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PRACTICAL AND STEREOCONTROLLED SYNTHESES OF BOTH (1R*,3S*)- AND (1R*,3R*)-3-(2-CHLORO-3,3,3-TRIFLUORO-1-PROPENYL)-2,2-DIMETHYLCYCLOPROPANECARBOXYLATES

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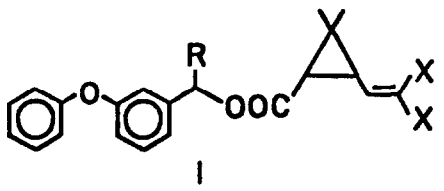
The title compounds of (1R,3S*) configuration were prepared from 3-formyl-2,2-dimethylcyclopropanecarboxylate by addition of CF_3CCl_2ZnCl, acetylation, and reductive β-elimination with zinc, whereas the (1R*,3R*) isomer was derived from $Me_2C{=}CHCH(OH)CCl_2CF_3$ by diazoacetylation, Cu(II) catalyzed intramolecular cyclization, and the zinc reduction.*

In the last decade, a great deal of effort has been made in search for new synthetic pyrethroids of high activity, and many derivatives, e.g. permethrin (**1a**),[1] cypermethrin (**1b**),[2] and deltamethrin (**1c**),[3] have been developed and used currently. New fluorinated analogs **2**[4] having $CH{=}C(Cl)CF_3$ group in place of $CH{=}CCl_2$ moiety are found recently to exhibit more potent activity:[4] typical examples are cyhalothrin[5] and bifenthrin. Although several synthetic methods for **2** are reported,[4] the stereochemical aspects seem to remain unsolved yet. Highly efficient aldehyde-addition of CF_3CCl_2ZnCl reagent[6] allowed us to establish a practical and stereocontrolled synthesis of both (1R*,3S*)- and (1R*,3R*)-**2**.

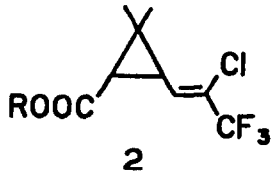


1

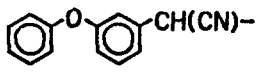
a: X = Cl, R = H (permethrin)

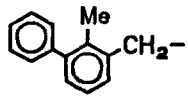
b: X = Cl, R = CN (cypermethrin)

c: X = Br, R = CN (deltamethrin)



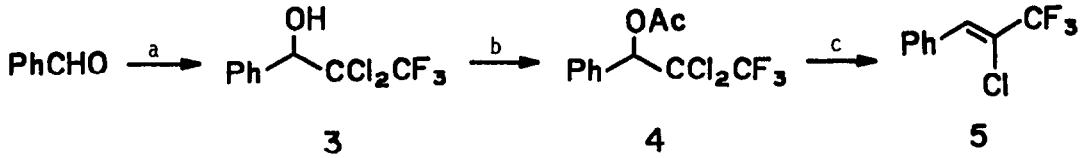
2

R =  (cyhalothrin)

R =  (bifenthrin)

Our strategy is based on the transformation of formyl group to $CH{=}C(Cl)CF_3$ group by (1) addition of CF_3CCl_2ZnCl reagent, (2) activation of the resulting hydroxyl group of the adduct, and (3) reductive β-elimination.

