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FLUORINATED CYCLOPROPANECARBOXYLIC ACIDS AND THEIR DERIVATIVES

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SUMMARY

The addition of halofluorocarbenes such as :CF_2, :CClF or :CBrF, generated from the appropriate halofluoromethanes with bases, to butadiene or isoprene gives the corresponding 1-vinyl substituted halofluorocyclopropanes in moderate to good yield. The vinyl group facilitates the carbene addition and permits a subsequent wide derivatisation. Several transformations including hydroboration, oxidation and Curtius degradation are presented. Furthermore, replacement of the chlorine atom in 2-chloro-2-fluorocyclopropanecarboxylic acid derivatives by hydrogen is achieved catalytically with Raney nickel. This sequence provides a convenient route to mono-fluorine substituted cyclopropane carboxylic acids.

INTRODUCTION

In the course of our continuing studies of fluorine-containing building blocks for the synthesis of biologically active substances we became interested in the synthesis of small ring compounds using industrially available chemicals. Recent developments in such widely differing fields as antimycotical azoles [1] or antibacterial quinolonecarboxylic acids [2] in which a cyclopropyl group enhances activity and selectivity prompted us to look for a broadly applicable synthesis of functionalised fluorine-containing cyclopropanes.

Fluorinated cyclopropanes can be prepared by addition of fluoro-substituted carbenes, i.e. difluoro-, halofluoro- or monofluorocarbene, to double bonds [3]. The stability of fluorinated carbenes increases and, consequently, their electrophilicity decreases with the number of fluorine atoms [4].

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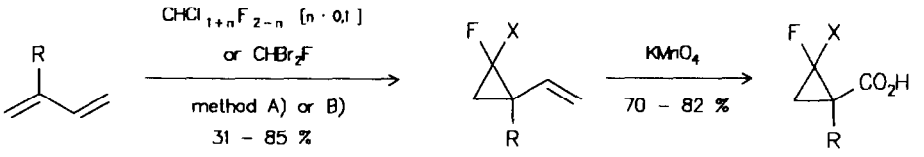
Therefore, we chose dienes (butadiene and isoprene) as electron rich alkene components in which the electron releasing vinyl group facilitates the carbene addition and permits a subsequent wide derivatisation.

This approach was shown to be successful by Graham et al. who synthesised 2,2-difluorocyclopropane carboxylic acid, its acid chloride and its amide by this route [5]. Only two other publications address this topic. ^{13}C-spectra of syn- and anti-2-fluoro-cyclopropanecarboxylic acid ethyl esters are given but preparative details are lacking [6]. Furthermore, the synthesis of syn-1-amino-2-fluorocyclopropane appears in the patent literature without any reference to the origin of the starting material [7].

RESULTS AND DISCUSSION

Synthesis of fluoro-substituted cyclopropanecarboxylic acids

Commercially available halomethanes served as inexpensive carbene sources. The generation of the difluorocarbene was accomplished by the method of Buddrus et al. [8,9] (method A) which was also applied to the addition of chlorofluorocarbene to butadiene. In all other cases, the carbenes were generated using the phase transfer conditions of Weyerstahl et al. [10] (method B) which resulted in better yields. The addition of the halocarbenes to isoprene were regioselective (> 95%). The products of the attack on the electron rich double bond were pure after one distillation. Bis-addition occured only to a minor extent, if at all. The reactions of the chloro- and bromofluorocarbenes were non-stereoselective within the degree of experimental error. Our results are summarised in Table 1.



1a R H
1b R CH_3

2a - 2e

3a - 3e

Oxidation of the vinylcyclopropanes 2 with potassium permanganate in water led in a straightforward manner to the desired 2-halo-2-fluorocyclopropanecarboxylic acids 3 (see Table 2). All reactions were performed on a scale of several moles.

