The Conformation of Derivatives of *O*-Aryllactic Acid used as Chiral Reagents in Structure Determination. NMR and X-Ray Structure Analysis of Diastereoisomeric Menthol Esters

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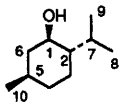
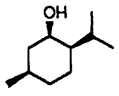
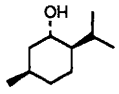
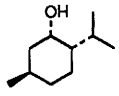
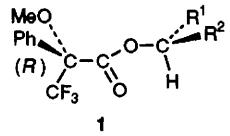
The ^{1}H NMR analysis of *O*-aryllactic esters allows the attribution of the absolute configuration to alcohols according to a new model with H^{α} in the acid plane in a hitherto unprecedented conformation.

The tendency of chiral α-substituted carboxylic acids to formation of a preferential rotamer in esters and amides is currently used for the NMR determination of absolute configuration.[1] Scheme 1 shows the conformations of derivatives of MTPA **1**, *O*-methoxymandelic acid **2** and α-phenylbutyric acid **3** [acids in (*R*)-configuration]. The methine protons, O-CO and one substituent of the acid: CF_3 in **1**, OMe in **2**, and Et in **3** respectively, lie roughly in a common plane. The stereodifferentiation of R^1 and R^2 depends on the precise position of the phenyl ring (anisotropically induced high-field

Table 1 ^{1}H NMR spectral nonequivalence[a] of esters of (−)-menthol, (+)-neoisomenthol, (+)-isomenthol and (+)-neomenthol with (*R*)- and (*S*)-PFPLA **4** (400 MHz, $CDCl_3$)

Menthol		4	Ester	δ(Me-8,9)[b]	Δδ	δ(Me-10)	Δδ	δ(5-H)	Δδ	δ(6-H_{eq})	Δδ	δ(7-H)	Δδ
	(1*R*,2*S*,5*R*)-(−)	(*R*)-Acid	**7**	0.56, 0.72	>0	0.88	0	1.45	0	1.95	<0	1.41	>0
		(*S*)-Acid	**8**	0.72, 0.85		0.88		1.45		1.65		1.83	
	(1*R*,2*R*,5*R*)-(+)	(*R*)-Acid	**9**	0.70, 0.77	>0	1.05	<0	1.86	<0		<0	1.06	>0
		(*S*)-Acid	**10**	0.83, 0.84		0.93		1.55				1.77	
	(1*S*,2*R*,5*R*)-(+)	(*R*)-Acid	**11**	0.83, 0.93	<0	0.81	>0	1.63	>0			1.71	<0
		(*S*)-Acid	**12**	0.84, 0.74		0.92		1.85				1.51	
	(1*S*,2*S*,5*R*)-(+)	(*R*)-Acid	**5**	0.83, 0.87	<0	0.66	>0	1.01	>0	1.75	>0	1.41	<0
			5[c]	0.81, 0.82		0.64		0.93				1.41	
		(*S*)-Acid	**6**	0.68, 0.75		0.84		1.57		1.90		0.93	

[a] Δδ = resonance of ester of (*S*)-acid minus that of ester of (*R*)-acid. [b] **5** and **6** C-H and H-H COSY experiments, **7**–**12**: unambiguous attribution of 5-H, 7-H and all methyl groups by 1D-COSY experiments: H. Kessler, S. Mronga and G. Gemmecker, *Magn. Reson. Chem.*, 1991, **29**, 527. [c] In C_6D_6.



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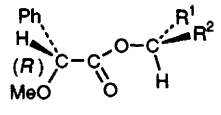

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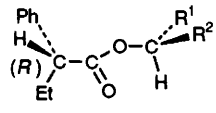

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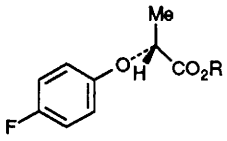
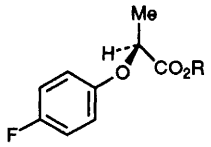


(*R*)-**4** R = H
5 R = (+)-neomenthol



(*S*)-**4** R = H
6 R = (+)-neomenthol

shift of protons facing Ph). This means that the position of the substituent in the acid plane is crucial for the accuracy of the method.†

