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DIRECTED RESOLUTION OF 2-FLUORO-2-METHYLHEXANOIC ACID

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SUMMARY

The applicability of Helmchen's methods for the separation and determination of absolute configuration of enantiomers via diastereoisomeric phenylethylamides has been tested with 2-fluoro- and 2-methylhexanoic acids, then successfully applied to 2-fluoro-2-methylhexanoic acid.

INTRODUCTION

Chiral organofluorine compounds are of wide biological interest. In this respect, optically pure α-fluorocarboxylic acids are important intermediates and are of biological importance themselves as enzymatic blocking agents [1]. We have been interested for some years in the synthesis of several 16-fluoroprostaglandin analogues [2]. Following Corey's scheme of synthesis [3], the preparation of diastereoisomerically pure final compounds [4] can be easily accomplished starting with optically pure α-fluoro-

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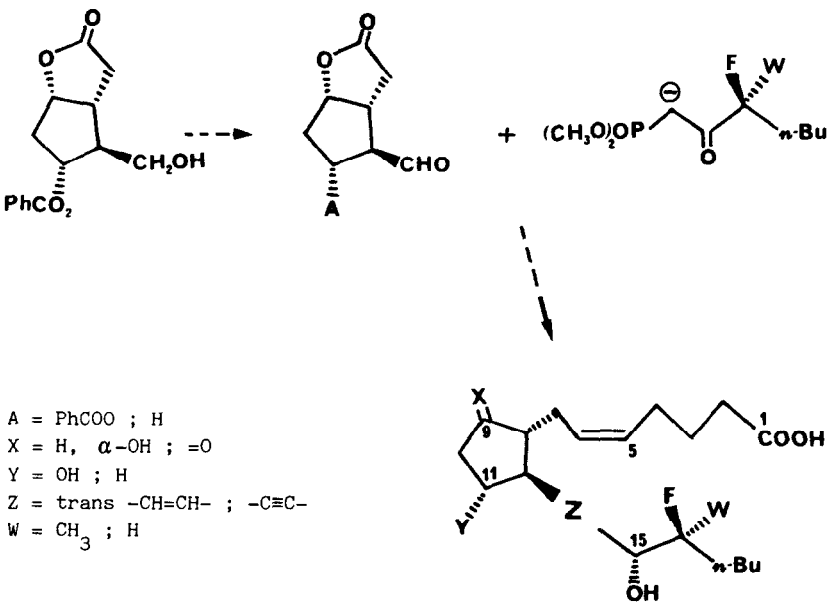
carboxylic acids of known absolute configuration, to secure the final C-16 stereochemistry (see Scheme 1).

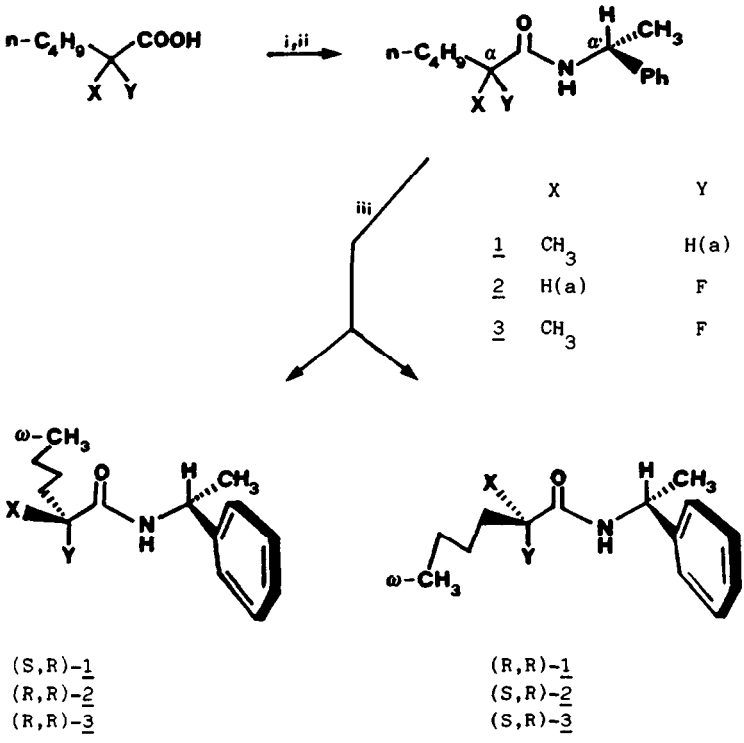


Scheme 1. Synthesis of (16S)-16-fluoro-PG analogues

Determination of absolute configurations of α-fluoroacids (or esters) by chemical methods (ethyl 2-fluoropropionate [5]; dimethyl fluorosuccinate [6]) and by ^{1}H-NMR (2-fluoro-3-methylpentanoic acid [7]) or CD (methyl 2-fluoro-3-cyclohexylpropionate [8]) correlations have been reported. G. Helmchen has proposed a general method [9], termed 'directed resolution', to achieve separation and simultaneous determination of absolute configuration and enantiomeric purity of chiral acids, alcohols or amines via diastereoisomeric amides (as in our case) or esters. However, data regarding the applicability of the method to α-fluoroacids have not been reported yet. In particular, we describe herein the determination of the absolute configuration of 2-fluoro-2-methylhexanoic acid [10].

