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Stereoselective Synthesis of Trifluoromethyl Group Containing Cyclopropane Lactones

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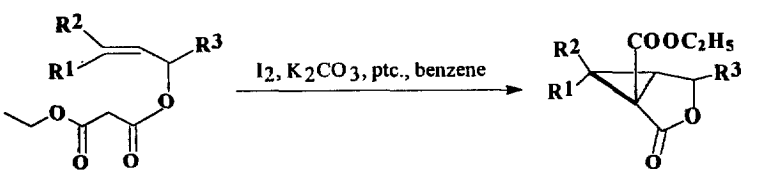
Abstract: Malonic acid esters of *trans*-1-substituted-3-trifluoromethyl-2-butene-1-ols underwent stereoselective, SET induced cyclization reaction sequence in the presence of iodine, potassium carbonate and quaternary ammonium salt. The allyl substituents of the starting materials influenced the diastereoisomeric composition of the new products. © 1997 Elsevier Science Ltd.

Trifluoromethyl group containing organic compounds are becoming increasingly important to the development of more effective medicines and agricultural chemicals[1]. It is due to the high electronegativity, stability and lipophilicity of the trifluoromethyl group which often induces significant changes in the chemical, physical and physiological nature of the organic molecules[1,2]. There are some methods published for the synthesis of fluoro[3] or trifluoromethyl group[4] containing cyclopropane derivatives, an important class of compounds found in natural and unnatural biologically active substances[5].

Recently a new, convenient route to the multisubstituted cyclopropane derivatives was published by our laboratory[6]. The method is based upon a SET induced reaction sequence of non activated olefines with CH-acids (like malonic acid esters) in the presence of iodine, potassium carbonate and lipophilic quaternary ammonium salt (ptc.).



1 **2**

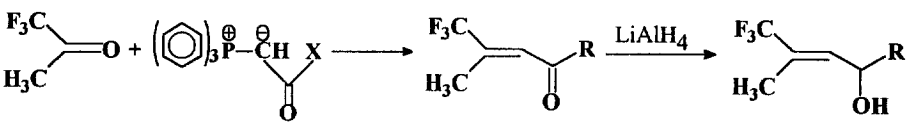
R^1, R^2, R^3: H or alkyl group

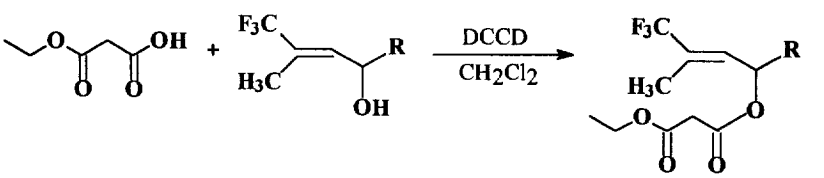
Scheme 1

The yield increased when the CH-acid moiety and the olefinic bond were in a proper position in the same molecule. In this case cyclopropane derivatives anellated to a lactone ring were formed in an intramolecular reaction[6] (Scheme 1). The protocoll was successfully extended to the synthesis of cyclopropane phosphonic acid esters[7], too.

Introduction of a trifluoromethyl group into the starting material (**1**) at R^1 position is a new, quite exciting modification of the reaction both in theoretical and practical point of view. The strong electron withdrawing group changes the character of the olefinic π-bond which is fully involved in the radical process. Furthermore, a new chiral center forms at C(6) position in the product **5** (R^1 = CF_3 in compound **2**) hence the stereoselectivity of the radical reaction can be monitored. On the other hand **5a**, **5b** and **5c** are useful for the stereoselective synthesis of the trifluoromethyl analogues of pyrethroids[8], aminocyclopropanecarboxylic acids (ACC)[9] and other natural products as terpenes and fatty acids[10].

Aiming at the synthesis of compounds **5a-c** *trans*-1-substituted-3-trifluoromethyl-2-butene-1-ols (**3**) were prepared first. Using the literature methods, 1,1,1-trifluoromethyl-2-propanone and the corresponding phosphorous ylide were reacted[11] followed by the reduction of the oxo compounds[12] formed (Scheme 2).