Conformations with the acid H^α in the *gauche* conformation with respect to C=O and CH of the secondary alcohol (in **2** or **3**) have not yet been observed; moreover they have been considered as irrelevant in the conformational equilibrium.[2] In this communication we present results which show that these conformations are predominant in esters of *O*-aryl substituted carboxylic acids. Easily accessible from alkyl lactates and phenols in high optical purity[3,4] these chiral acids have only scarcely been used for chiral analysis.[5] We have recently shown that arylfluorinated derivatives of lactic acid, *e.g.* **4**, constitute interesting reagents for determination of the optical purity of alcohols, amines or amino acids.[6]

Typical sizes of ^{19}F NMR non-equivalence are 0.115 ppm (octan-2-ol) or 0.137 ppm (α-methylbenzylamine) with low and high limits from 0.007 ppm (2-ethylhexylamine) to 0.336 ppm (methyl ester of phenylalanine), respectively. The efficiency of **4** has also been demonstrated by the ^{19}F NMR separation of all diastereoisomers of the four isomeric menthols (8 resonance lines). The subtle dependence of the fluorine resonances on small structural changes in very similar systems made us consider its use in the determination of the absolute configuration. Several diastereoisomeric hydrogens and all methyl groups are well separated in the ^{1}H NMR spectra of the menthol esters (Table 1). The population of the preferred conformer is only slightly influenced by the solvent. The chemical shifts of the menthyl methyl groups in **5** are very similar in $CDCl_3$ and C_6D_6. However, an appreciable solvent effect of the lactic methyl (δ 1.58 in $CDCl_3$ and 1.42 in C_6D_6) is apparent.

The different high- and low-field variations were only compatible with a conformation blocking the α-proton of the acid part in the acid plane.[7] These observations are nicely confirmed by the X-ray analysis of crystals (from hexane) of neomenthol diastereoisomers **5** and **6** (Figs. 1 and 2).‡ Both crystal structures reveal some remarkable features.§ The

† The exact position of OMe in **1** and **2** depends on the nature of the other substituents.

‡ The distances have been established with MacMoMo (molecular modelling program, Max Dobler, ETH Zürich).

§ *Crystal data* for **5**, $C_{19}H_{27}FO_3$, M_r = 32242, orthorhombic, space group $P2_12_12_1$, a = 11.484(5), b = 18.988(9), c = 6.627(4) Å, V = 1881.3(2) Å^3, Z = 4, $F(000)$ = 696, D_c = 1.138 g cm^{-3}, data collection on CAD 4-diffractometer; Mo-Kα radiation (λ = 0.71069 Å), μ = 0.768 cm^{-1}, crystal size 0.4 × 0.4 × 0.5 mm, ω–2θ scan, θ_{max} = 24, Δω = 0.8 + 0.35tanθ, T = 298 K, R = 0.0410, R_w = 0.0362 for 2147 unique reflections with $I > 3\sigma(I)$.

Crystal data for **6**, $C_{19}H_{27}FO_3$, M_r = 322.42, orthorhombic, space group $P2_12_12_1$, a = 11.798(5), b = 18.962(9), c = 8.422(4) Å, V = 1884.0(2) Å^3, Z = 4, F (000) = 696, D_c = 1.137 g cm^{-3}, data collection on CAD 4-diffractometer; Mo-Kα radiation (λ = 0.71069 Å), μ = 0.766 cm^{-1}, crystal size 0.3 × 0.8 × 0.8 mm, ω–2θ scan, θ_{max} = 24, Δω = 1 + 0.35tanθ, T = 298 K, R = 0.0437, R_w = 0.0409 for 1482 unique reflections with $I > 3\sigma(I)$.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