RESULTS AND DISCUSSION

Racemic 2-fluoro-2-methylhexanoic acid was synthesized by alkylation of 2-fluorohexanoic acid, in turn obtained from 1-hexene according to known procedures [1]. Diastereoisomeric (R)-phenylethylamides were then prepared and separated as usual. In order to confirm the conformational model that underlies the method, we also converted 2-fluoro- and 2-methylhexanoic acids of known absolute configurations [11] into the corresponding (R)-phenylethylamides.*



(S,R)-1
(R,R)-2
(R,R)-3

(R,R)-1
(S,R)-2
(S,R)-3

Scheme 2. i) $SOCl_2$; ii) (R)-phenylethylamine; iii) chromatographic separation.

* 2-Fluorohexanoic acid was resolved via diastereoisomeric salts with (+)-ephedrine. The methylester of the (-)-enantiomer ($[\alpha]_D$ -1.63°, c = 1, MeOH) showed in the CD spectrum a positive maximum at 210 nm ($\Delta\varepsilon$ +0.75, c 0.14 g/l, MeOH), indicating S absolute configuration [8].

Simple inspection of the ^{1}H-NMR spectra of enriched mixtures of diastereoisomeric amides reveals differences between the chemical shifts of the X substituent in α position. Surprisingly, even the terminal methyl of the aliphatic chain (ω-CH_3) shows marked differences, as reported in Table 1 and illustrated for compound 3 in Fig. 1.

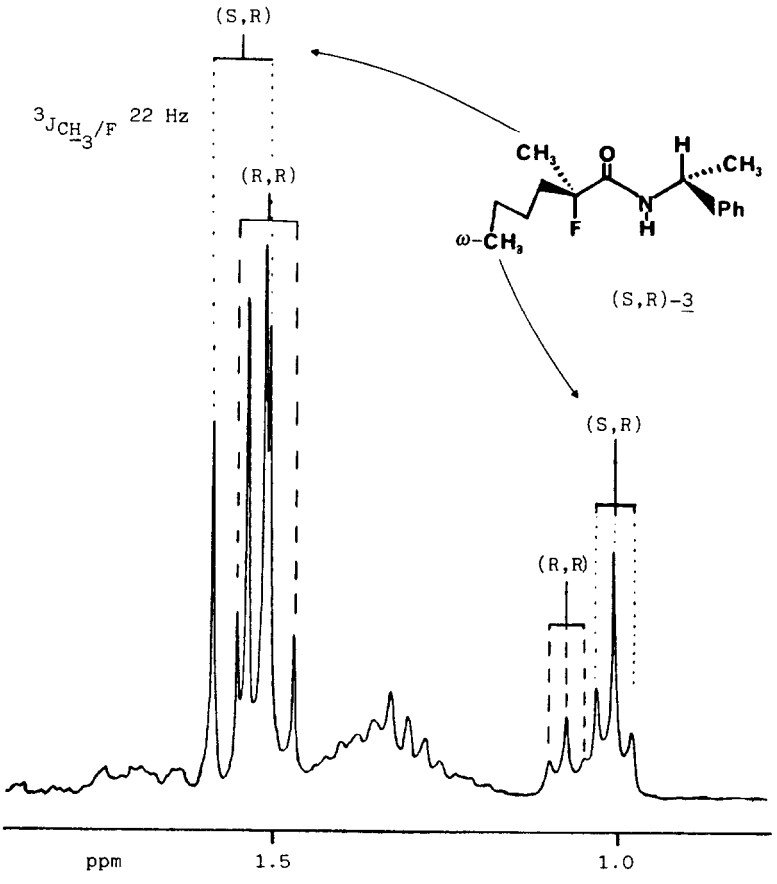


Fig. 1. ^{1}H-NMR spectrum ($CDCl_3$, 200 MHz, high field portion shown) of the mixture of diastereoisomeric (R)-phenylethylamides of 2-fluoro-2-methylhexanoic acid. (R_f <) : (R_f >) ~ 2.5:1.

TABLE 1

Selected ^{1}H-NMR (200 MHZ) and ^{19}F-NMR (188.6) data of diastereoisomeric (R)-phenylethylamides 1, 2, 3 and of (R)-phenylglycinolamides 4 in C_6D_6 and $CDCl_3$. Values are in ppm from TMS and $CFCl_3$ (internal standards) respectively.