The replacement of a chlorine atom in chlorofluorocyclopropanes by hydrogen can be achieved with Bu_3SnH [11] or sodium in liquid ammonia [12] and, as was shown in one case, with Raney nickel in the presence of ethylenediamine [13]. For economic reasons we submitted the 2-chloro-2-fluorocyclopropanecarboxylic acids 3b and 3d to the last method. We obtained for R=CH_3 (3d) the corresponding syn/anti-2-fluoro-1-methylcyclopropanecarboxylic acid 4b in good yield. With R=H (3b), the product of the reaction was reproducibly the single isomer 4a in low yield (ca. 10%) (see Table 2). The assignment of the configuration was established by means of homonuclear decoupled NMR spectroscopy. The coupling constants were iteratively optimised for a ABMXY spin system with fluorine as Y nucleus. Due to the small vicinal coupling constant of the hydrogen atoms at C-1 and C-2 with J_{12}=1.4 Hz, we assign 4a the anti-configuration. All other coupling constants are in accordance with this interpretation (see Experimental section). Presumably, degradation of either syn-isomer of 3d or 4a occurred.

The ethyl esters of 3b and 3d gave comparable results under these conditions.

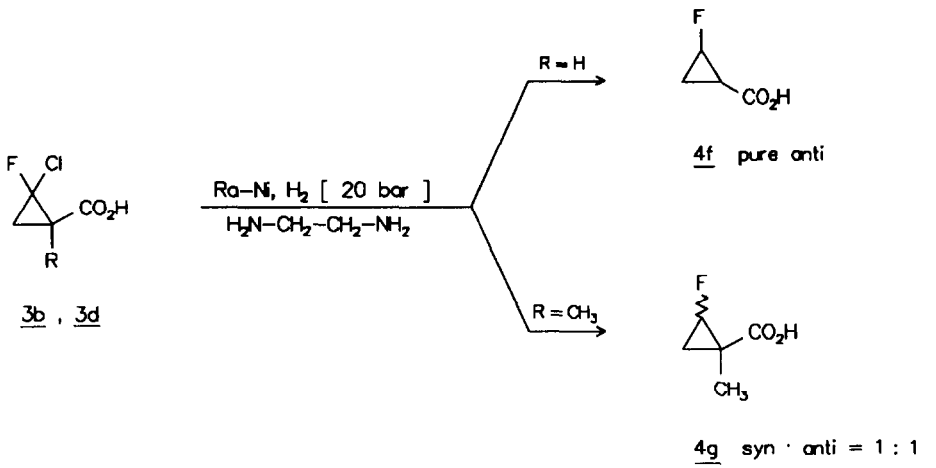


TABLE 1

2-Halo-2-fluoro-substituted vinylcyclopropanes 2

Compound	R	X	Method*	Yield	syn:anti**	bp (mm Hg)	Ref.
2a	H	F	A	46%	-	52-53°C (760)	8
2b	H	Cl	A	31%	ca. 1:1	88-89°C (760)	9
2c	CH_3	F	A	33%	-	72°C (760)	8
2d	CH_3	Cl	B	85%	ca. 1:1	109-110°C (760)	9
2e	CH_3	Br	B	74%	ca. 1:1	29-31°C (0.01)	nc

*Method A) epichlorohydrine, Bu_4NBr, 120°C, ca. 20 bar.
Method B) NaOH, H_2O, CH_2Cl_2, Bu_4NBr, 10°C.