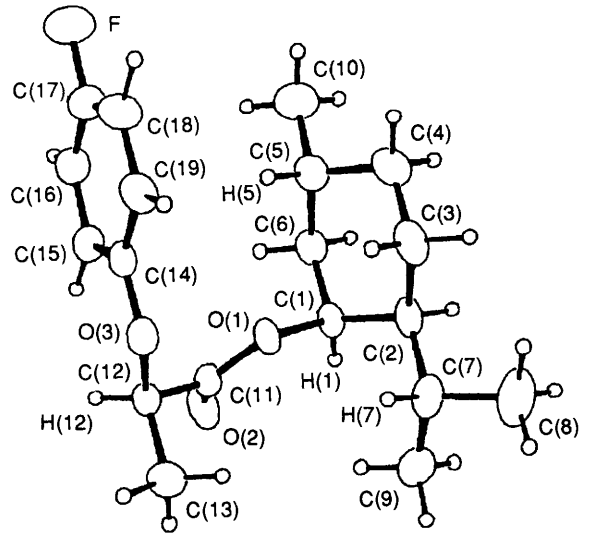


Fig. 1 View of the structure of **5**. Selected distances (Å) and angles (°) C(19)–C(5) 4.08, H(19)–H(5) 3.57, C(15)–C(5) 4.03, C(19)–H(5) 3.08, C(13)–C(9) 4.48, C(13)–C(7) 4.55, dihedral angle H(1)–H(12) 61.05.

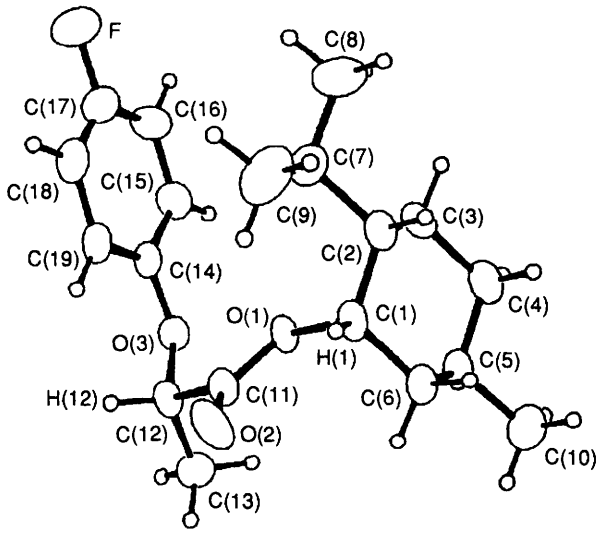


Fig. 2 View of the structure of **6**. Selected distances (Å) and angles (°) C(19)–C(7) 3.92, C(15)–C(7) 4.11, C(19)–C(9) 4.06, H(15)–H(7) 3.68, C(13)–C(5) 4.76, C(13)–C(10) 5.58, dihedral angle H(1)–H(12) 13.04.

synperiplanar conformation of the ester carboxylic group,[8] exclusive axial configuration of neomenthol oxygen[9] together with the proximity of the aryl group to distinct groups of the enantiomeric alcohols is clearly demonstrated. The most striking observation in both compounds is the parallel arrangement of the phenyl ring and the plane of the menthol cyclohexanes. This geometry results in the aromatic ring being close to the isolated methyl [C(10)] in **5**, and to the isopropyl in **6**. Comparably short atomic distances are found between aromatic protons and H(5) in **5** (3.57 Å), and H(7) in **6** (3.68 Å). In contrast, steric proximity of the lactic methyl with the menthol is only observed in the (*R*)-PFPLA ester **5** (PFPLA = *p*-fluorophenoxylactic acid) involving the isopropyl proton (Me_{lact}–$H_{i\text{-}pr}$ 2.96 Å) and methyl (Me_{lact}–$Me_{i\text{-}pr}$ 3.38 Å). The predicted (NMR) coplanarity of H(1) and H(12) is slightly deformed in this latter compound (dihedral angle: 61°) compared to **6** with a nearly perfect alignment (dihedral angle: 13°). The high downfield shifts in the ^{1}H NMR spectra of PFPLA esters are in full accordance with the crystal structure. Likewise, the extension[10] of Mosher's method[11] is applicable to lactic acid derivatives (*e.g.* effect on methyl groups, Δδ values in Table 1).

The ^{1}H NMR assignments according to the Mosher model have been confirmed by X-ray structure analysis in many cases.[12] However anomalies have been reported due to sterical crowding.[13] We have shown that the interconversion of the methyl and aryl group in *O*-methoxymandelic acid endows reagents such as *O*-aryllactic acids with different conformational preferences. As far as simple chiral compounds are involved, these reagents are useful for the determination of absolute configurations according to a new model (acid H^{α} in the acid plane). Application to more complex structures remains to be shown. The extremely simple and general access[3,4,6] combined with the easy modification of the aryl moiety should make these reagents interesting complements to existing fluorinated[11,14,15] and other chiral reagents.[16]

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