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# A STEREOCONTROLLED ACCESS TO VICINAL DIFLUOROALKANES

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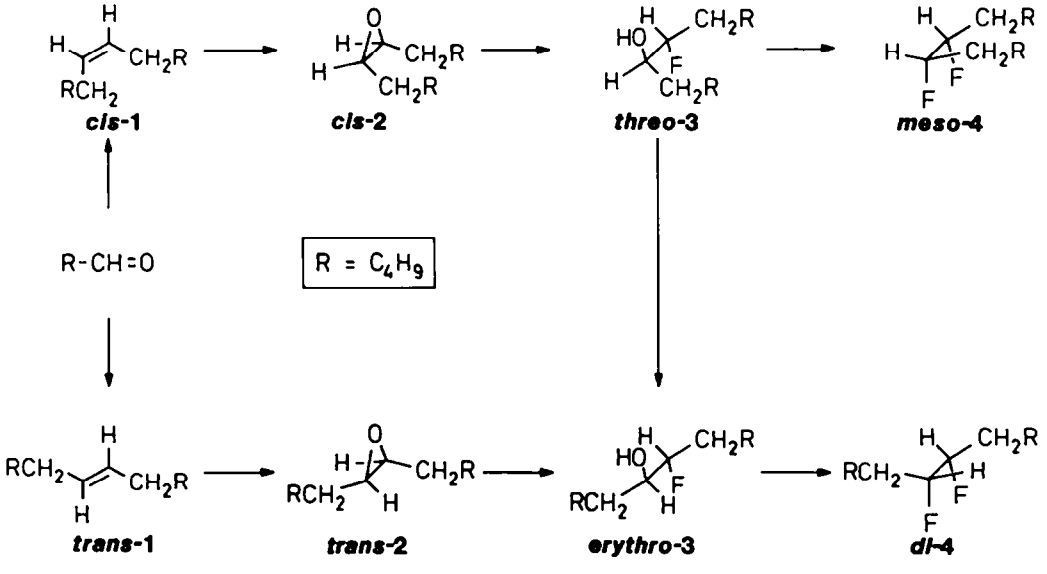
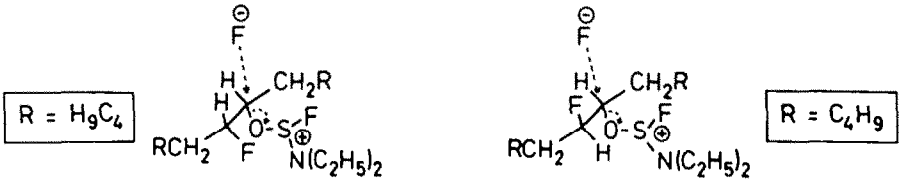
Summary. - *An expedient method for the preparation of diastereomerically and, by extension, even enantiomerically pure vicinal difluoroalkanes is described. The two fluorine atoms are introduced in two consecutive steps : ring opening of an oxirane by addition of hydrogen fluoride and subsequent treatment of the resulting fluorohydrine with diethylaminosulfur trifluoride.*

For the elimination study described in the preceding article *meso*- and *dl*-6,7-difluorododecane were required. They were readily prepared in 42% and, respectively, 33% over-all yield starting with *cis*- and *trans*-6-dodecene (*cis*- and *trans*-**1**), both obtained by stereoselective Wittig olefination [1, 2]. Treatment of the alkenes with monoperphthalic acid led to the corresponding oxiranes (*cis*- and *trans*-**2**) which reacted with hydrogen fluoride in the presence of triethylamine [3] to afford the fluorohydrines (*threo*- and *erythro*-**3**, respectively). These two diastereoisomers could be easily interconverted by applying the Mitsunobu inversion method [4]. The replacement of the hydroxy group by a second fluorine atom was accomplished with diethylaminosulfur trifluoride in the presence of pyridine and the resulting difluoro-alkanes (*meso*- and *dl*-**4**, respectively) were isolated as pure stereoisomers (mp 20 - 21°C and 35 - 36°C).