** Assignment based on NMR data.

TABLE 2

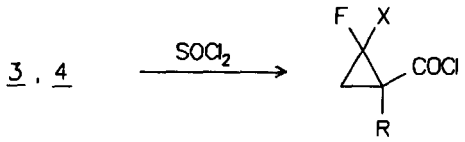
2-Fluoro-substituted cyclopropanecarboxylic acid 3 and 4

Compound	R	X	Yield	syn:anti*	bp (mm Hg)	mp	Ref.
3a	H	F	79%	-	-	61-62°C	5
3b	H	Cl	70%	ca. 1.3:1	57°C (0.04)	-	nc
3c	CH_3	F	77%	-	61-63°C (0.05)	59-61°C	nc
3d	CH_3	Cl	82%	ca. 1:1	77-78°C (0.1)	-	nc
3e	CH_3	Br	76%	ca. 1:1	-	oil	nc
4f	H	H	10%	-	-	41-42°C	nc
4g	CH_3	H	76%	ca. 1:1	108-110°C (25)	-	nc

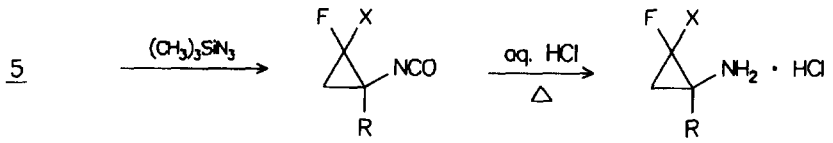
* Assignment based on NMR data.

Derivatisations

The cyclopropanecarboxylic acids 3 and 4 were converted to the corresponding acid chlorides 5 without difficulty (see Table 3). Curtius degradation to the isocyanates 6 and their hydrolysis to the amines 7 were achieved in moderate yields (see Table 4).



