Nuclear Overhauser effects in diastereoisomeric vinyl ethers for the precise structure determination of chiral alcohols

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In methylene vinylethers 3–5 NOE effects allow the establishment of the proximity of four hydrogen atoms in line thus confirming more rigorously the absolute configuration of secondary alcohols previously determined in *O*-aryl lactic esters.

NMR analysis of diastereoisomeric esters, amides and related derivatives is extensively used for the determination of enantiomeric excess, but also for the attribution of absolute configurations to one of the enantiomeric partners.[1] The latter method is still empirical with derivatives of MTPA (α-methoxy-α-trifluoromethylphenylacetic acid, Mosher's acid),[2] MPPA (α-methoxyphenylpropionic acid),[3] α-alkylphenylpropionic acids[4,5] or PFPLA (*p*-fluorophenoxylactic acid)[6] though in many cases X-ray structure analyses have confirmed[5,7] (or not[8]) the NMR assignments. The method relies on three essentials (*a*) the conformation of the ester linkage which is *syn*-periplanar,[9] (*b*) the coplanarity of an acid substituent, the carboxylate C(= O)–O and the alcohol methine in a common plane (acid plane) and (*c*) the presence of a (aromatic) π-system not lying in the acid plane.

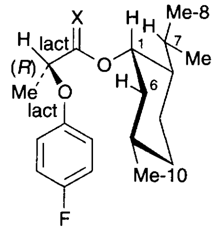
The crucial factor is the acid substituent in the acid plane which places the aromatic group in front of one of the alcohol substituents and the interpretation of the observed anisotropical high field shifts. There are no general rules which functional group might preferentially be at these relative positions; the overall conformational picture depends on the combination of all substituents. *O*-methoxy, for example, does not have the same orientation in MTPA (out of the acid plane) as it does in MPPA esters (in the acid plane). Even more confusing MPPA esters do not adopt the same preferential conformation as MPPA amides.[10] In addition to these uncertainties, erroneous assignments have been made with MTPA due to the distortion, by sterical factors, of the Dale–Mosher conformation.[11,12] It would be beneficial for the reliability of the NMR method if a secondary 'effect' could be used to confirm the anisotropy effects.

Direct spacial correlations between the two chiral centres have been tried with nuclear Overhauser (NOE) experiments.[13] However, the inverse six power rule of the internal distance renders difficult any direct NMR visualizing of the spatial neighbourhood.[†] Recently we described fluorinated *O*-aryllactic acids as chiral reagents where the acid methine proton lies in the acid plane.[6] It had been possible to confirm the NMR interpretation by X-ray structure analyses of esters with (+)-neomenthol. Dihedral angles of 61 and 13° have been found in the crystalline structure between the acid and alcohol methine protons of compounds **1** and **2**, respectively. However, direct NOE interactions between the acid and the alcohol are not visible in **1** and **2**, as well as in similar esters. We anticipated that changing the ester C=O into a methylene group by transforming the ester into an enol ether would create a situation with four hydrogens in line in the former 'acid plane' and thus permit us to visualize the proximity of these hydrogens *via* NOE interactions in cascade. It is known that enol ethers adopt the same *cis*- or *syn*-periplanar conformations as carboxylic esters,[15] the diamagnetic effects known with the esters should also be operative in the enol ethers.

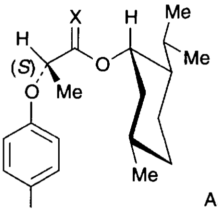
Neomenthyl esters **1** and **2** were easily methylenated with Tebbe's reagent[16] to the corresponding enol ethers **3** and **4** (yield 40–50%). The proton NMR spectra were very similar to those of the esters and, importantly the same diamagnetic high field shifts could be observed in the enol ethers, Table 1.[‡]

In both compounds NOESY experiments showed interactions between proximal hydrogens and, notably between H_{lact} and the *syn* proton of $=CH_2$, the two protons of the methylene group as well as *anti*-H of methylene with *H*-1 of neomenthol (*syn* and *anti* with respect to the former lactic part). One dimensional NOE difference measurements allowed a quantification. It should be noted that any *O*-aryl lactic acid[17] may be used, and that these NOE effects have also been obtained with derivatives of (*R*)-(+)-2-(2-methyl-4-chlorophenoxy) propionic acid[§] *e.g.* **5** containing various alcohols like isopropanol **5a**[¶] and other chiral menthols, borneol and octanol **5b–e**.

