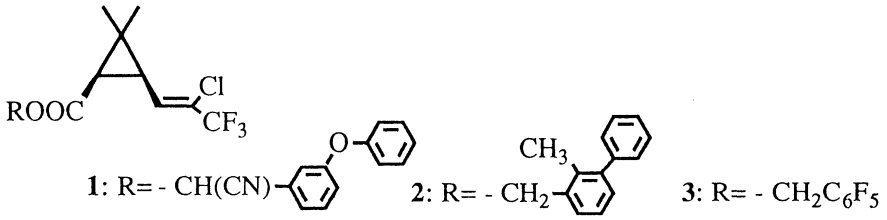
CHEMISTRY LETTERS, pp. 703-706, 1994.

A Practical and Efficient Synthesis of Fluorinated Pyrethroids. *cis*-3-(2-Chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylates

Mayumi NISHIDA,† Takamasa FUCHIKAMI,* and Kiyosi KONDO
Sagami Chemical Research Center, 4-4-1 Nishi-Ohnuma, Sagamihara, Kanagawa 229

A practical and efficient route to fluorinated pyrethroids has been developed which involves the selective formation of the *cis* cyclopropane ring using intramolecular alkylation of the haloaldehyde and a novel transformation of the aldehydes to the corresponding esters *via* the cyanohydrins.

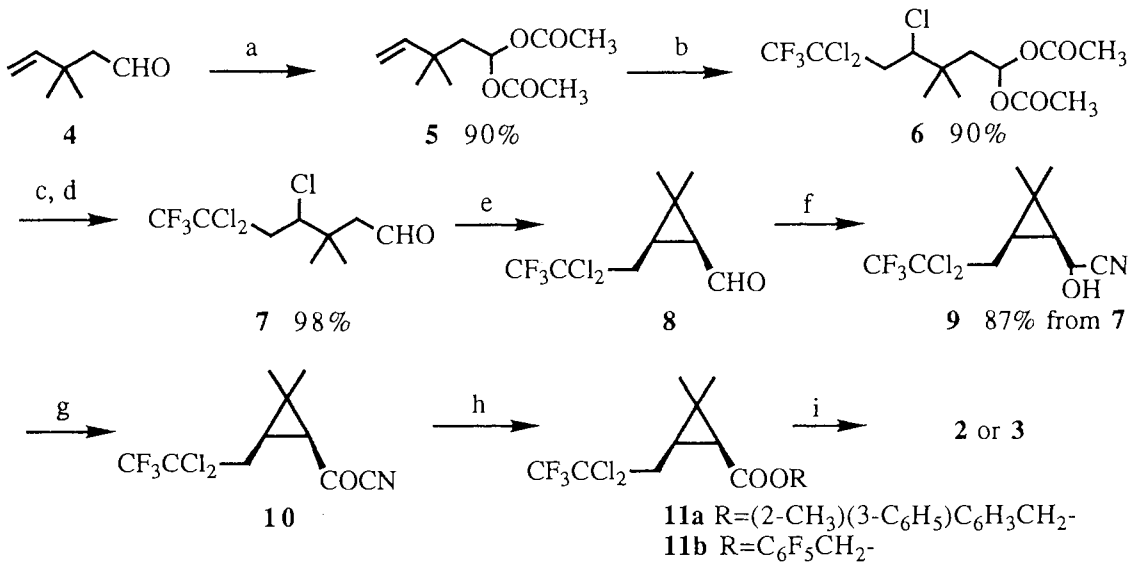
Fluorinated pyrethroids such as cyhalothrin (**1**) and bifenthrin (**2**) are well-known to have strong insecticidal activities, which are influenced by the stereochemistry of the substituents on the cyclopropane ring.[1] Namely, thermodynamically less stable *cis* compounds are more potent than the *trans* isomers.[1] Therefore, the stereocontrolled formation of the *cis* cyclopropane ring is a very important consideration in organic synthesis.[2] We wish to report here a practical and efficient route to the fluorinated pyrethroids, which involves a stereocontrolled synthesis of the *cis* disubstituted fluorinated cyclopropanecarbaldehyde using intramolecular alkylation of the haloaldehyde and a novel transformation of aldehydes to esters *via* cyanohydrins.



Initially, we examined the synthesis of 4,6,6-trichloro-7,7,7-trifluoro-3,3-dimethylheptanal (**7**), which is a suitable precursor for cyclization to fluorinated *cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropanecarbaldehyde (**8**). Direct addition of trifluorotrichloroethane to 3,3-dimethyl-4-pentenal (**4**) under various conditions using AIBN, benzoylperoxide, CuCl,[3] $Fe(CO)_5$, or $RuCl_2(PPh_3)_3$ as catalyst gave poor yields (less than 25%) of the adduct **7**. These results suggest that the initially formed trifluorodichloroethyl radical may react with the formyl moiety (e.g., abstraction of hydrogen atom from the aldehyde)[4] in preference to the olefin moiety (addition to the carbon-carbon double bond).