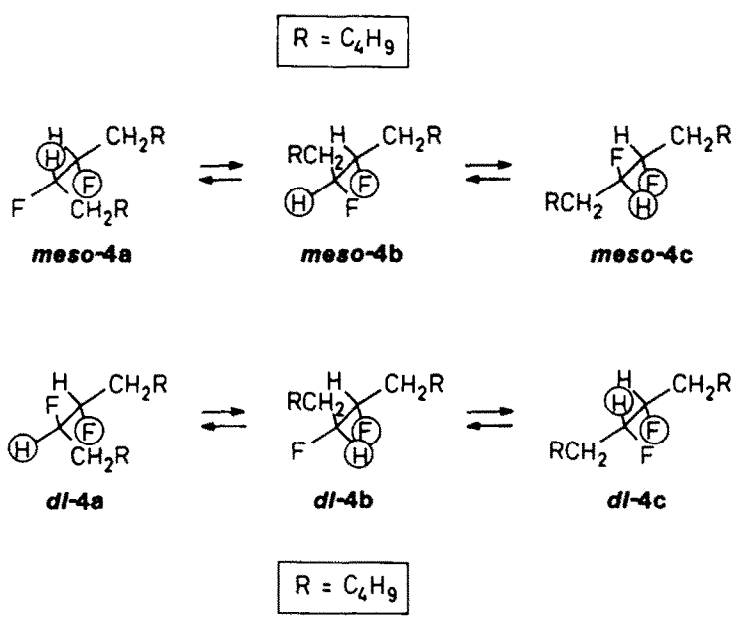


The hydroxy/halogen substitution proceeded more rapidly and cleanly with the *threo*-fluorohydrine (*threo*-3) than with its *erythro*-isomer. Already on previous occasions *dl*-difluorides were found to form only sluggishly and with low yields. [5] We tentatively attribute these reactivity differences in the two diastereomeric series to an eclipsing orientation of the halogen in the *erythro*-fluorohydrine with respect to the approaching fluoride ion (transition state **5b**). No such unfavorable electrostatic interaction is experienced by the *threo*-isomer (transition state **5a**).



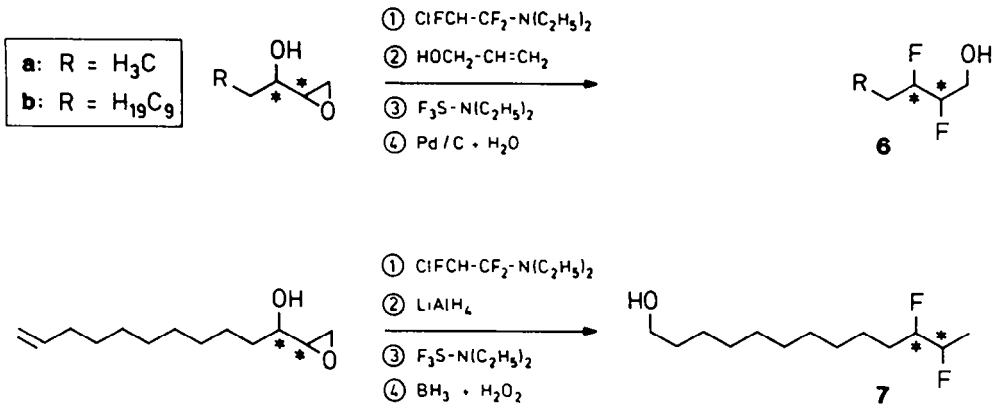

**5a** **5b**

As others have already pointed out [6], *dl*-diastereomers of *vic*-difluoroalkanes should widely prefer that conformation (*dl*-**4c**) in which the two alkyl groups occupy an *anti*-planar and the fluorine atoms a *gauche*-position over the others (*dl*-**4a** and *dl*-**4b**). In contrast, *meso*-diastereomers are expected to populate all three available conformations (*meso*-**4a**, its mirror-image *meso*-**4b** and *meso*-**4c**) with roughly equal probabilities. The observed $^3J_{HF}$-coupling constants of 14 and 22 Hz (*meso*- and *dl*-**4**, respectively) agree well with these assumptions.




Is it really inevitable to choose a multi-step sequence, as we have done, if one simply wishes to introduce two vicinal fluorine atoms into a paraffinic chain ? Not necessarily. Elementary fluorine can be added to alkenes in a clean *syn*-mode if radical scavangers are present [6]. Although it is yet unknown whether this method can be applied to large-scale preparations, it is certainly a very attractive one. The route via fluorohydrines, however, has distinct advantages if not only diastereomerically pure but also enantiomerically pure fluorinated compounds are the targets. Since optically active oxiranes are readily accessible by asymmetric epoxidation [7] or other convenient methods, they may serve as precursors to chiral, functionalized difluoroalkanes. We have exemplified

this approach by the synthesis of 2,3-difluoro-1-pentanol (**6a**), 2,3-difluoro-1-tridecanol (**6b**) and 11,12-difluoro-1-tridecanol (**7**) [5].