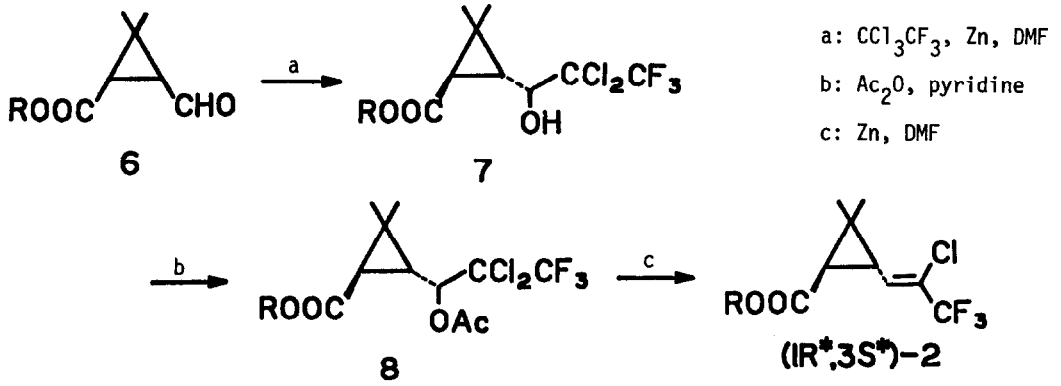
The first step is assured by the results reported in the preceding paper. The second and the last steps were studied using benzaldehyde as the model. The benzaldehyde-CCl_2CF_3 adduct **3** was converted into the acetate **4** (Ac_2O-pyridine, r.t., overnight), which was then treated with zinc powder (1.2 mol) in dimethylformamide (DMF) (50 °C, 2 h). The desired 2-chloro-3,3,3-trifluoro-1-phenylpropene **5**[7] was produced in 84 % overall yield. The mesylate of **3** also underwent the reductive elimination to give **5** in 65 % yield. The acetate **4** was directly obtained in 79 % yield, when benzaldehyde and CF_3CCl_3 (1.2 mol) were treated with zinc powder (1.2 mol) in the presence of acetic anhydride (1.2 mol) in DMF (0 °C, 2 h - r.t., 3 h).



3 4 5

a: CCl_3CF_3, Zn, DMF; b: Ac_2O, pyridine; c: Zn, DMF

These findings were successfully applied to 3-formyl-2,2-dimethylcyclopropanecarboxylates **6**.[8] The addition of CF_3CCl_2ZnCl[6] to **6** proceeded in good yields. The adducts **7**[9] were transformed to (1R*,3S*)-**2** [(Z) : (E) = 86 : 14 to 93 : 7][10] by the acetylation and reductive elimination with zinc. Results are summarized in Table 1.



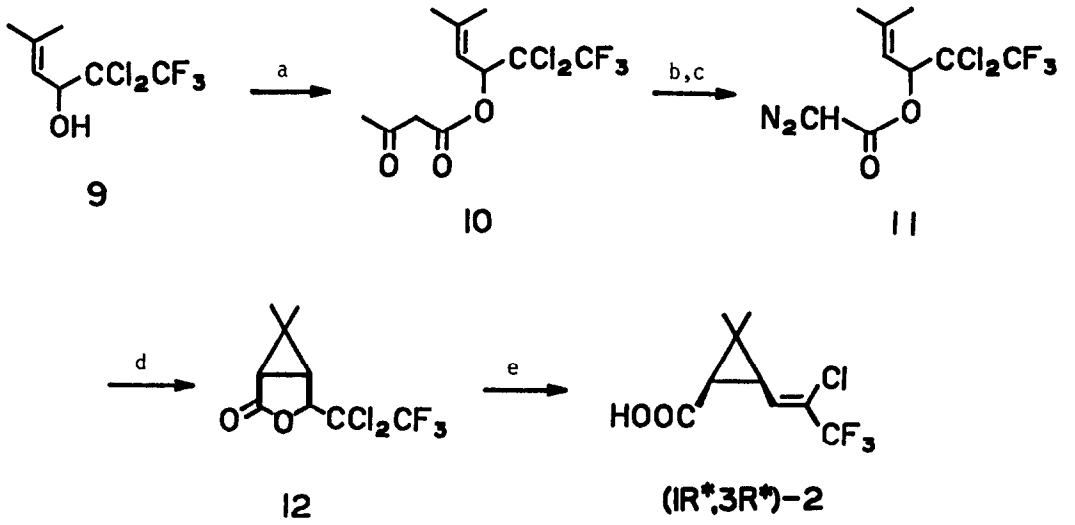
6 7 8 (1R*,3S*)-2

Table 1. Transformation of **6** to (1R*,3S*)-**2**

R	step a (%)	step b (%)	step c (%)
Et-	58	93	86
3-PhO-$C_6H_4CH_2$-	74	98	74
2-Me-3-Ph$C_6H_3CH_2$-	86	100	95
$C_6F_5CH_2$-	71	—	—

