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From Difluorocyclopropene to Difluorocyclopropylidene.

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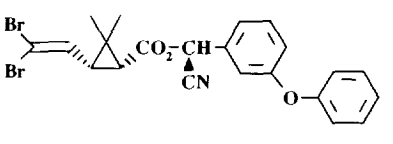
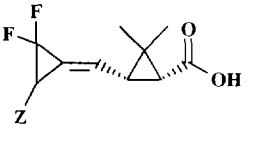
Abstract : *A new stereoselective reductive transposition of α -hydroxy difluorocyclopropene allowed the easy preparation of several substituted difluorocyclopropylidene compounds.*

INTRODUCTION

Pyrethroïds are a worldwide used family of safe insecticides with low application rates and low mammalian and environmental toxicity. They are esters, characterized by an acid part generally containing a dihalovinyl cyclopropane moiety, as for example in one of the most successful commercial products of this group : Deltamethrine[1]. Within an ongoing programme towards new insecticidal pyrethroïd ester analogues of Deltamethrine, we planned to synthesize a new acid moiety containing a difluorocyclopropylidene substructure.



Deltamethrine



target

To our knowledge, such a substructure has not yet been described in the chemical literature. It is worth noting that the cyclopropylidene moiety is being studied more and more for its high reactivity in cycloaddition reactions[2]. Most of the synthetic schemes used for the preparation of the cyclopropylidene skeleton were carried out only with compounds bearing alkyl substituents[3]. In our opinion, these methods would be not useful in our series (fluorine atoms, pyrethroïd skeleton). Moreover, we needed a versatile synthesis to allow us to prepare more highly substituted synthons.

We chose the following retrosynthetic scheme, owing to the description of one difluorocarbene addition to propargylic acetate[4] and in house methodology originating from a Roussel Uclaf industrial key intermediate : the optically active 1R cis-caronaldehyde[5].

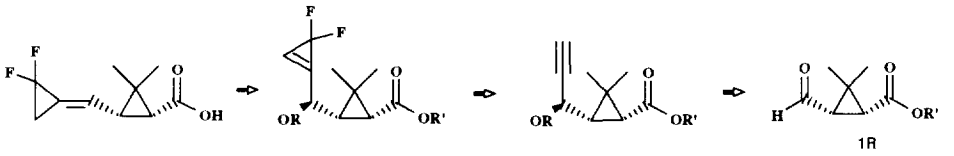


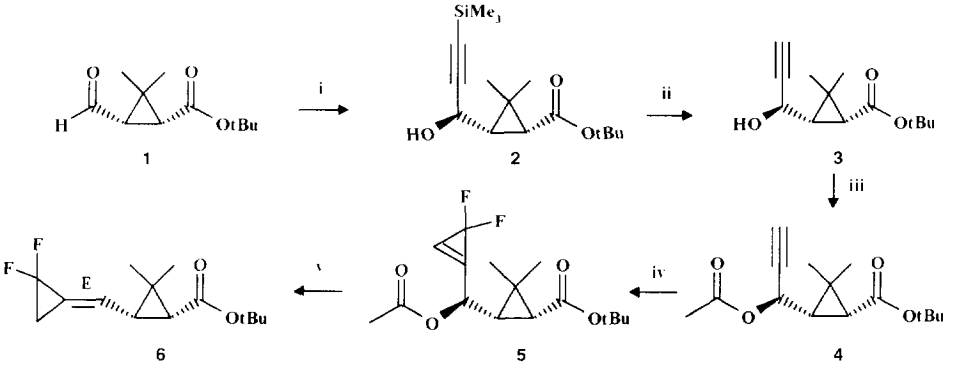
Figure 1 : Retrosynthetic scheme

In this scheme, the last step involved a transposition of the cyclopropenyl double bond, a not previously described reaction, whatever the substituents on the cyclopropenyl ring are.