†Present address: Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 063.

Indeed, we found that the addition of CF_3CCl_3 to the carbon-carbon double bond of 3,3-dimethyl-4-pentenal diacetyl acetal (**5**) proceeded smoothly; 4,6,6-trichloro-7,7,7-trifluoro-3,3-dimethylheptanal diacetyl acetal (**6**) was obtained in 90% isolated yield by heating of **5** (23 mmol) with CF_3CCl_3 (84 mmol), $Fe(CO)_5$ (3.8 mmol), and pyridine (6.2 mmol) at 100 °C for 30 h in an autoclave. Thus, the desired fluorinated haloaldehyde **7** was prepared in three steps from **4** in 79% overall yield as shown in Scheme **1**.[5]



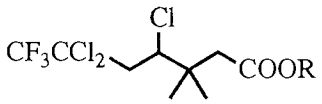
Scheme 1.

a, $(CH_3CO)_2O$, conc. H_2SO_4, Py; b, CF_3CCl_3, $Fe(CO)_5$, Py; c, MeOH, cat. TsOH; d, acetone - H_2O (3 :1), cat. TsOH; e, DBU, DMF; f, KCN, sat. $NaHSO_3$; g, $(COCl)_2$, DMSO, Et_3N; h, ROH; i, PhH, DBU.

Cyclization of the haloaldehyde **7** using intramolecular alkylation *via* the enamine took place on treatment with an equimolar amount of pyrrolidine in ether at 0 °C. However, the stereochemistry of the formed 3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethylcyclopropanecarboaldehyde (**8**) was found to be exclusively *trans*. In constant, the desired *cis* isomer was obtained selectively (*cis* : *trans* = 8 : 1)[6] when an amine having strong basicity such as DBU or DBN was employed in DMF at 0 °C.[7] It is not clear now why intramolecular cyclization *via* the enolate affords the *cis* isomer while cyclization *via* the enamine affords the *trans* isomer.

Next, we examined a transformation of aldehydes to esters *via* acyl cyanides derived from the oxidation of cyanohydrins. It is well-known that the oxidation of cyanohydrins to acyl cyanides is very difficult because acyl cyanides formed *in situ* act as acylating agents with the remaining free cyanohydrins.[8] In fact there are few reports of such transformation where activated cyanohydrins such as allylic or benzylic derivatives can be converted into methyl or ethyl esters by oxidation using *t*-butyl hydroperoxide[9] or manganese dioxide.[10] Under these conditions the acyl cyanides formed *in situ* simultaneously react with methanol or ethanol used as solvent which can not be oxidized by the oxidants used. Since this reaction is limited to the syntheses of esters of rather simple alkyl groups, it does not seem to be applicable to our compounds. However, we thought that the oxidation of cyanohydrins under the Swern oxidations followed by additions of a variety of alcohols would

afford the corresponding esters. Under the Swern oxidations the cyanohydrins can be converted into the corresponding acyl cyanides smoothly *via* the sulfonium salts which have no reactivity with the product acyl cyanides. Thus *cis*-3-(2,2-dichloro-3,3,3-trifluoropropyl)-2,2-dimethyl-1-(cyanohydroxymethyl)cyclopropane (**9**) derived from cyclopropanecarbaldehyde **8** was subjected to Swern conditions, followed by addition of 2-methyl-3-phenylbenzyl or pentafluorobenzyl alcohol, to afford the desired esters, 2-methyl-3-phenylbenzyl *cis*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (**11a**) and pentafluorobenzyl *cis*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate (**11b**) in good yields.[11] This procedure is a highly general and practical method for the one-pot conversion of cyanohydrins to esters with the use of 1-2 molar equivalent of alcohols. Heptanal **12**, **13** and cyclopropane **14**, **15**, **2** were also synthesized by the same procedure in the yields shown in parentheses based on each precursor. Obtained esters **11a** and **11b**



12 R=CH_3 (100%)
13 R=(2-CH_3)(3-C_6H_5)$C_6H_3CH_2$- (72%)

14 R^1= Cl_2C=CH-, R^2= Et (100%)
15 R^1= Cl_2C=CH-, R^2= (3-C_6H_5O)$C_6H_4CH_2$- (85%)
2 R^1= Cl(CF_3)C=CH-, R^2= (2-CH_3)(3-C_6H_5)$C_6H_3CH_2$- (84%)

Fig. 1.

were treated with DBU in benzene at reflux temperature to yield the desired pyrethroids quantitatively without epimerization of the cyclopropyl ring. The overall yield from 3,3-dimethyl-4-pentenal (**4**) to bifenthrin (**2**) was 59% in 8 steps.