	R_f*	X	Y	**	$\delta_{\omega\text{-}CH_3}$				δ_X				δ_Y			
					C_6D_6	$\Delta\delta$***	$CDCl_3$	$\Delta\delta$	C_6D_6	$\Delta\delta$	$CDCl_3$	$\Delta\delta$	C_6D_6	$\Delta\delta$	$CDCl_3$	$\Delta\delta$
1	>	CH_3	H	S	0.85	0.06	0.88	0.06	1.02	-0.07	1.09	-0.04	1.73	0.04	2.15	-0.01
	<			R	0.79		0.82		1.09		1.13		1.69		2.16	
2	>	H	F	R	0.83	0.06	0.92	0.05	4.77	-0.13	4.83	-0.05	-189.9	-0.2	-190.6	-0.1
	<			S	0.77		0.87		4.90		4.88		-189.7		-190.5	
3	>	CH_3	F	R	0.90	0.13	0.92	0.10	1.46	-0.09	1.52	-0.05	-156.8	-0.2	-157.1	-0.1
	<			S	0.77		0.82		1.55		1.57		-156.6		-157.0	
4	>	CH_3	F	S	0.87	0.13	0.91	0.07	1.41	-0.12	1.50	-0.06	-156.7	0.2	-156.7	0.1
	<			R	0.74		0.84		1.53		1.56		-156.9		-156.8	

* SiO_2, C_6H_{12} - AcOEt 7/3. **Configuration of acid moiety. *** $\Delta\delta = \delta(R_f >) - \delta(R_f <)$.

The conformational preference around the NH-C_α bond has been already investigated and established [9a]. On the assumption that the observed differences must be ascribed for the most part to the strong anisotropic effect of the phenyl group, the NMR data clearly indicate that, in the preferred conformation of the acid moiety, the fluorine atom (or H_a in compound 1) lies on the medium plane (amide plane) of the molecule (Scheme 2). In effect, δ_Y is the chemical shift least affected by diastereoisomeric change, 0.2 ppm being a very low difference for the fluorine nucleus if compared with the large chemical shift range. This is also confirmed in compounds 2 and 3 by the existence of a hydrogen bond between the fluorine and the amidic NH [12]. Moreover, consistently with the conformational model assumed, $\Delta\delta_{\omega\text{-}CH_3}$ and $\Delta\delta_X$ for compounds 1 and 2, of known absolute configurations, show a behaviour of opposite sign (Table 1) that can be easily correlated with the relative configuration acid-amine. The diastereoisomeric amide with the ω-CH_3 signal at higher fields has the aliphatic chain on the same side of the phenyl group in the conformation depicted in Scheme 2. The contrary is true for the X group. On the basis of these considerations, the absolute configuration of compounds 3 can be now straightforwardly derived. The (R,R) configuration can be safely assigned to the less polar amide ($R_f >$) and the (S,R) to the other one (Fig. 1). The chromatographic behaviours are in keeping with Helmchen's rule.

Unfortunately, α-fluoroamides are extremely difficult to hydrolyze: we observed no hydrolysis at all in a wide variety of conditions. The problem was circumvented by using (R)-phenylglycinol in place of (R)-phenylethylamine, in order to facilitate the acid hydrolysis via an intramolecular O,N-acyl shift. The presence of the hydroxy group does not modify the conformational behaviour of this type of amides [9c], whereas the configurational characteristics are inverted*.

Thus, we could recover pure (S)-2-fluoro-2-methylhexanoic acid from the amide with higher chromatographic mobility (S,R)-4.

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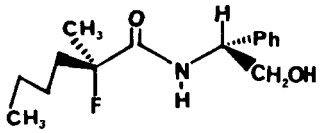
*See facing page.



(S,R)-4

EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer 141 Polarimeter. IR spectra were taken on a Perkin-Elmer 683 Infrared Spectrometer. ^{1}H-NMR (200 MHz) and ^{19}F-NMR (188.6 MHz) spectra were recorded on a Varian XL-200 instrument; δ values are in ppm from TMS and $CFCl_3$ as internal standards respectively.

(RS)-2-fluoro-2-methylhexanoic acid

To a solution of diisopropylamine (0.12 mmoles) in THF (50 ml) were added first a solution of n-BuLi (62 ml, 2M in hexane) at -20°C in a nitrogen atmosphere, then a solution of (RS)-2-fluorohexanoic acid (49.3 mmoles) in THF (30 ml). The mixture was stirred for 1.5 h at -15°C. Then MeJ (9.2 ml, 147.9 mmoles) was added. The mixture was allowed to stand for 2h at room temperature, then it was acidified and extracted with ether (5 x 50 ml). The combined organic extracts were washed with water, dried over Na_2SO_4 and evaporated. The residue (6.51 g) was purified by column chromatography on silica gel, using cyclohexane-ethyl acetate 60/40 as eluent. Yield 5.8 g (74.5%). Analysis : found C 56.99%; H 8.96; F 12.67.