RESULTS AND DISCUSSION

Part 1

The cis-caronaldehyde was esterified by the t-butyl trichloroacetimidate[6] to give the t-butyl ester **1** which was then subjected to the condensation of trimethylsilylacetylene to afford only one isomer (expected as R at the newly created asymmetric carbon because of the easy lactonisation of the adduct when the reaction is carried out at higher temperature). After desilylation and acetylation, we faced our first key step.



i) $HC{\equiv}CSiMe_3$/BuLi/THF/1h, -60°, 79 %. ii) K_2CO_3/MeOH/3h, rt, 82%.
iii) Ac_2O/Pyridine/6h, 20°, 94 %. iv) CF_2ClCO_2Na/diglyme/4h, 160°, 67%
v) K-selectride/THF/1h, -20°, 72%.

Scheme 1 : synthesis of target 1

At the beginning of this work, as far as we know, only one example[4] of difluorocarbene addition onto a triple bond was known, and the compounds obtained did not seem very stable.

Among the numerous ways of generating the difuorocarbene we have tried[7-9] only the thermolysis of sodium chlorodifluoroacetate gave good results[4]. It worked only with the acetate **4** and not with the free hydroxyl group probably due to the easy opening of the dimethyl cyclopropyl ring. The acetate group also served as a leaving group in the next step.

For this next key step, we considered the system as being essentially allylic and looked for a soft nucleophilic reducing agent. Assuming that an SN_2' reaction is related to nucleophilic addition to α, β unsaturated ketone, we tried known double bond reducing agents in such a system. Firstly, we used the copper hydride of Stryker[10]. The reduction/transposition went smoothly and afforded a 92 % yield of an E/Z (1/1) mixture of the target ester. Moreover, the K-Selectride[11(TM)] afforded a good yield of the E isomer alone (the stereochemistry was based on the vinylic proton NMR shift and comparison with literature[12]). There is a large amount of data on syn or anti addition during SN_2' reactions[13] and it is not our aim to extend this work but in this case, the molecule appears to be blocked in a rigid conformation explaining this result and allowing only syn or anti addition. We thought that the observed stereoselectivity with boron hydride is due to a chelation between the boron atom and the etheral oxygen atom of the acetate group (hard-hard interaction). From molecular modelling results[14], two possible conformations A and B (see figure 2) allow the geometry of the attack postulate by SN_2' theory.

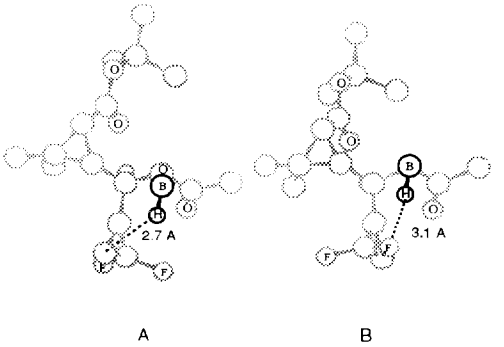


Figure 2 : conformational analysis of reduction transition state.

(the two conformations differ by 180° rotation around the C-C side chain single bond ; the hydride is only represented as a B-H bond with the boron atom complexed to the oxygen along the 2p orbital)

As we can see, there is no reason for a steric preference for an anti or syn addition and either direction can lead to exclusive E formation but only boron complexation can give a rigid system with a syn addition. Moreover, in the A conformation, leading to the E isomer, the complexation along the oxygen 2p doublet shows that the hydride ion is 2.7 Å from the attacked carbon and 3.7 Å from the nearest fluorine atom giving a pseudo chair six-centre system; in the B conformation leading to the Z isomer, it is the contrary : H-C 3.1 Å ; H-F 2.2 Å (but as shown on

Figure **2** , nearer to its p orbitals) with a boat like conformation. Such a complexation has been used to explain preferential attack in the gibberelin family[15]. With copper hydride, there is probably no complexation (copper is not a good complexant of oxygen : hard-soft interaction), and so free rotation and (or) syn and anti attack gave a mixture of Z and E product (see Figure **2**). All this information also contributed to the debate about $SN_{2'}$: in our type of structure where SN_2 is impossible on the 1' carbon and where development of partial positive charge (SN_1 type) on this carbon leads to very easy opening of the dimethylated cyclopropane (well known problems of pyrethrinoid chemists), the concerted $SN_{2'}$ is the only possibility.

