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New Fluorinated *O*-Aryl Lactic Acids: Use as Chiral Derivatizing Agents (CDAs) and Determination of their Enantiomeric Purity with Achiral Diols

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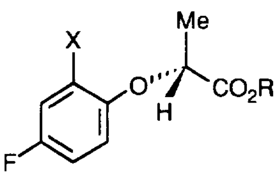
Abstract The modification of the aromatic part of fluorinated *O*-aryl lactic acids allows the improvement of the fluorine NMR δΔ values in diastereomeric esters, but also the observation of other nuclei such as Hg (δΔ > 6 ppm). The enantiomeric purity of chiral acids has been determined through the *dl*- and *meso* compounds formed from achiral diols.

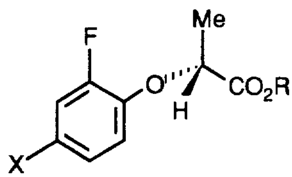
The design and development of reagents for NMR analysis of chiral compounds remains a topical subject.[2] We have recently shown that arylfluorinated[3] derivatives of lactic acid are easily accessible reagents that are suitable for the determination of enantiomeric excess[4] and the attribution of absolute configuration of alcohols according to a new model.[5] Most interestingly, with *p*-fluorophenoxylactic acid **1a** (PFPLA) it was possible to separate all eight diastereoisomers in the ^{19}F NMR spectra.[4]

In order to study the influence of the aromatic substitution patterns on the chemical shift non-equivalence of diastereomeric esters (^{1}H- and ^{19}F-NMR) we synthesized[6] various substituted fluorophenoxylactic acids **1b-e** and **3b-c**[7] which, in addition to the fluorine atom carried other substituents in different positions. Some ^{19}F δΔ values of the diastereomeric esters with (±)-menthol are shown in Figure 1. The cyano group produces a negative effect on δΔ values; however, the incorporation of additional groups with contrasting polarities such as bromine, iodine or HgCl leads to a noticable increase of the chemical shift difference of diastereomeric fluorine. Interestingly the *best* reagent is the phenylmercury compound **1e** (X = HgCl) with δΔ of 0.48 ppm in the menthol esters **2e**. The ^{199}Hg chemical shift difference amounts to 6.41 ppm.



(*R*)-**1** R = H
2 R = (±)-menthol

2a X = H, (0.281, ref. 4)
2b X = CN, (0.16)
2c X = Br, (0.414)
2d X = I, (0.365)
2e X = HgCl, (0.48)
4a X = H, (0.281)
4b X = Cl, (0.414)
4c X = Br, (0.443)



(*R*)-**3** R = H
4 R = (±)-menthol

Figure 1. Various substituted fluorophenoxylactic derivatives. The magnitude (ppm) of the nonequivalence (δΔ) in the ^{19}F-NMR spectrum is given in brackets.

Chiral reagents should be enantiomerically pure and, having in hand a number of new compounds we looked for a simple and rapid method to verify the enantiomeric excess of the synthesized acids. Analysis with chiral chromatography[8] is well established for these types of compounds but the required column is not always available. Moreover the analysis after derivatization (*e. g.* with chiral alcohols) raises the question of kinetic resolution and, evidently, the purity of the chiral derivatizing agent (CDA).[9]

The conceptually simple way to determine enantiomeric purities of chiral acids by analyzing diastereomeric derivatives from **achiral** reagents has recently been described with dinuclear praseodymium complexes.[10] The method, already formulated by Horeau[11] is based upon the simple principle that condensing two molecules of a racemic mixture (*RS*) on the achiral agent A leads to a diastereomeric mixture of enantiomers *R*-A-*R* (and *S*-A-*S*) and the *meso* compound *R*-A-*S* (*S*-A-*R*). The ratio of enantiomers to *meso* compound reflects the enantiomeric composition of the racemic (scalemic) mixture. In principle this method could apply for any 'dimeric' product, even without agent A provided the 'dimerization' leads to substrates with two (or more) identical sides without modification throughout the reaction. Feringa[12,13] was the first to show the practical use of non chiral agents (phosphorous chlorides) for the determination of enantiomeric purities of alcohols[14], thiols[15] and amines.[16] Examples with Si[17] and metal complexes[18] have also appeared.

The feasibility of the approach has been demonstrated by lactonization of chiral carboxylic acids. However, as already noted by Horeau,[19] lactonization[20] leads, in many cases, to an epimerization of the stereogenic carbon in the acids. We now find that better results can be obtained when diesters from achiral dialcohols such as 2,2-dimethyl 1,3-propandiol are used for the analysis. These diesters are easily formed without kinetic resolution *via* current esterification procedures[21] and no epimerization in the acid moiety occurs.

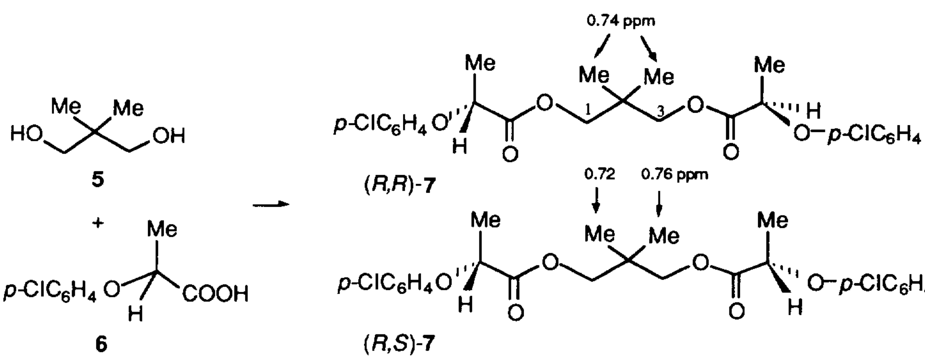


Figure 2.