Moreover, fluorohydrines offer much versatility. Their hydroxy group may not only be replaced by fluorine but also by chlorine, bromine, iodine or a variety of other nucleophiles. Finally it may be converted to a *p*-toluenesulfonyloxy moiety or another good leaving group, which can be eliminated under the impact of potassium *tert*-butoxide [8]. Thus, 1-fluoroalkenes [9] become very easily accessible.

## EXPERIMENTAL PART

For general remarks see the first article [10] of this series.

*cis*-6-Dodecene (*cis*-1)

A mixture of hexyltriphenylphosphonium bromide (235 g, 0.55 mol), sodium amide (42 g, 0.55 mol) and potassium *tert*-butoxide (6.2 g, 0.050 mol) in dry ether (1 L) was vigorously stirred 2 h at 25°C. At -75°C hexanal (50 g, 0.50 mol) was added in the course of 1 h dropwise to the mixture which was kept overnight at 25°C before water (500 mL) was added. The reaction mixture was extracted with diethyl ether (3 x 200 mL). The combined ether solution was evaporated under reduced pressure. The residue was triturated with hexane (250 mL) and triphenylphosphine oxide was separated by filtration and washed with hexane (250 mL). After drying ($CaSO_4$) and evaporation of the solvent, distillation of the residue afforded 70.7 g (84%) of a colourless liquid which did not crystallize even when cooled down to -75°C; bp 53 - 54°C/3 mmHg; $n_D^{20}$ 1.4342.

IR (film) : 3010 (m, $\nu$[=C-H]), 2960 + 2930 + 2860 (s, $\nu$[-C-H]), 1655 (vw, $\nu$[C=C]), 1465 (m, $\delta[CH_2]$), 1380 (w, $\delta[CH_3]$).

$^1$H-NMR : 5.35 (2 H, *t*-like *m*, *J* ~ 5), 2.03 (4 H, *q*, *J* 6.0), 1.3 (12 H, *m*), 0.90 (6 H, *t*, *J* 6.8).

MS : 168 (25%; $M^+$), 111 (10%), 97 (19%), 83 (29%), 69 (79%), 55 (100%).

Analysis : calc. for $C_{12}H_{24}$ (168.3) C 85.63%, H 14.37%; found C 85.97%; H 14.37%.

**cis-6,7-Epoxy-dodecane** *(cis-2)*

To a solution of *cis*-6-dodecene (170 g, 0.42 mol) in diethyl ether (2 L), monoperphthalic acid [11] (0.25 kg, 0.83 mol) was added in the course of 20 min at 25°C. After 24 h stirring the reaction mixture was filtered and vigorously shaken with a saturated aqueous solution of sodium thiosulfate (250 mL). The aqueous layer was reextracted with diethyl ether (2 x 100 mL). The combined organic layers were washed with water (2 x 100 mL), a saturated solution of sodium hydrogencarbonate (3 x 250 mL) and brine (200 mL), and dried. After stripping off the solvent, the residue was distilled to afford 66.5 g (86%) of a colorless liquid; bp 73 - 74°C/3 mmHg; mp -10 to -8°C; $n_D^{20}$ 1.4338; *cis/trans*-ratio 97 : 3 (according to gas chromatography (50 m OV-1701, 130°C).

IR (film) : 2960 + 2935 + 2865 (s, $\nu$[-$\dot{C}$-H]), 1465 (m, $\delta$[$CH_2$]), 1382 (w, $\delta$[$CH_3$]).

$^1$H-NMR : 2.90 (2 H, *pent*-like *m*, $J \sim 4$); 1.4 (16 H, *m*); 0.91 (6 H, *t*-like *m*, $J \sim 6$).

MS (c.i.): 202 (100%, $M^+ + NH_4$), 185 (2%), 113 (7%), 82 (3%).