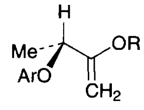
In **3** the NOE interactions are highest for the four protons in line: H_{lact}–H_{syn} (3.1%), H_{syn}–H_{anti} (21.8 and 26.8%) and H_{anti}–H-1 (10.5%), but other, weaker interactions exist between H_{anti}–H-6_{eq} (3.7%), H_{syn}–H_{arom} (1.8%) or H_{syn}–Me_{lact} (0.7%). The H_{syn}–H_{arom} NOE is not existent in the other diastereoisomer **4**.[||] In the (−)-menthyl compound **5b** derived from (*R*)-(+)-2-(2-methyl-4-chlorophenoxy) propionic acid the NOE effects[**] are approximatively the same as in **3** and **4**. The NOE



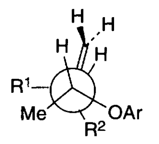
1 X = O
3 X = CH_2



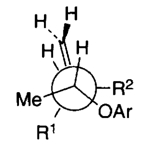
2 X = O
4 X = CH_2



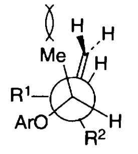
Ar = *o*-Me, *p*-Cl-phenyl
5a R = isopropyl
b R = (−)-menthol
c R = (+)-menthol
d R = (*R*)-octanol
e R = (−)-borneol



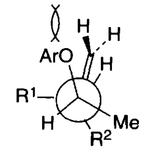
(*R*)-**6a**



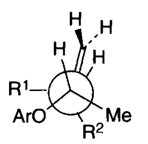
(*R*)-**6b**



(*R*)-**6c**



(*R*)-**6d**



(*S*)-**7**

Table 1 ^1H NMR spectral nonequivalence of esters and vinyl ethers derived from (−)- and (+)-menthol and (*R*)-PFPLA (400 MHz, $CDCl_3$)

Compound	X	δ (Me-8,9)[a] (isopropyl)	δ (Me-10)	δ (H-5)	δ (H-6_{eq})	δ (H-7)
1	O[b]	0.83/0.87	0.66	1.01	1.75	1.41
3	CH_2	0.85/0.91	0.75	1.4	2.03	1.6
2	O[b]	0.68/0.75	0.84	1.57	1.90	0.93
4	CH_2	0.72/0.86	0.85	1.6	2.12	1.4

[a] Unambiguous assignments of 5-H, 7-H and all methyl groups by 1D-COSY experiments[22]. [b] Ref. 6.

correlations are in favour of the proximity of four hydrogen atoms represented in (*R*)-**6a** and (*R*)-**6b** [extended Newman projections, (*S*)-**7** representing one conformation of the opposite diastereoisomer] and provide confirmation of their alignment more or less in a common plane. Smaller NOEs (to OAr, Me and H-6_{eq}) testify the deviation of this plane and conformational mobility approaching these respective groups towards the proximal hydrogen.

The transformation of C = O into C = CH_2 increases the steric crowding in the 'acid plane' rendering the direct alignment of all atoms, which was nearly perfect in ester **2**, more difficult. At the same time the approach of the more bulky groups (Me, *O*-aryl) to this plane becomes less easy, too. Thus the proton in the 'acid part' adopts preferent conformations close to (*R*)-**6a** and (*R*)-**6b** (extended Newman projections). Mainly these two conformations are compatible with the very weak (or absent) NOE interactions between H_{syn} and the methyl or the aromatic group and much less with (sterically more hindered) structures such as (*R*)-**6c** and (*R*)-**6d**.