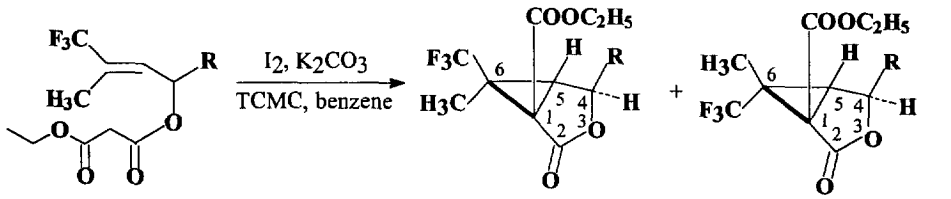


Scheme 2

Monoethyl malonate[13] reacted smoothly with **3a**, **3b** and **3c**, respectively, in the presence of dicyclohexylcarbodiimide (Scheme 2). The products (**4a**, **4b** and **4c**) are new compounds; they were purified by column chromatography and fully characterized by spectroscopic methods.

For preparation of the target molecules (**5a-c**) a benzene solution of iodine was added in small portions to the mixture of the given ester (**4**), dry, solid potassium carbonate and tricaprylmethylammonium chloride

(TCMC) in hot benzene (Scheme 3). The reactions were monitored by TLC and the compositions of the crude products were determined by gas chromatography and ^{1}H-NMR and ^{19}F-NMR spectroscopy. The expected products were isolated with satisfactory yields as mixtures of only two diastereoisomers in which the trifluoromethyl group situated *exo* (*exo*-CF_3-**5**) or *endo* (*endo*-CF_3-**5**) position (Scheme 3).



R = H **4a** — *exo*-CF_3-**5a** (37 %) — *endo*-CF_3-**5a** (63 %)
R = CH_3 **4b** — *exo*-CF_3-**5b** (65 %) — *endo*-CF_3-**5b** (35 %)
R = C_6H_5 **4c** — *exo*-CF_3-**5c** (73 %) — *endo*-CF_3-**5c** (27%)

Scheme 3

There are three asymmetric centers (at C(1), C(5) and C(6)) in compound **5a** while a fourth (at C(4)) can be found in **5b** and **5c**, respectively. The relative configurations of C(1) and C(5) asymmetric centers is given by the cyclopropane and lactone ring anellation in all cases. Positions of the methyl (**5b**) and phenyl (**5c**) groups were determined from the ^{1}H-NMR spectra. The chemical shift values and coupling constants of H(4) and H(5) atoms of **5** are collected in Table 1. The molecular modelling studies have shown the H(4)$_{endo}$-C(4)-C(5)-H(5) torsion angle to be at about 90° therefore the coupling constant between H(4)$_{endo}$ and H(5) has to be close to zero as it was found in the spectra of **5b** and **5c** samples. The same torsion angle in the theoretically existing other isomer (where the R group would be in *endo* position) is near to zero hence H(4)$_{exo}$-H(5) coupling should appear in the spectra according to the Karlplus rule. The spectroscopic data confirmed that the lactone ring closuring reaction is stereospecific regarding to the C(4) asymmetric center. The methyl and phenyl substituents situated exclusively in *exo* position in **5b** and **5c**, respectively. These observations are in good accordance with our results obtained in the nonfluorinated series of model compounds[6].

The two diastereoisomeric products differ in the configuration of the C(6) asymmetric center, only (Scheme 3). Identification of the *exo*-CF_3-**5** and *endo*-CF_3-**5** isomers was accomplished by the comparison of the ^{1}H-NMR spectra and the ^{19}F-decoupled ones of **5a**, **5b** and **5c**, respectively. As a consequence of the cyclopropane ring geometry the trifluoromethyl group is situated close to the H(5) atom in the *exo*-CF_3-**5** isomers hence weak H-F coupling can be observed on the H(5) signal in the proton spectra (0.7-0.8 Hz; Table 1). On the other hand H(5) and the CF_3 group are far away from each other in the *endo*-CF_3-**5** isomers.