5a – 5e



6a – 6c 7a – 7c

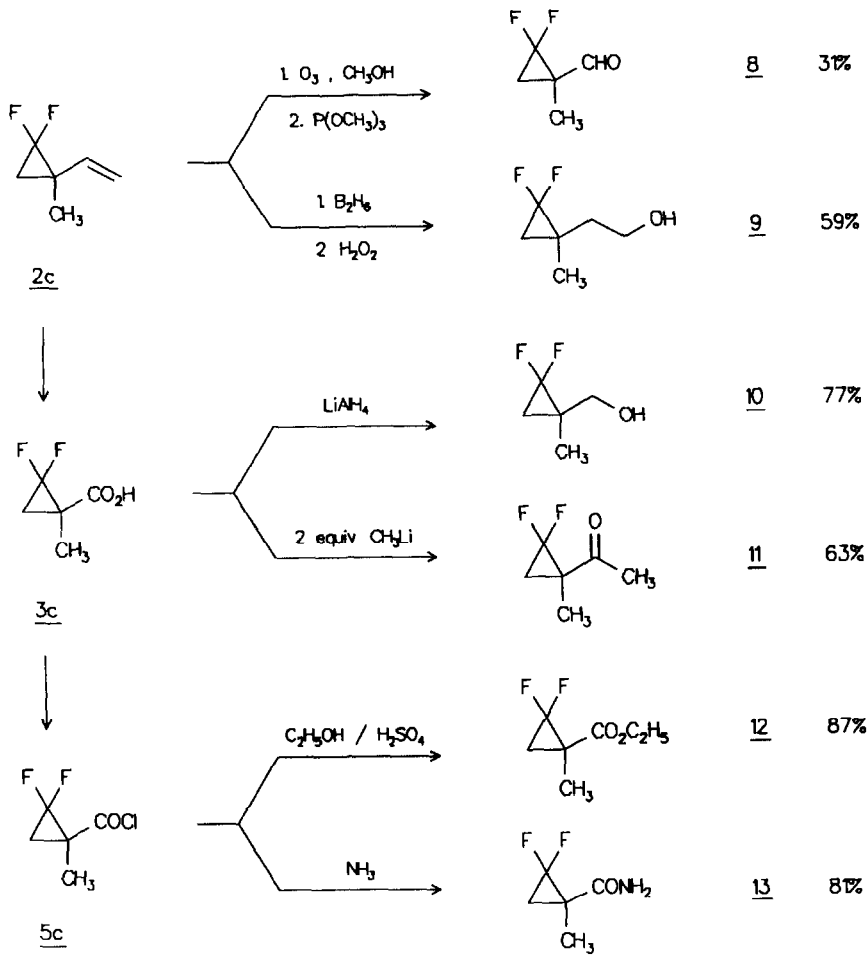
TABLE 3

2-Fluoro-substituted cyclopropanecarboxylic acid chlorides 5

Compound	R	X	Yield	syn:anti*	bp (mm Hg)	Ref.
5a	H	F	94%	-	110-112°C (760)	5
5b	H	Cl	87%	1.8:1	40-41°C (20)	nc
5c	CH_3	F	77%	-	121-122°C (760)	nc
5d	CH_3	Cl	97%	ca. 1:1	84-85°C (100)	nc
5g	CH_3	H	93%	ca. 1:1	58-60°C (100)	nc

* Assignment based on NMR data.

Various transformations of the vinyl group are possible without affecting the cyclopropane structure. The following scheme shows some of these reactions using 2c as an example (X= F, R= CH_3). Standard methods were applied without optimisation.



Scheme.

TABLE 4

2-Fluoro-substituted cyclopropane isocyanates 6 and 1-aminocyclopropane hydrochlorides 7

Compound	R	X	Yield	syn:anti	Phys. Data
6a nc	H	F	53%	-	bp: 64-65°C (760)
6b nc	H	Cl	- [a]	-	-
6c nc	CH_3	F	47%	-	bp: 95-97°C (760)
7a nc	H	F	83%	-	mp: 132-134°C (decomp.)
7b nc	H	Cl	72%[b]	ca. 1.8:1[c]	mp: 139-141°C (decomp.)
7c nc	CH_3	F	61%	-	mp: 140-142°C (decomp.)

[a] Solution of 6b in toluene was submitted to hydrolysis without isolation.

[b] based on 5b

[c] GC-area; assignment based on 3b

EXPERIMENTAL

Materials were used as purchased. Butadiene and isoprene as well as the halomethanes were technical grade. ^1H and ^{19}F NMR data were recorded on a Bruker WA-80 (^1H: 80 MHz, ^{19}F: 75,39 MHz) and AM-360 (^1H: 360 MHz) or a Varian XLAA 200 (^1H: 200 MHz) in $CDCl_3$ versus $(CH_3)_4Si$ (^1H) or CClF3 (^{19}F) and are given for all new compounds except for the acid chlorides and isocyanates whose spectra deviate only slightly from their parent compounds. The spin system of 4f was calculated using the programme PANIC by Bruker. MS-data were obtained using a Finnigan MAT 8200 spectrometer.

Synthesis of 2-halo-2-fluoro substituted vinylcyclopropanes 2 (Table 1)

Method A)

286 g (5.3 moles) butadiene, 680 g (6.5 moles) $CHCl_2F$, 656 g (7.1 moles) 3-chloroepoxypropane, 10 g (0.03 moles) Bu_4NBr and 2 g (0.018 moles) hydroquinone were

heated to 120°C in a steel vessel for 5 hours. Direct fractionation of the reaction mixture gave 206 g of product mixture which consisted of 90% syn- and anti-2-chloro-2-fluoro-1-vinylcyclopropane, 2b (ca. 1:1, yield 31%).

Method B)

To a well-stirred mixture of 680 g (10 moles) isoprene, 100 g (0.31 moles)Bu_4NBr, 3000 ml CH_2Cl_2, 1500 ml H_2O and 1500 g NaOH, were added 1200 g (11.65 moles) $CHCl_2F$ at 10°C over ca. 9 hours. The mixture was diluted with water and extracted with CH_2Cl_2. After drying, distillation gave 1140 g of syn- and anti-2-chloro-2-fluoro-1-methyl-1-vinylcyclopropane, 2d (ca. 1:1, yield 85%).

2e (nc) was prepared by this method from isoprene and $CHBr_2F$ in 74% yield (^1H NMR: 1.23-1.95 ppm (5 H), 5.11-5.30 ppm (2 H), 5.61-5.82 ppm (1 H) MS: 178/ 180 (M^+), 99 (M^+-Br, base peak)).