*In fact, (R)-phenylglycinol and (R)-phenylethylamine, owing to a change in the priority sequence, are characterized by opposite spatial distributions of groups, although having the same specification of chirality (R). As the chromatographic behaviour and the spectral properties are determined by the relative configuration, this entails the inversion of configuration of the acid moiety for the amides derived from (R)-phenylglycinol with respect to the corresponding (R)-phenylethylamides.

$C_7H_{13}FO_2$ requires C 56.74%; H 8.84; F 12.82. IR ($CHCl_3$) : 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 0.91 (3H, t), 1.42 (4H, m), 1.55 (3H, d, J 21.0 Hz), 1.85 (2H, m), 10.15 (1H, br).

(RS)-N-((R)-α-methylbenzyl)-2-fluoro-2-methylhexanamide (3)

Three equivalents of $SOCl_2$ were added to 9.5 mmoles of (RS)-2-fluoro-2-methylhexanoic acid. The mixture was stirred at ambient temperature for 15 min, then it was heated at 70 °C for 2 h. The excess of thionyl chloride was eliminated with a nitrogen stream and trapped with KOH. The crude acyl chloride was diluted with ether and added dropwise to a solution in ether of (R)-phenylethylamine (54 mmoles) at 0°C. After the amine hydrochloride was filtered off, the ethereal solution was washed successively with HCl 0.1 N, water, then dried over anhydrous Na_2SO_4 and concentrated in vacuum to give 2.45 g of crude crystalline product. The diastereoisomeric amides were separated by chromatography over silica gel using 25% ethyl acetate in hexane as eluent.

The (R)-phenylethylamides from (R) and (S)-2-fluorohexanoic, (R) and (S)-2-methylhexanoic acids were obtained similarly. All analytical and spectroscopic properties were in accordance with the structures. Selected ^{1}H-NMR and ^{19}F-NMR data are reported in Table 1.

(RS)-N-((R)-α-hydroxymethylbenzyl)-2-fluoro-2-methylhexanamide (4)

With the same procedure described above, compound (4) was prepared and the mixture of diastereoisomeric amides thus obtained was chromatographed on silica gel. The column was eluted with hexane-ethyl acetate (8/2 to 7/3). (S,R)-4 : IR (KBr) : 3530, 3340, 1640 cm^{-1}; $[\alpha]_D$ -64.5° (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 0.91 (3H, t), 1.50 (3H, d, J 22 Hz), 3.82 (2H, m), 5.03 (1H, m), 7.12 (1H, br d), 7.35 (5H, m); ^{19}F-NMR ($CDCl_3$) : δ -156.7.(R,R)-4 : $[\alpha]_D$ - 27.1° (c = 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) : δ 0.84 (3H, t), 1.56 (3H, d, J 22 Hz), 5.04 (1H, m), 7.12 (1H, br d), 7.34 (5H, m); ^{19}F-NMR ($CDCl_3$) : δ -156.8.

(S) and (R)-2-fluoro-2-methylhexanoic acid

The first eluted amide (S,R)-4 (380 mg) was heated under reflux for 10 h with 4N HCl (8 ml) in dioxane-water 1:1 (4 ml). At room temperature the mixture was partitioned with ether, then the organic solution was extracted with $NaHCO_3$. The aqueous phase is acidified to pH = 0 with HCl, re-extracted with AcOEt and dried over Na_2SO_4. Removal of the solvent in vacuum yielded 185 mg of the corresponding acid. $[\alpha]_D$ = -5.68° (c = 1, $CHCl_3$). From (R,R)-4, (R)-2-fluoro-2-methylhexanoic acid was obtained. $[\alpha]_D$ = +5.75° (c = 1, $CHCl_3$).

CONCLUSION

Our results suggest that Helmchen's methods may be extended and applied to 2-fluoroalkanoic acids. In addition, we have shown that considerable and consistent chemical shift nonequivalence is induced not only for the substituents on the alpha carbon, but also for groups (i.e. ω-CH_3) far away from the chiral position.

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10 Optical resolution via diastereoisomeric amides and assignment of absolute configuration of 2-fluoro- and 2-fluoro-2-methylhexanoic acids has been claimed by Holland et al. (Hoffmann-La Roche Inc., U.S. Pat. 4 187 381), but no method for stereochemical determination has been described yet.

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12 δ_{NH} remains practically unchanged after dilution (c 4 to 0.4%), in contrast with the NH signal of compound 1.