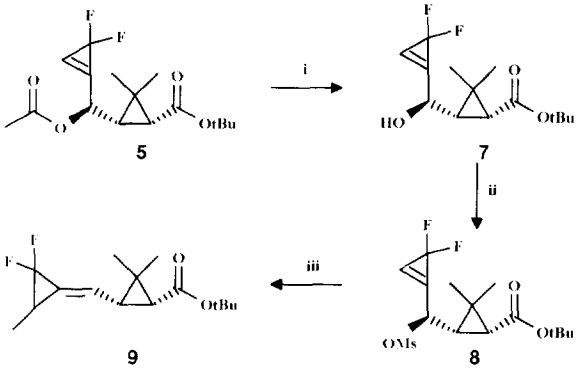
Part 2

To study the variation of the biological response , we prepared several substituted compounds with the same strategy, thus showing the potential scope of the reaction.

ForZ=Me, two paths were used.

Path 1 : addition of propynyllithium instead of TMSA in the first condensation and following the same scheme as above resulted in only one E isomer again but with erratic and low yield of the carbene condensation. In this case, the hydride addition is diastereoselective with 1-3 transfer of chirality.

Path 2 : use of a soft nucleophilic "methyl" instead of hydride in the last transposition gave improved results. It succeeded very well with methyl cyanocuprate[16] as the nucleophile and mesylate as the leaving group (acetate was an insufficient leaving group and gave poor results). The mesylate was obtained after hydrolysis of the carbene addition product and reaction of the resulting alcohol with mesyl chloride.



i) NaOH 1N/MeOH/2h, 0°, 98 %. ii) CH_3SO_2Cl/TEA/Et_2O/1h30, 0°, 100 %.
iii) MeLi/CuCN/THF/30mn, -20°, 73 %.

Scheme 2 : synthesis of methylated adduct

In the last methylating transposition we obtained an 80/20 mixture of Z and E isomers, but only two out of the four possible isomers (so, only one configuration on the newly created asymmetric carbon). The NMR showed that the minor isomer is the same as the one obtained in the first path (E on the double bond). The fact that we obtained the same isomer with the methyl attack on a

probable mixture of conformations involved a syn hydride/anti methyl or an anti hydride/syn methyl hypothesis. The possible six membered ring boron complex with the acetate group shown previously and some litterature on lithiocuprate describing an anti attack[17] prompted us to choose the first one. So we can postulate an anti addition of nucleophilic methyl giving a mixture of E "*R*" and Z "*S*" adducts, depending on the conformation. Unfortunately, no X-ray analysis was possible on these poorly crystallized compounds to ensure our hypothesis.

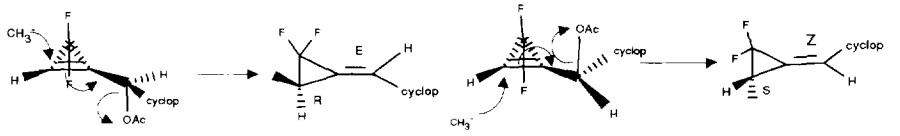
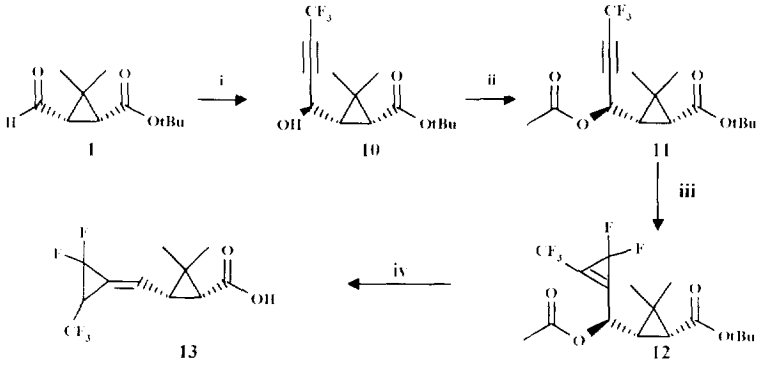