In the ^{19}F-decoupled proton spectra the multiplicity of the H(5) signal decreased while the intensity increased in the cases of *exo*-CF_3-**5** isomers. Furthermore, the multiplicity of the H(4) signal of the *endo*-CF_3-**5a** isomer changed from ddq to dd (Table 1). The original coupling structure is due to the proximity effect of the CF_3 group in that molecule.

Table 1. Chemical Shifts and Coupling Constants of H(4) and H(5) in the Product Isomers

Compound	H(4)			H(5)		
	δ (ppm)	multipl.	*J* (Hz)	δ (ppm)	multipl.	*J* (Hz)
5a ***exo-CF₃***	4.46	dd	11.0, 6.0	2.75	dt like m	6.0, 1.0
^{19}F-decoupled:	*4.46*	*dd*	*11.0, 6.0*	*2.75*	*dd*	*6.0, 1.6*
endo- CF₃	4.55	ddq	11.0, 5.1, 1.0	2.90	dd	5.1, 0.7
^{19}F-decoupled:	*4.55*	*dd*	*11.0, 5.1*	*2.90*	*dd*	*5.1, 0.7*
5b ***exo- CF₃***	4.69	q	6.3	2.47	t like m	0.8
^{19}F-decoupled:	*4.69*	*q*	*6.3*	*2.47*	*s*	-
endo- CF₃	4.48	q	6.3	2.68	s	-
^{19}F-decoupled:	*4.48*	*q*	*6.3*	*2.68*	*s*	-
5c ***exo- CF₃***	5.48	s	-	2.73	t like m	0.7
^{19}F-decoupled:	*5.48*	*s*	-	*2.73*	*d*	*1.0*
endo- CF₃	5.24	s	-	2.96	d	0.8
^{19}F-decoupled:	*5.24*	*s*	-	*2.96*	*d*	*0.8*

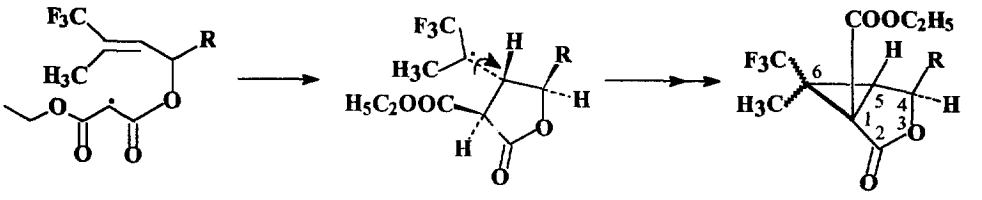
The ^{19}F-NMR chemical shift values were not sensitive to the substitution of C(4) atom but the *exo/endo* ratio at C(6) changed dramatically with it as it was indicated by the integration values of the fluorine signals of the isomers (Table 2).

Table 2. ^{19}F-NMR Chemical Shift Values and Relative Intensities in the Product Isomeric Mixtures

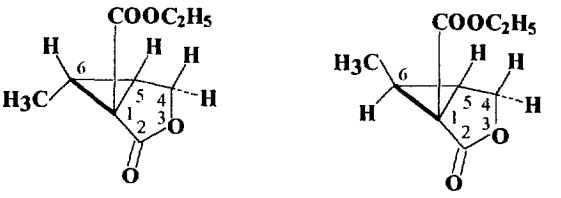
Compound	R	*Exo-CF₃*-**5**		*Endo-CF₃*-**5**	
		δ (ppm)	(%)*	δ (ppm)	(%)*
5a	H	-66.5	37	-69.5	63
5b	CH_3	-66.2	65	-69.6	35
5c	C_6H_5	-66.0	73	-69.5	27

*The relative integral values are in good accordance with the gas chromatographic data

The observed stereoselectivity can be rationalized on the basis of a reaction mechanism postulated earlier by us[6,7]. It has been shown that in these transformations the SET induced multistep process involves formation of a radical intermediate of type **6** which undergoes cyclization reaction (Scheme 4). Both 6-endo-trig and 5-exo-trig[14, 15] reaction is permitted in these cases. (According to the ESR spetroscopic data the six membered lactone ring formation is dominating in the series of phosphorous ester analogs[7] but the five membered lactone ring (**7**) was proposed to exist as an intermediate in the carboxylic acid ester series[6].)