Independent of the nature of the acid the presence of the 2,2-dimethyl 1,3-propandiol unit permits ^{1}H analysis of diastereotopic CH_3 groups at C_2 and the two CH_2 groups (C_1 and C_3). Due the the C_2 axis in (*R,R* or *S,S*)-**7** both methyl groups are isochronous and show simply one NMR resonance at 0.74 ppm. In the *meso* compound (*R,S*)-**7** these CH_3 groups are magnetically different and give 2 singlets at 0.72 and 0.76 ppm. Typical $\delta\Delta$ values of the C_2-methyl groups in the *meso* compounds of about 20 chiral acids are in the range of 0.01 - 0.14 ppm and, in most cases, all 3 signals are well separated in the diastereomeric diester mixtures.[22] The protons at C_1 (or C_3) are diastereotopic and anisochronous in both diastereomers and show AB patterns with characteristic shift differences of the A and B part (*R,R* or *S,S*)-**7**[23] δ_A 3.817, δ_B 3.829 J_{AB}= 10.8 Hz and (*R,S*)-**7** δ_A 3.74, δ_B 3.82, J_{AB}= 10.8 Hz. The ^{1}H NMR spectra (400 MHz) of diesters **7** with scalemic mixtures of 2-(4-chlorophenoxy) propionic **6** (racemic to >99% ee of (*R*)-isomer) are shown in Figure 3. Less than 0.5 % of enantiomeric impurities are easily distinguished by ^{1}H NMR.

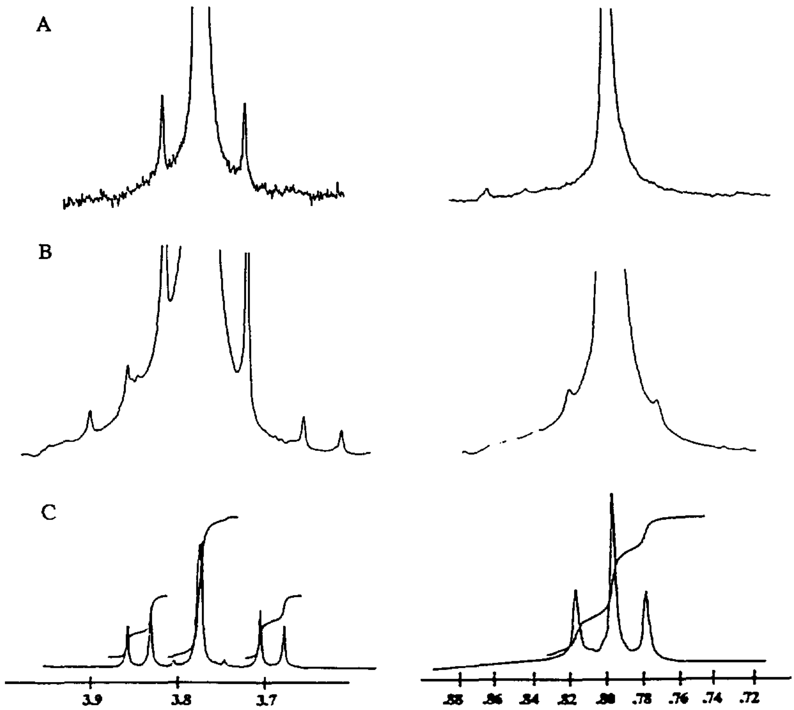


Figure 3. ^{1}H NMR (400 MHz) spectra of $C_{1(3)}$ methylene and C_2 methyl hydrogens of **7**; A. from pure acid (*R*)-**6**, B. 99% (*R*)-**6**, C. racemic mixture of **6**.

In summary we have shown that additional aromatic substituents can improve ^{19}F NMR $\delta\Delta$ values of diastereomeric esters with 2-(fluorophenoxy)propionic acids. The ^{1}H NMR analysis of the *dl* and *meso* diesters with (achiral) 2,2-dimethyl 1,3-propandiol permits to determine the enantiomeric purity of these substrates and, more generally, of 2-substituted alkanoic carboxylic acids. This very practical method with cheap compounds,[24] a simple esterification procedure and routine NMR analysis seems especially valid for the detection of high enantiomeric purities of carboxylic acids.

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22. Selected proton resonances of *dl* and *meso* diesters of type **7** with the following acids [(δ CH_3) at C_2]: **1a** 0.74 and 0.72/0.76; **3a** 0.75 and 0.75/0.76; 2-phenoxy propionic acid 0.71 and 0.69/0.74; 2-(2,4-dichlorophenoxy) propionic acid 0.76 and 0.75/0.77; *O*-methoxy-mandelic acid 0.60 and 0.52/0.66; 2-phenyl butyric acid 0.68 and 0.65/0.71 ppm.
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