Figure 3 : "anti" methyl attack on the two conformations

Part 3

In this part we prepared the trifluoromethylated product using the trifluoropropyne as starting material and the same scheme as in part 1. Every step gave good yields, especially the addition of difluorocarbene. This latter result seemed strange if we consider the difluorocarbene as an electrophilic carbene[18]. The polarization of the double bond does not interfere with the reductive transposition anymore (only one isomer was obtained with the double bond expected as E and the new created asymetric carbon as "S"). These compounds are rather unstable. The use of "CF_3Cu" in a second path strategy failed.



i) $HC{\equiv}CCF_3$/BuLi/THF/50mn, -60°, 68 %. ii) Ac_2O/Pyridine/3h, 20°, 100 %.iii)CF_2ClCO_2Na/ diglyme/2h, 160°, 66 %. iv) K-selectride/THF/20mn, -70°, 78% after tBu cleavage. **Scheme 3 : synthesis of trifluoromethylated adduct**

Conclusion

During this work, we synthesize the new difluorocyclopropylidene substructure, using new methodology to reach these compounds. The difluorocarbene addition on propargylic esters appears quite general as does the SN_2' reductive transposition. Despite the fact that this new set

of reaction was carried out only in pyrethroid chemistry, we believe that this concept can be used for many propargylic systems and may lead to adducts capable of being involved in cycloaddition reactions. The acids obtained with such a substructure and esterified with appropriate alcohols, give compounds with very good insecticidal activities[19] which prove to be stable for months.

EXPERIMENTAL SECTION

NMR spectra were recorded using $CDCl_3$ as solvent at 250MHz and ^{19}F NMR were recorded in the same solvent at 282.38 MHz relatively to $CFCl_3$. IR were recorded in chloroform solution. Column chromatographies were carried out on 100 parts of silica gel Merck 9385. The reactions were conducted under a dry nitrogen atmosphere and used commercial pure grade solvents.

Addition of acetylenics to the 1R cis caronaldehyde ester 1 and acetylation of the adducts.
Scheme 1 : In a three necked flask, were introduced 130 ml of THF and 13.8 ml (99.6 mmol) of trimethylsilylacetylene (Fluka). At -60°, 50 ml of 1.6 M nBuLi in hexane were added within 1 h and the resulting solution was warmed to -35° during one more hour. At -60° a solution of 15 g of aldehyde **1** in 40 ml of THF was then introduced and the reaction medium was left standing at the same temperature until completion (1 h). It was poured on saturated KH_2PO_4 solution and extracted with isopropyl ether. After chromatography (hexane/diisopropyl ether 8/2), the resulting silyl compound **2** (79 % yield) was treated 3 h at rt with potassium carbonate in methanol affording the free acetylenic adduct **3** in 82 % yield. NMR : 1.2 (s), 1.24 (s) (Me gem) ; 1.45 (s) (tBu) ; 1.46, 1.55 (m) (H cyclopropyl) ; 2.47 (d J=2.5Hz) (H-≡) ; 4.79 (dd, J=2.5 and 4 Hz) (CH-OH) ; IR : OH 3600 cm^{-1} ; H-≡ 3308 cm^{-1} , C=O 1704 cm^{-1}. 8.5 g of the alcohol in 25 ml of pyridine were acetylated with 10.8 ml of acetic anhydride during 6 h at rt. After pouring on NaH_2PO_4 solution and diisopropylether extraction, the dried evaporated solution was chromatographed (hexane/diisopropylether 7/3) on silica gel to afford 9.44 g (94 % yield) of the solid acetate **4**(mp : 67.2° C).
Scheme 3 : In the same way, the trifluoropropynyllithium was prepared at -40° by bubbling the trifluoropropyne gas into the nBuLi/THF solution until the disappearance of phenanthroline color and then the aldehyde 1 was added at -60°. After usual work up and chromatography, the trifluoropropynyl adduct **10** was obtained in 68 % yield. NMR : 1.22 (s), 1.32 (s) (Me gem) ; 1.45 (s) (tBu) ; 1.46, 1.64 (m) (H cyclopropyl) ; 5.01 (qd after D_2O exchange) (CH-OH) ; IR : OH 3600cm^{-1} , C≡C 2265 cm^{-1} ; C=O 1709 cm^{-1}. This alcohol was acetylated as above to afford 11 in quantitative yield.