Analysis : calc. for $C_{12}H_{24}O$ (184.3) C 78.20%, H 13.12%; found C 78.19%, H 13.11%.

**(6*R**, 7*R**)-7-Fluoro-6-dodecanol** *(threo-3)*

The heterogenous mixture of *cis*-6,7-epoxydodecane (66 g, 0.36 mol) and the 3:1 complex of hydrogen fluoride and triethylamine (58 g, 0.36 mol) was stirred for 3 h at 150°C. Then it was poured into ice-water and extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with a saturated solution of sodium hydrogencarbonate (2 x 150 mL) and brine (2 x 200 mL), before drying. After evaporation of the solvent, the residue was recrystallized from hexane. White crystals of 7-fluoro-6-dodecanol were obtained; 60 g (81%); mp 59 - 60°C; *erythro/threo* 2 : 98 (according to gas chromatography : 50 m OV- 1701, 140°C).

IR (KBr) : 3390 (s, $\nu$[ OH]), 2950 + 2920 + 2850 (s, $\nu$[-$\dot{C}$-H]), 1465 (m, $\delta$[$CH_2$]), 1365 (m, $\delta$[$CH_3$]).

$^1$H-NMR : 4.33 (1 H, *dddd*, *J* 48.7, 8.5, 5.0, 3.5), 3.56 (1 H, *d* of symm. *m*, $J_{HF}$ 18.5), 2.10 (1 H, *s*), 1.5 (16 H, *m*), 0.90 (6 H, *t*-like *m*, $J \sim 7$).

MS (c.i.): 222 (100%, $M^+ + NH_4$), 202 (2%), 100 (2%), 83 (5%).

Analysis : calc. for $C_{12}H_{25}FO$ (204.3) C 70.54%, H 12.33%; found C 70.97%, H 12.37%.

**(6*S**, 7*R**)-6,7-Difluorododecane** *(meso-4)*

To a solution of 7-fluoro-6-dodecanol (40.9 g, 200 mmol) in $CH_2Cl_2$ (360 mL), a solution of diethylaminosulfur trifluoride (37.1 g, 230 mmol) in $CH_2Cl_2$ (40 mL) was added in the course of 30 min dropwise at -50°C. The temperature was raised to -15°C, and pyridine (27.4 mL, 26.9 g, 340 mmol) was added dropwise in the course of 15 min. The reaction mixture was kept overnight (16 h) at 25°C before being poured into ice-water and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with 5% hydrochloric acid (3 x 100 mL), saturated aqueous solution of sodium hydrogencarbonate (3 x 150 mL) and brine (3 x 150 mL). After drying and evaporation of the solvent, the residue was taken up in hexane (500 mL) and filtered through a short column filled with silica gel (approx. 250 g). The eluent was concentrated and cooled to -50°C. Difluorododecane was obtained as colorless crystals (25 g, 61%) which melted at ordinary temperature; bp 64 - 65°C/3 mmHg; mp 20 - 21°C; $n_D^{20}$ 1.4135; *meso/dl*-ratio 99 : 1 (according to gas chromatography : 50 m OV-1701, 130°C).

IR (film) : 2980 + 2950 + 2880 (s, $\nu$[-$\dot{C}$-H]), 1470 (m, $\delta$[$CH_2$]), 1375 (w, $\delta$[$CH_3$]).

$^1$H-NMR : 4.48 (2 H, *dd* of symm. *m*, $J_{HF} \sim 48, 14$), 1.5 (16 H, *m*), 0.90 (6 H, *t*-like *m*, $J \sim 7$).

$^{19}$F-NMR : -129.8 (symm. *m*).

MS (c.i.) : 224 (14%, $M^+ + NH_4$), 166 (27%), 137 (16%)), 123 (23%), 109 (51%), 95 (100%), 81 (79%).

Analysis : calc. for $C_{12}H_{24}F_2$ (206.3) C 69.86%, H 11.72%; found C 70.26%, H 11.83%.