It should be noted that only (1R*,3R*) isomers of 7[11] were isolated, though (1R*,3R*)/(1R*,3S*) mixtures (4 to 6 : 1) of **6** were employed. The CF_3CCl_2 adducts of the (1R*,3S*) isomers of **6** apparently underwent lactonization under the reaction conditions to give rise to a bicyclic lactone **12** (< 10 % yield). Actually, pure (1R*,3R*)-**6** (R = Me) did not give any trace of **12**. Since (1R*,3R*)-**6** are easily prepared from the (1R*,3R*)/(1R*,3S*) mixtures by base catalyzed epimerization,[12] this route is applicable to the synthesis of (1R*,3S*)-**2**.

The other (1R*,3R*) isomer of **2** (R = H) was synthesized stereospecifically according to the following scheme.[13] The alcohol **9**[6,14] was treated with diketene in the presence of K_2CO_3 catalyst at 80 °C to give the acetylacetate **10** (88 % yield), which was converted into the diazoacetate **11** by treatment with a slight excess of tosyl azide and triethylamine (r.t., 1.5 h) followed by alkaline hydrolysis with 1.2 M aqueous solution of sodium hydroxide (3 mol, r.t., 1 h) (82 % yield from **10**). The dioxane solution of **11** was added over 2.5 h to the refluxing dioxane solution of $Cu(acac)_2$ (3 mol%), and the reflux was continued for 1.5 h to give rise to the lactone **12** in 75 % yield. Final reductive elimination was effected with zinc powder in DMF solution at 60 °C for 3 h to afford (1R*,3R*)-**2** (R = H) without epimerization in 84 % yield.



9 10 11 12 (1R*,3R*)-2

a: diketene, K_2CO_3; b: TsN_3, NEt_3; c: NaOH; d: $Cu(acac)_2$; e: Zn, DMF

The method disclosed herein provides an easy way to both (1R*,3R*)- and (1R*,3S*)-**2** under high stereocontrol. In particular, practicability of our process should be emphasized: most of reagents are commercially available, and the reaction conditions of each step are mild.

Acknowledment. We thank FMC Corporation for a geneous gift of (2-methyl-3-phenylphenyl)methanol.

References and Notes

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5. P. D. Bentley, R. Cheetham, R. K. Huff, R. Pascoe, and J. D. Sayle, *Pestic. Sic.*, **11**, 156 (1980).
6. M. Fujita, T. Morita, and T. Hiyama, the preceding paper.
7. The ratio (Z) : (E) = 79 : 21 (^{19}F-NMR analysis). The stereochemistry was assigned by ^{13}C-NMR by J_{H-CF_3} value ($J_{trans} > J_{cis}$).
8. The aldehyde esters **6** were easily prepared by ozonolysis of the corresponding chrysanthemates (81-89 % yield).
9. The mesylate of **7** was also converted into **10** in 95 % yield.
10. The (Z) : (E) ratios did not depend on the stereochemistry of the side chain of **8** significantly.
11. Two stereoisomers of (1R*,3R*)-**7** were formed in a ratio of ca. 1:1.
12. S. Julia, M. Julia, and G. Linstrumelle, *Bull. Soc. Chim. Fr.*, **1964**, 2693.
13. Transformation of 4-trichloromethyl-6,6-dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-one to (1R*,3R*)-2-(2,2-dichloroethenyl)-3,3-dimethylcyclopropanecarboxylic acid is carried out with zinc in acetic acid: K. Kondo, T. Takashima, A. Negishi, K. Matsui, T. Fujimoto, K. Sugimoto, C. E. Hatch III, and J. S. Baum, *Pestic Sci.*, **11**, 180 (1980); C. E. Hatch III, J. S. Baum, T. Takashima, and K. Kondo, *J. Org. Chem.*, **45**, 3281 (1980). However, under the same conditions, **12** was not converted into **2**.
14. The zinc mediated reductive elimination was applied to the acetate **i** derived from **9**, and we obtained a diene **ii** in 82 % yield [(Z):(E) = 85:15]. The diene **ii** is successfully transformed to **2** by the reaction with ethyl diazoacetate.[4a]

i ii

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