Difluorocarbene addition
Scheme 1 : To the acetate **4** (10.7 g, 40.12 mmol) in 50 ml of dry diglyme at 160° C was added during 3 h a solution of 61.18 g (0.4 mol) of CF_2ClCO_2Na (dried for one night at 120° C under vacuum) in 230 ml of dry diglyme. After a further hour, the reaction medium is cooled at rt and poured onto saturated NaH_2PO_4 solution . This solution was filtered through Celite and extracted with diisopropyl ether. After usual work-up and chromatography (Hexane/ diisopropyl ether 85/15), the difluorocyclopropene **5** is obtained in 67 % yield as an oil. NMR : 1.22 (s), 1.39 (s) (Me gem) ; 1.44 (s) (tBu) ; 1.44, 1.62 (m) (H cyclopropyl) ; 2.09 (s) (OAc) ; 6.07 (dm, J= 10.5Hz) (CH-O) , 7.36 (m) (CH=) . ^{19}F : -106 ppm (dt) , -106.8 ppm (dt) (CF_2) (J_{F-F}=110 Hz ; $^3J_{H-F}$=2Hz)
Scheme 3 : In the same way, to 0.41 g (1.23 mmol) of the trifluoroacetylenic acetate**11** in 4 ml of diglyme at 160° C was added 1.97 g (12.94 mmol) of CF_2ClCO_2Na in 12 ml of diglyme during 1 h. After work-up and chromatography (Hexane /diisopropyl ether 95/05), the difluorocyclopropene **12** was obtained in 66 % yield (0.31 g) (mp = 33°2). NMR : 1.23 (s), 1.40 (s) (Me gem) ; 1.44 (s) (tBu) , 1.45, 1.71 (m) (H cyclopropyl) ; 2.09 (s) (OAc) , 6.17 (qd, J=11

and 2 Hz) (CH-O) ^{19}F : -62.9 ppm (CF_3) (J_{F-F}=3.5 Hz and $^5J_{H-F}$=2Hz) ; (-106.6 ppm) (one CF_2) (dq) (J_{F-F}=111 and 3.5 Hz) ; -107.5 ppm (ddq) (one CF_2) (J_{F-F}=111 and 3.5 Hz ;$^5J_{H-F}$=2Hz).

Reductive transposition with Stryker's reagent.

To 8.57 g of the acetate **5** (27.09 mmol) in170 ml of toluene at rt, 26.6 g of $(Ph_3PCuH)_6$ (Aldrich) were added. After 1h at the same temperature, 80 ml of pentane and 80 ml of diethylether were added and the flask was left opened . After 2h the mixture was filtered through Celite, evaporated to dryness and chromatographed (Hexane /CH_2Cl_2 95/05) to give the Z isomer (Rf=0.15), 3.19 g (45 % yield) of **6** as an oil and the E isomer, 3.33 g (47% yield) of **6** as a white solid (mp : 33.8° C).NMR. Z:1.22(s) 1.31 (s) (Me gem) ; 1.45 (s) (tBu) ; 1.75 (d, J=8.5Hz) 1.97 (m) (H cyclopropyl) ; 1.97 (m) (CH_2 methylenecyclopropane) ; 6.42(dqui J=3.5 and 10 Hz) (H vinylic Z). NMR E: 1.23 (s) 1.32 (s) (Me gem) ; 1.45 (s) (tBu) ; 1.78 (d, J=8 Hz) 1.87 (m) (H cyclopropyl) ; 1.94 (m) (CH_2 methylenecyclopropane) ; 6.80 (td J=3.5 and 10 Hz) (H vinylic E).