Synthesis of 2-halo-2-fluoro-substituted cyclopropanecarboxylic acids

To a solution of 112.5 g (0.91 moles) of 2d in 10 l H_2O were added 474 g (3 moles) $KMnO_4$ in small portions. The reaction mixture was allowed to stand for 36 hours. After filtration the mixture was acidified with sulfuric acid and extracted with CH_2Cl_2. The organic layers were thoroughly dried and distilled to give 115 g syn- and anti-2-chloro-2-fluoro-1-methylcyclopropanecarboxylic acid 3d (yield 83%).
The same procedure was used to prepare 3a-e (Table 2).

3b (nc): ^1H NMR: 1.70-2.08 ppm (2 H), 2.20-2.69 ppm (1 H), 9.5 ppm (s, 1H); ^{19}F NMR: 126.4 ppm (syn) and 145.1 ppm (anti) (ca. 1.3:1)

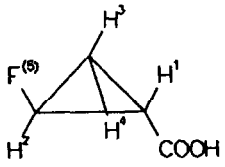
3c (nc): ^1H NMR: 1.2-1.4 ppm (m, 1 H), 1.42 ppm (m, 3 H), 2.22 ppm (m, 1 H), 9.8 ppm (s, 1 H); ^{19}F NMR: 135 ppm (AB-system, 2 F)

3d (nc): ^1H NMR: 1.30-1.55 ppm (4 H), 2.07 ppm (dd, JHF=8.5Hz, J_{HH}=7.5 Hz) and 2.41 ppm (dd, J_{HF}= 17.5Hz, J_{HH}=7.5 Hz) (ca. 1:1, 1 H), 8.5 ppm (s, 1 H)

3e (nc): ^1H NMR: 1.30-1.70 (m,4 H), 2.10-2.55 ppm (m, 1 H), 7.9 ppm (s, 1 H)

Synthesis of 2-fluoro-substituted cyclopropanecarboxylic acids 4

A mixture of 100 g (0.65 moles) of 3d, 237 g (3.9 moles) 1,2-diaminoethane, 1500 ml ethanol and 25 g freshly prepared Raney-nickel was stirred at 80°C with 20 bar hydrogen for 8 hours. The catalyst was filtered off and washed with dilute hydrochloric acid and water. The acidic filtrate was extracted with ether, the organic layers were dried and distilled to give 61 g of syn- and anti-2-fluoro-1-methylcyclopropanecarboxylic acid, 4g (yield 76%). The same conditions were applied in the case of 3b and resulted in formation of the pure trans-2-fluorocyclopropanecarboxylic acid, 4f (yield 10%).



4f (nc): ^{1}H NMR: 1.38 ppm (dddd, H^4), 1.55 ppm (dddd, H^5), 2.09 ppm (ddd, H^1), 4.85 ppm (dddd, H^2) with J_{12}= 1.4 Hz, J_{13}= 10.5 Hz, J_{14}= 6.5 Hz, J_{15}= 16.9 Hz, J_{23}= 3.6 Hz, J_{24}= 6.3 Hz, J_{25}= 63.6 Hz, J_{34}= -6.7 Hz, J_{35}= 21.1 Hz, J_{45}= 13.1 Hz; ^{19}F NMR: 204.9 ppm (m, 1 F)

4g (nc): 1.03 ppm (m, 1 H), 1.28 ppm (d, J= 3 Hz 3H), 1.35 ppm (m, 1 H), 4.51 ppm (dm, J= 64 Hz, 1 H) and 1.14 ppm (dm, J= 20 Hz, 1 H), 1.42 ppm (d, J= 2 Hz, 3 H), 2.02 ppm (dm, J= 20 Hz, 1 H), 4.89 ppm dm, J= 64 Hz, 1 H); ^{19}F NMR: 201.0 ppm (dddq, J= 64 Hz, J= 22 Hz, J= 12 Hz, J= 3 Hz, 1 F) and 203.0 ppm (dddq, J= 64 Hz, J= 21 Hz, J= 14 Hz, J= 2 Hz, 1 F)