References

1) P. D. Bentley, R. Cheetham, R. K. Huff, R. Pascoe, and J. D. Sayle, *Pestic. Sic.*, **11**, 56 (1980).
2) M. Fujita, T. Hiyama, and K. Kondo, *Tetrahedron Lett.*, **27**, 2139 (1986).
3) T. Okano, T. Uekawa, and S. Eguchi, *Bull. Chem. Soc. Jpn.*, **62**, 2575 (1988).
4) B. Giese, "Radical in Organic Synthesis: Formation of Carbon-Carbon Bonds," Pergamon Press (1986).
5) All new compounds obtained here exhibited satisfactory spectral and analytical data.
6) Two isomers were easily separated by column chromatography on silica gel, *trans*-**8** (colorless oil) : ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.20 (s, 3H), 1.30 (s, 3H), 1.63 (t, *J* = 5 Hz, 1H), 2.00 (bq, *J* = 5 Hz, 1H), 2.30 (dd, *J* = 14 and 4 Hz, 1H), 2.50 (dd, *J* = 14 and 6 Hz, 1H), 9.50 (d, *J* = 5 Hz, 1H); IR (neat) 1705, 1260, 1200, 1180 cm^{-1}.
cis-**8** (colorless oil) : ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.22 (s, 3H), 1.28 (s, 3H), 1.78 (dt, *J* = 8 and 6 Hz, 1H), 1.97 (dd, *J* = 8 and 3 Hz, 1H), 2.67 (d, *J* = 6 Hz, 2H), 9.75 (d, *J* = 3 Hz, 1H); IR (neat) 1705, 1275, 1210, 1190 cm^{-1}.
7) It may be more practical that the reaction mixture was directly treated with sodium cyanide and sodium hydrogen sulfate so as to be converted into cyanohydrin **9** (*cis* : *trans* = 8 : 1) in 87% yield from **7** without isolation of **8**, because of high volatility of **8**.

trans-**9** (colorless oil): ^{1}H NMR ($CDCl_3$: 100MHz) δ 0.7 - 1.4 (m, 2H), 1.13 (s, 3H), 1.20 (s, 3H), 2.35 (d, J = 6 Hz, 2H), 3.0 - 3.5 (m, 1H), 4.0 - 4.3 (br, 1H).

cis-**9** (colorless oil): ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.10 (s, 3H), 1.20 (s, 3H), 1.0 - 1.7 (m, 2H), 2.15 (dd, J = 15 and 9 Hz, 1H), 2.60 (dd, J = 15 and 9 Hz, 1H), 3.8 - 4.4 (m, 2H).

8) S. Hüning, and R. Schaller, *Angew. Chem. Int. Ed. Engl.*, **21**, 36 (1982).

9) T. Naota and S. Murahashi, and E. Nakajima, *Tetrahedron Lett.*, **26**, 925 (1985).

10) E. J. Corey, N. W. Tilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).

11) The representative procedure is as follows : To a solution of oxalyl chloride (1.1 mmol) in CH_2Cl_2 (5 ml), was added DMSO (2.2 mmol) at -78 °C under argon atmosphere, followed by the addition of a solution of the cyanohydrin **9** (*cis* : *trans* = 8 : 1) (1 mmol) in CH_2Cl_2 (3.0 ml). After stirring for 30 min, Et_3N (5.0 mmol) was added. The reaction mixture was then stirred for 15 min at -78°C and without cooling bath for 15 min. An additional amount of CH_2Cl_2 (5 ml) and a solution of 2-methyl-3-phenylbenzyl alcohol (2.0 mmol) in CH_2Cl_2 were then added at -78 °C. The reaction mixture was gradually warmed up to room temperature over 50 min. Usual workup afforded ester **11a** (*cis* : *trans* = 8 : 1) (80%). The *cis* and *trans* isomers were separated by silica gel column chromatography.

trans-**11a** (colorless oil): ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.17 (s, 3H), 1.27 (s, 3H), 1.49 (d, J = 4.5 Hz, 1H), 1.83 (q, J = 4.5 Hz, 1H), 2.20 (s, 3H), 2.27 (dd, J = 12 and 4.5 Hz, 1H), 2.47 (dd, J = 12 and 4.5 Hz, 1H), 5.20 (s, 2H), 7.1-7.5 (m, 8H); IR (neat) 1725 cm^{-1}

cis-**11a** (colorless oil): ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.23 (s, 6H), 1.53 (dt, J = 9 and 6 Hz, 1H), 1.73 (d, J = 9 Hz, 1H), 2.20 (s, 3H), 2.59 (dd, J = 16 and 4.5 Hz, 1H), 2.83 (dd, J = 16 and 4.5 Hz, 1H), 5.20 (s, 2H), 7.1-7.5 (m, 8H); IR (neat) 1730 cm^{-1}.

cis-**11b** was synthesized in the same way.

cis-**11b** (colorless oil): ^{1}H NMR ($CDCl_3$: 100MHz) δ 1.25 (s, 6H), 1.55 (dt, J = 9 and 6 Hz, 1H), 1.79 (d, J = 9 Hz, 1H), 2.55 (dd, J = 15 and 6 Hz, 1H), 2.79 (dd, J = 15 and 6.0 Hz, 1H), 5.20 (s, 2H); IR (neat) 1740 cm^{-1}.

(Received January 21, 1994)