*trans*-**6-Dodecene** (*trans*-**1**)

To a slurry of hexyltriphenylphosphonium bromide (47.0 g, 110 mmol) in tetrahydrofuran (120 mL), a solution of lithium bromide-containing phenyllithium in diethyl ether (0.43 M, 260 mL) at 0°C was stirred for 15 min at 25°C and then cooled to -75°C before hexanal (10.0 g, 100 mmol) was added dropwise in the course of 10 min. After additional 20 min at -75°C, a solution of phenyllithium in diethyl ether (0.43 M, 260 mL) was added dropwise in the course of 15 min. The temperature was allowed to raise to -30°C where it was kept 15 min. Again at -78°C, a diethyl ether solution of hydrogen chloride (3.1 M, 50 mL) was added dropwise in the course of 10 min. Finally, the precipitate was treated with potassium *tert*-butoxide (16.8 g, 150 mmol) and stirred 2 h at 25°C. After addition of water (150 mL), the reaction mixture was extracted with diethyl ether (3 x 150 mL). The dried organic layers were evaporated under reduced pressure. After adding hexane (150 mL), triphenylphosphine oxide was separated by filtration and washed with hexane. After drying ($CaSO_4$) and evaporation of the solvent, distillation of the residue afforded a colorless liquid (9.6 g, 57%), bp 55 - 56°C/3 mmHg, mp -34 to -33°C, $n_D^{20}$ 1.4333.

IR (film) : 3010 (m, $\nu$[=C-H]), 2950 + 2975 + 2850 (s, $\nu$[-C-H]), 1625 (vw, $\nu$[C=C]), 1460 (m, $\delta[CH_2]$), 1375 (w, $\delta[CH_3]$).

$^1$H-NMR : 5.41 (2 H, *tt*, *J* 3.8, 1.6), 2.00 (4 H, *q*-like *m*, *J* ~ 5.5), 1.3 (12 H, *m*), 0.93 (6 H, *t*, *J* 7.1).

MS : 168 (12%, $M^+$), 97 (15%), 83 (35%), 69 (100%), 55 (95%), 41 (81%).

Analysis : calc. for $C_{12}H_{24}$ (168.3) C 85.63%, H 14.37%; found C 85.74%, H 14.23%.

*trans*-**6,7-Epoxydodecane** (*trans*-**2**)

To a solution of *trans*-6-dodecene (8.4 g, 50 mmol) in diethyl ether (200 mL), monoperphthalic acid [11] (29.6 g, 100 mmol) was added in the course of 15 min at 25°C. After 24 h stirring the reaction mixture was filtered and vigorously shaken with a saturated aqueous solution of sodium thiosulfate (50 mL). The aqueous layer was reextracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with a saturated solution of sodium hydrogencarbonate (3 x 25 mL), water (2 x 25 mL) and brine (50 mL), and dried ($CaSO_4$). After stripping off the solvent, the residue was distilled to afford a colorless liquid (7.7 g, 84%), bp 63 - 64°C/ 3 mmHg, mp -16 to -15°C, $n_D^{20}$ 1.4310, *cis/trans* ratio 2 : 98 (according to gas chromatography : 50 m OV-1701, 130°C).

IR (films) : 2950 + 2920 + 2850 (s, $\nu$[-C-H]), 1460 (m, $\delta[CH_2]$), 1020 (m, $\nu$[C-O]).

$^1$H-NMR : 2.68 (2 H, *p*-like *m*, *J* ~ 3.5), 1.4 (16 H, *m*), 0.93 (6 H, *t*-like *m*, *J* ~ 7).

MS (c.i.) : 202 (100%, $M^+ + NH_4$), 113 (6%).

Analysis : calc. for $C_{12}H_{24}O$ (184.3) C 78.20%, H 13.12%; found C 78.19%, H 13.12%.

(6*S**, 7*R**)-**7-Fluoro-6-dodecanol** (*erythro*-**3**)

A mixture of *trans*-6,7-epoxydodecane (6.8 g, 37 mmol) and hydrogen fluoride-triethylamine 3 : 1 complex (7.1 g, 44 mmol) was heated for 3 h to 150°C. The reaction mixture was poured into ice-water and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with a saturated solution of sodium

hydrogencarbonate (3 x 50 mL) and brine (3 x 50 mL). After drying and evaporation of the solvent, the residue was recrystallized from hexane at -50°C. The product obtained, 7-fluoro-6-dodecanol (6.2 g, 82%), was a colorless liquid at ordinary temperature, bp 82 - 83°C/3 mmHg; mp 18 - 19°C; $n_D^{20}$ 1.4332; *erythro/threo*-ratio 97 : 3 (according to gas chromatography : 50 m OV-1701, 140°C).