In contrast to Mosher type,[2,3] alkyl propionic[4] and lactic esters,[6] diastereoisomeric metal complexes can offer rigid structures instead of conformational equilibria. In such a case it has been possible to assign the absolute configuration of chiral phosphines unambiguously by NOE enhancement studies of the diastereoisomeric $[o\text{-}\overline{C_6H_4CHMeNMe_2Pd}Cl]_2$ complexes.[18] Contrary to the restricted mobility in these orthometallated structures, the cascade NOE in vinyl ethers from *O*-aryl lactic esters accounts for the first example of rigorous attribution of absolute configuration (to chiral alcohols) with a conformationally mobile system. This method combines NMR parameters such as chemical shift differences with the establishment of spacial proximity. The experimentally simple approach involves esterification[19] and alkylation with Tebbe's reagent,[16] requiring only cheap and easily accessible reagents,[17,20] and utilises routine NMR methodology.[21]

Footnotes

† Weak NOE correlations (0.07–0.61%) have recently been described in MTPA and other methoxy-naphthalene and -binaphthyl esters. For the cases documented with reproduction of the NMR spectra the NOE effects are in contradiction to the phenyl induced high field shifts of MTPA: both diastereoisomeric menthyl esters show the same NOE correlation between phenyl (as well as methoxy) and the isopropyl protons.[14]

‡ *Selected spectroscopic data* for **3**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.86–6.92 (m, 2 H), 6.79–6.84 (m, 2 H), 4.48 (q, *J* 6.5 Hz, 1 H, H_{lact}), 4.32 (m, *J* 7 Hz, 1 H, H-1); 4.13 (d, *J* 2.4 Hz, 1 H, H-$12_{syn\text{-}lact}$), 3.95 (d, *J* 2.4 Hz, 1 H, H-$12_{anti\text{-}lact}$), 2.03 (dddm, J_1 13.9, J_2 5.7, J_3 3.4 Hz, 1 H, H-6_{eq}), 1.65–1.75 (m, 2 H, H-3 and H-4_{eq}), 1.55–1.65 (m, 1 H, H-7), 1.47 (d, *J* 6.4 Hz, 3 H, Me_{lact}), 1.32–1.45 (m, 2 H, H-5 and H-3_{ax}), 0.88–0.98 (m, 1 H, H-2_{ax}), 0.79–0.85 (m, 1 H, H-4_{ax}), 0.73–0.79 (m, 1 H, H-6_{ax}), 0.91 (d, *J* 6.7 Hz, 3 H, Me-9), 0.85 (d, *J* 6.7 Hz, 3 H, Me-8), 0.75 (d, *J* 6.6 Hz, 3 H, Me-10); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.14 (C-12), 157.29 (d, *J* 237 Hz), 154.17 (d, *J* 2 Hz), 116.84 (d, *J* 8 Hz), 115.51 (d, *J* 23 Hz), 80.99 (C-12), 75.30 (C-13_{lact}), 71.99 (C-1), 47.66 (C-2), 36.31 (C-6), 34.98 (C-4), 29.56 (C-7), 26.52 (C_5), 25.27 (C-3), 22.24 (Me-10), 21.32 (Me-9), 20.88 (Me_{lact}), 20.72 (Me-8).

§ BASF, Ludwigshafen. We thank the BASF company for a gift of this enantiopure compound.

¶A polarisation transfer between one diastereotopic methyl group and the acid phenyl has been claimed[13] in the MPPA isopropylester. We have not been able to repeat this experiment.

‖ Values for **4** H_{lact}–H_{syn} (3.4%), H_{syn}–H_{anti} (21.5 and 27.7%) and H_{anti}–H-1 (11.4%); other weaker interactions: H_{anti}–H-6_{eq} (3.3%), H_{syn}–H_{arom} (1.8%) or H_{syn}–Me_{lact} (0%).

** Proton chemical shifts for **5a** δ 4.49 (H_{lact}), 4.12 (H_{syn}), 3.96 (H_{anti}), 3.75 (H-1), 2.17 (H-6_{eq}), 2.20 (Me_{arom}), 1.50 (Me_{lact}); NOE effects: H_{lact}–H_{syn} (2.0%), H_{syn}–H_{anti} (14.9 and 17.5%) and H_{anti}–H-1 (7.4%), H_{anti}–H-6_{eq} (3.0%), H_{syn}–H_{arom} (0.9%), H_{syn}–Me_{lact} (0.7%), H_{syn}–Me_{arom} (0.8 ± 0.4).

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