envisaged as a rational way to increase the shielding effect, and hence $\Delta\delta$ values, the accompanying changes in structure and conformer populations limit the efficacy of this approach.

As an alternative approach we decided to replace the benzene ring of **1-5** by a larger aromatic system like

Table 1. Selected chemical shifts (ppm) of AMAs esters[a].

Acid:	(-)-Menthol							i-Propanol
Aryl group	Conf.	δMe_8	δMe_9	δMe_{10}	$\Delta\delta_8$	$\Delta\delta_9$	$\Delta\delta_{10}$	$\Delta\delta$
1(MTPA):	R	0.91	0.78	0.87	0.17	0.04	0.07	0.07
C_6H_5	S	0.74	0.74	0.94				
2 (MPA):	R	0.63	0.43	0.89	0.21	0.26	0.05	0.12
C_6H_5	S	0.85	0.69	0.84				
3:	R	0.76	0.67	0.87	0.04	0.10	0.07	0.04
C_6F_5	S	0.80	0.77	0.80				
4: 4-MeO-	R	0.73	0.56	0.93	0.12	0.16	0.06	0.08
-C_6H_4	S	0.86	0.73	0.87				
5:2,3,4-Tri-	R	0.64	0.49	0.88	0.22	0.25	0.05	0.11
MeO-C_6H_2	S	0.87	0.75	0.83				
6:	R	0.31	0.01	0.87	0.52	0.65	0.11	0.21
1-Naphthyl	S	0.83	0.66	0.76				
7:	R	0.47	0.34	0.80	0.41	0.35	0.04	0.14
2-Naphthyl	S	0.88	0.69	0.84				
8:	R	0.04	-0.10	0.86	0.79	0.75	0.10	0.31
9-Anthryl	S	0.84	0.65	0.76				

[a] Recorded in $CDCl_3$; chemical shifts vs δ ($CDCl_3$) = 7.26 ppm; T= 298 K.

naphthyl (compounds **6** and **7**) or anthryl (**8**). Gratifyingly, the ^{1}H-NMR spectra of the i-propyl and (-)-menthyl esters of these compounds show $\Delta\delta$ values two to three times greater than those obtained with MPA (**2**) derivatives (Table 1). Since MM and AM1 calculations showed that the geometries and relative conformer populations of the R and S forms of the esters of **6** and **7** are about the same as in MPA (**1**), the superior efficacy of **6** and **7** must be due to the ring current and effective shielding area being larger in the naphthyl system than in the phenyl system. In the case of the esters of **8**, NMR showed that conformational equilibrium is in both configurations strongly biassed in favour of SP conformation (in R: shielded; in S: non-shielded). This causes the signals corresponding to Me-8 and Me-9 to appear at a remarkable high field (δ= 0.04 and δ= -0.10) in the R derivative. Therefore compound **8** produces the greatest separation of signals obtained so far with any reagent and this also allows its use for the determination of enantiomeric purity by NMR. The generality of application of optically pure AMAs **6** and **8** as reagents for recognition of absolute stereochemistry was additionally confirmed with a series of chiral alcohols and amines chosen to cover a wide scope of steric possibilities near the chiral center. Thus, the (R) and (S)-2-methoxy-2-(1-naphthyl)acetic acids (**6**) were tested with (S)-(+)-2-hydroxy-3-methyl butyric acid methyl ester (**9**), with (R)-(-)-2-butanol (**10**) and with (-)-isopulegol (**11**) and the (R) and (S)-2-methoxy-2-(9-anthryl)acetic acids (**8**) with (1S)-(-)-borneol (**12**), with (S)-(-)-sec-phenethyl alcohol (**13**) and with (S)-mandelic acid methyl ester (**14**). The amines (L)-leucine methyl ester, (L)-phenylalanine methyl ester and with (L)-tryptophan methyl ester were also used as substrates. In all cases, the absolute configurations deduced using the Mosher-Trost empirical model were found to be the correct ones. A selection of $\Delta\delta$ obtained are shown in Figure 3 (for comparison purposes, values obtained with MPA or MTPA are shown in parenthesis).[6]

The reagents developed (**6** and **8** especially) are manifestly superior to the standard **1** and **2** and should allow wider and more reliable application of the Mosher-Trost method. The understanding of the role played by electronic and conformational factors based on modelling by MM or semiempirical methods proved invaluable for the rational design of new NMR reagents.

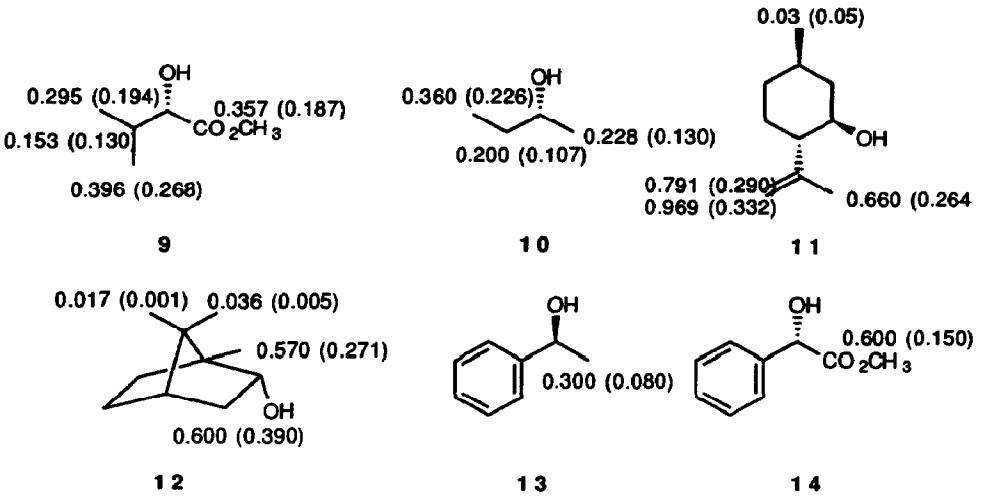

Figure 3

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References and Notes

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3. Dale, J. A.; Mosher, H. S., *J. Am. Chem. Soc.*,**1968**, *90*, 3732.
4. Enantiomerically pure compounds **3**, **6** and **7** were prepared from the cyanohydrin of the corresponding arylaldehide and the resulting racemic mixture resolved *via* crystallization of the α-phenylethylamine salts. Compound **4** was obtained from the hydroxyacid and resolved as above. Compounds **5** and **8** were prepared by acylation with ethyl oxalyl chloride of the aromatic hydrocarbon followed by reduction of the aryl keto ester with (R) and (S)-Alpine-Borane^{R}. The esters and amides of **2-8** 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.
5. MM and AM1 molecular orbital calculations were carried out using the Insig II program running on Silicon Graphics Iris computer. MM and MD calculations were performed with the CVFF force field. See: Roberts, V. A.; Osguthorpe D. I.; Wolf, J.; Genest, M.; Hagler, A.T., Proteins: Structure, Function and Genetics. **1988**, *4*, 31.
6. Data for the MPA derivatives of **10** and **13** taken from Ref.1a. Data for the MTPA esters of **14** taken from: Dale, J. A.; Dull, D. L. and Mosher, H. S., *J. Org. Chem.*,**1969**, *34*, 2543. The (R) and (S)-MPA esters of **9**, **11** and **12** were prepared for this work.

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