IR (film) : 3360 (s, $\nu$[ OH]), 2950 + 2920 + 2850 (s, $\nu$[-$\dot{C}$-H]), 1460 (m, $\delta$[ $CH_2$ ]), 1375 (m, $\delta$[ $CH_3$]), 1060 (m, $\nu$[ C-O ]).

$^1$H-NMR : 4.38 (1 H, *dddd*, *J* 48.0, 9.5, 4.2, 2.5), 3.70 (1 H, *ddt*, *J* 15.5, 8.5, 3.6), 2.30 (1 H, *s*), 1.5 (16 H, *m*), 0.90 (6 H, *t*-like *m*, *J* ~ 7).

MS (c.i.) : 222 (100%, $M^+$ + $NH_4$), 202 (2%), 100 (1%), 83 (3%).

Analysis : calc. for $C_{12}H_{25}OF$ (204.3) C 70.54%, H 12.33%; found C 70.96%, H 12.27%.

To a solution of (6*R**, 7*R**)-7-fluoro-6-dodecanol (44 g, 0.21 mol), triphenylphosphine (56 g, 0.21 mmol) and 3,5-dinitrobenzoic acid (45 g, 0.21 mol) in tetrahydrofuran (0.2 L) was added dropwise in the course of 40 min at 25°C. After keeping for 24 h at 25°C, the solvent was evaporated and the residue was washed twice with hexane and finally recrystallized from hexane. The solid mixture of triphenylphosphine oxide and 3,5-dinitrobenzoate was dissolved in tetrahydrofuran (0.3 L). A solution of methanol (0.20 L) and 1 N aqueous solution (0.16 L) of potassium hydroxide was added dropwise in the course of 20 min at 0°C. The reaction mixture was kept for 3 h at 25°C before being poured into water (500 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with a saturated solution of sodium hydrogencarbonate (3 x 100 mL) and brine (3 x 100 mL), and dried. After evaporation of the solvent, hexane was added and triphenylphosphine oxide was separated by filtration and washed with hexane. Concentration of the solution and distillation of the residue afforded a colorless liquid (31 g, 72%), bp 82 - 83°C/ 3 mmHg, mp 18 - 19°C, $n_D^{20}$ 1.4332; *erythro/threo* ratio 98 : 2.

**(6*R**, 7*R**)-6,7-Difluorododecane** *(dl-4)*

To a solution of 7-fluoro-6-dodecanol (30.6 g, 150 mmol) in $CH_2Cl_2$ (270 mL) at -50°C, a solution of diethylaminosulfur trifloride (29.0 g, 180 mmol) was added dropwise in the course of 20 min. The temperature was raised to -15°C and pyridine (24.2 mL, 23.7 g, 300 mmol) was added dropwise in the course of 10 min to the reaction mixture, which was kept overnight (15 h) at 25°C. Afterwards it was poured into ice-water and extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with 5% hydrochloric acid (3 x 100 mL), saturated aqueous solution of sodium hydrogencarbonate (3 x 100 mL) and brine (3 x 100 mL). After drying and evaporation of the solvent, the residue was taken up in hexane (500 mL) and filtered through a short column filled with silica gel (approx. 250 g). The eluent was concentrated and cooled to -50°C. Difluorododecane was obtained as colorless crystals (14.9 g, 48%), mp 35 - 36°C, *meso/dl*-ratio 1 : 99 (according to gas chromatography : 50 m OV-1701, 130°C).

IR (KBr) : 2940 + 2970 + 2850 (s, $\nu$[-$\dot{C}$-H]), 1465 (m, $\delta$[ $CH_2$ ]), 1370 (w, $\delta$[$CH_3$]).

$^1$H-NMR : 4.4 (2 H, *dd* of symm. *m*, $J_{HF}$ ~ 48, 22), 1.5 (16 H, *m*), 0.90 (6 H, *t*-like *m*, *J* ~ 7).

$^{19}$F-NMR : -133.6 (symm. *m*).

MS (c.i.) : 224 (100%, $M^+$ + $NH_4$), 166 (30%), 137 (15%), 123 (25%), 109 (42%), 95 (66%), 81 (49%).

Analysis : calc. for $C_{12}H_{24}F_2$ (206.3) C 69.86%, H 11.72%; found C 70.04%, H 11.72%.

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