Synthesis of the cyclopropanecarboxylic acid chlorides 5

A mixture of 51 g (0.33 moles) 3d and 60 g (0.5 moles) $SOCl_2$ was refluxed until gas evolution had ended. Distillation gave 54 g of a mixture of syn- and anti-2-chloro-2-fluoro-1-methylcyclopropanecarboxylic acid chloride, 5d (yield 97%).
The same procedure was used to prepare 5a - 5c, and 5g (Table 3).

Synthesis of the isocyanates 6

30.9 g (0.2 moles) of 5c were added at 30°C to a solution of 28 g (0.24 moles) $(CH_3)_3SiN_3$ in 120 ml toluene. The temperature was raised to 90°C and held until gas evolution had ended (the reaction was monitored by IR-spectroscopy: azide at 2130 cm^{-1},

isocyanate at 2250 cm^{-1}). Distillation gave 12.5 g 2,2-difluoro-1-methylcyclopropane isocyanate, 6c (yield 47 %).

6a and 6b were prepared in the same manner, although 6b was not isolated but instead its toluene solution was submitted directly to hydrolysis.

Synthesis of the amino-hydrochlorides 7

To 200 ml conc. hydrochloric acid were added 26.6 g (0.2 moles) 6c at 30°C. The mixture was heated to 60°C and was allowed to stir until gas evolution had ended. The solvent was evaporated and the residue was crystallised from ethyl acetate to give 17.5 g of 1-amino-2,2-difluoro-1-methylcyclopropane hydrochloride, 7c (yield 61%).
7a and 7b were prepared analogously (Table 4).

7a (nc): ^1H NMR (D_2O): 1.5-2.2 ppm (2 H), 3.2-3.4 ppm (1 H); ^{19}F NMR: 139.5 ppm (m, 2 F); MS: 93 (M^+-HCl), 36 (base peak)

7b (nc): ^1H NMR (D_2O): 1.8-2.3 ppm (2 H), 3.3-3.6 ppm (1 H); MS: 109/111 (M^+ - HCl)

7c (nc): ^1H NMR (D_2O): 1.8-2.2. ppm (2 H), 1.50 ppm (m, 3 H); ^{19}F NMR: 137 ppm (m, 2 F); MS: 107 (M^+-HCl)

Synthesis of 2,2-difluoro-1-methylcyclopropanecarboxaldehyde 8 (nc)

A solution of 59 g (0.5 moles) 2c in 500 ml methanol was treated at -78°C with ozone. After completion of the reaction a solution of 100 g (0.8 moles) $P(OCH_3)_3$ in 100 ml methanol was slowly added. The reaction mixture was allowed to warm to room temperature, diluted with 1N HCl and extracted with ether. Fractionation of the thoroughly dried extracts gave 18.3 g 2,2-difluoro-methylcyclopropanecarboxaldehyde, 8 (yield 31%).
bp: 78-80°C; IR: 1730 cm^{-1}; ^1H NMR: 1.34 ppm (t, J_{HF}= 2.5 Hz, 3 H), 1.60 ppm (m, 1 H), 2.20 ppm (m, 1 H), 9.17 ppm (t, J_{HF}= 1 Hz, 1 H).