Reductive transposition with K selectride.

Scheme 1 : To 250 mg of the acetate **5** (0.79 mmol) in 3 ml of THF at -50° C, 0.8 ml of 1 M K-Selectride in THF (Aldrich) was added. After 30 mn at the same temperature, the mixture was treated as usual and chromatographed (Hexane /diisopropyl ether 85/15) to give 167 mg (82 % yield) of **6E** as a white solid.

Scheme 3 : In the same way, the reduction was carried out at -60°C on the trifluorodifluorocyclopropene **12** (3.28 g) in 50 ml of hexane with 8.5 ml of K-Selectride to give the desired crude compound which was rather unstable and was immediately transformed in acid by cleavage of the tBu group with 6.6 ml of trifluoroacetic acid in 26 ml of CH_2Cl_2. After chromatography of the acid **13** (hexane/AcOEt 1/1) the overall yield was 78 % (1.8 g) ; NMR, 1.30 (s) 1.36 (s) (Me gem) ; 1.99 (d, J=8.5 Hz) 2.05 (t,) (H cyclopropyl) ; 2.89 (m) (CH-CF_3 methylenecyclopropane) ; 7.13 (m) (H vinylic). ^{19}F : -64.9 ppm (CF_3) (J_{F-F}=5.5 Hz) ; -126.2 ppm (one CF_2) (qdd) (J_{F-F}=179 and 5.5 Hz $^5J_{H-F}$=10Hz) ; -138.7 ppm (qdd) (one CF_2).

Synthesis of methylated adducts

Scheme 2 : 20 g of the acetate **5** in 200 ml of MeOH were treated at 0° C with 63.5 ml of 1 N aqueous NaOH solution during 2 h. After usual work-up, the crude alcohol **7** (17.24 g 98 % yield) is obtained as a white solid (mp : 74.2° C). NMR : 1.21 (s), 1.30 (s) (Me gem) ; 1.48 (s) (tBu) ; 1.28 (dd , J= 8 and 10.5 Hz), 1.65 (d J=8 Hz) (H cyclopropyl) ; 2.90 (s) (OH) ; 5.16 (dm, J=10.5Hz) (CH-O) ; 7.43 (q, J=2 Hz) (CH=). 17 g of this alcohol in 100 ml of diethylether at 0° C, were treated with 5 ml of mesyl chloride (1.05 eq.) and then with 9 ml of triethylamine (1.05 eq.) in 35 ml of diethylether. After 2 h the reaction is filtered and the filtrate was poured on saturated aqueous NaH_2PO_4. After usual work-up the crude mesylate **8** was isolated in 93 % yield (20.44 g) and used immediately. To 10 g of CuCN in 100 ml of THF at -20° C, 140 ml of 1.6M MeLi/Et_2O were slowly added. The resulting light green solution was slowly transferred by a cannula to a solution of 20.18 g of the above mesylate in 200 ml of THF at -30° C. 30 mn after the end of the addition, the reaction medium was poured on saturated aqueous NH_4Cl solution. The copper salts were filtered out through Celite and the filtrate treated as usual. After chromatography (hexane/CH_2Cl_2 9/1) the **9Z** isomer was isolated in 57 % yield (8.9 g) and the **9E** isomer in 15.6 % yield (2.44 g). NMR : Z 1.18 (dm) (CH_3), 1.23 (s) 1.31 (s) (Me gem) ; 1.45 (s) (tBu) ; 1.76 (m) 1.95 (m) (H cyclopropyl) , 2.14 (m) (H methylenecyclopropane) ; 6.38 (dq) (H vinylic). E : 1.23 (s l) (CH_3), 1.22 (s) 1.30 (s) (Me gem) ; 1.44 (s) (tBu) ; 1.70 to 1.86 (m, 2H) (H cyclopropyl) , 2.16 (m) (H methylenecyclopropane) , 6.72 (dq) (H vinylic).

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