Synthesis of 2-(2,2-difluoro-1-methylcyclopropyl)ethanol 9 (nc)

Diborane (0.23 moles), generated from $NaBH_4$ and $BF_3.OEt_2$ in diglyme, was introduced into a solution of 30 g (0.25 moles) 2c in 200 ml dry ether at 20°C. Stirring was continued for another hour and 135 ml 10% aq. NaOH were carefully added, followed

by 135 ml 30% aq. H_2O_2. After the reaction was complete, the organic layer was separated, dried and distilled to give 17.3 g 2-(2,2-difluoro-1-methylcyclopropyl)ethanol, 9 (yield 55%).
bp (20 mm): 65-67°C; ^{1}H NMR: 0.9-1.2 ppm (m, 3 H) 1.2 ppm (m, 3 H), 1.70 ppm (m, 1 H), 2.75 ppm (s, br. 1 H), 3.73 ppm (t, J= 7 Hz, 2 H)

Synthesis of (2,2-difluoro-1-methylcyclopropyl)methanol 10 (nc)

A solution of 50 g (0.35 moles) 3c in 50 ml dry ether was slowly added to a suspension of 25 g (0.66 moles) $LiAlH_4$ in 250 ml dry ether at room temperature. The mixture was refluxed for 4 hours, then, after cooling, hydrolysed with water and dilute hydrochloric acid and extracted with ether. The org. layer was separated, dried and distilled to give 35 g (2,2-difluoro-1-methylcyclopropyl)methanol, 10 (yield 77%).
bp: 136-139°C; ^{1}H NMR: 1.05 ppm (m, 1 H), 1.22 ppm (m, 1 H), 1.28 ppm (m, 3 H), 2.88 ppm (s, br. 1 H), 3.60 ppm (m, 2 H); ^{19}F NMR: 137.3 ppm (AB-system, 2 F)

Synthesis of (2,2-difluoro-1-methylcyclopropyl)methylketone 11 (nc)

A solution of 1.4 M CH_3-Li in hexane (333 ml, 0.5 moles) was added over 3 hours to a solution of 34 g (0.25 moles) 3c in 250 ml dry ether at -78°C under nitrogen. The mixture was stirred at -78°C for another hour, warmed to 0°C and poured into a mixture of 500 g ice and 50 ml conc. HCl. Extraction with ether, drying and distillation gave 21 g 1-acetyl-2.2-difluoro-1-methylcyclopropane, 11 (yield 63%).
bp: 58-60°C; IR: 1715 cm^{-1}; ^{1}H NMR: 1.30 ppm (ddd, $J_{HF,cis}$= 11.3 Hz, J_{HH}= 7.7 Hz, $J_{HF,\ trans}$= 5.0 Hz, 1 H), 1.51 ppm (dd, J= 2.9 Hz and 1.8 Hz, 3 H), 2.26 ppm (s, 3 H), 2.31 ppm (ddd, $J_{HF,\ cis}$= 13.0 Hz, J_{HH}= 7.7 Hz, $J_{HF,\ trans}$= 6.0 Hz, 1 H); ^{19}F NMR: 134.0 ppm (AB-system, 2 F)

Synthesis of ethyl 2,2-difluoro-1-methylcyclopropanecarboxylate 12 (nc)

A mixture of 15.5 g (0.1 moles) 5c and 35 ml ethanol was refluxed with a catalytical amount of sulfuric acid for one hour. Direct distillation gave 14.2 g 2.2-difluoro-1-methyl-cyclopropanecarboxylic acid ethyl ester, 12 (yield 87%).
bp: 141-142°C; ^{1}H NMR: 1.2-1.4 ppm (m, 1 H), 1.29 ppm (t, J= 7.2 Hz, 3 H), 1.42 ppm (q, J= 7.2 Hz, 2 H); ^{19}F NMR: 135 ppm (AB-system, 2 F)

Synthesis of 2,2-difluoro-1-methylcyclopropanecarboxylic acid amide 13 (nc)

A solution of 15.5 g (0.1 moles) 5c in 80 ml dioxane was saturated with NH_3 at room temperature. The solvent was evaporated and the residue was washed with water and dried to give 11.0 g 2,2-difluoro-1-methylcyclopropanecarboxylic acid amide, 13 (yield 81 %), mp: 125-127°C, MS:135 (M^+), 44 (base peak).

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