6 7 5



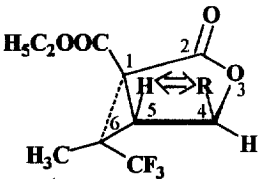
endo-CH_3-**8** (40 %)[6] *exo-CH_3*-**8** (60 %)[6]

Scheme 4

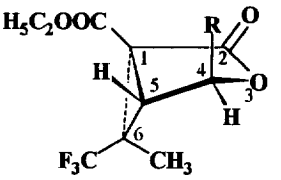
We suppose that the quality of the R group at C(4) governs the stereochemistry of the **6** → **7** cyclization reaction on a way that the bulky substituents can be situated alternately (up-down-up) around the lactone ring (**7**). Thus the exclusive *exo* position of the R group in the endproduct has been determined in this step.

As the relative position of the Me and CF_3 groups at C(6) is concerned we can see from the Table 2 that in the isomeric mixture of **5a** the *exo-Me* isomer (57 %, *endo-CF_3*) is the major product similar to the CF_3 free analogue[6] **8** (60 %, Scheme 4). From these facts one can conclude that in the ring closure leading to **5a**, in the building up of the transition state energy, the same types of forces work that act upon the formation of the CF_3 free analogue **8.** In other words, neither the steric bulkyness nor the electron density of the CF_3 group plays important role. Supposing a product like transition state for the cyclopropane ring formation[16] all considerations are attempted to visualize in Scheme 5 showing the transition state structures ***A*** (when R = H) and ***B*** (when R = methyl or phenyl), respectively (the newly forming bond is marked by dotted line).

The situation changes when the hydrogen atom at C(4) is replaced by methyl or phenyl group (**5b** and **5c**) and the *exo-CF_3* isomers become the major products (67 % and 73 %, respectively; Table 2). In these cases, according to the cyclopropane lactone model studies, an envelope like lactone conformation seems to be existing (structure ***B***) to avoid the strong steric repulsion between the C(4) substituent (methyl or phenyl) and the H(5) atom. Consequently, an additional factor comes in changing the energy relationships and favoring the *exo-CF_3* isomer: the repulsive effect between the CF_3 group and the oxygen atom of the lactone ring (in the *endo-CF_3*-**5** isomers). We can conlude on the basis of the experimental facts and the theoretical considerations that it is not the steric bulkyness but the electron density of the trifluoromethyl group which may be responsible for the stereochemistry of C(6) asymmetric center during the cyclopropane ring closuring process.



A (R = H)



B (R = methyl or phenyl)

Scheme 5

EXPERIMENTAL

All the commercially available chemicals were purchased from Merck GmBH., Hungary and they were used without any further purification. ^{1}H-NMR spectra were recorded on a Bruker WM-250 spectrometer, ^{19}F-NMR and ^{19}F-decoupled ^{1}H-NMR spectral data were collected on a Bruker 400-DRX spectrometer. Chemical shifts are given on the δ scale, δ(TMS)=0 ppm in the proton spectra, δ($CFCl_3$)=0 in the fluorine spectra in $CDCl_3$. Gas chromatographic measurements were carried out in a Fisons GC 8000 instrument equipped with mass selective detector MD 800 using DB-5 MS (30 m x 0.25 mm x 0.1 μm fused silica) column. Mass spectra were recorded in electron impact mode at 70 eV and 30 eV, 200 °C. TLC-s were developed on Merck Kieselgel 60 F_{254} plates with an eluent hexane-acetone (4:1). Column chromathography was carried out on Merck Kieselgel 60 to 200 mesh, with the same eluent in the cases of compounds **5**, while hexane was used for purification of compounds **4**.

Preparation of ethyl-((E)-1-substituted-3-trifluoromethyl-2-butene)-1-yl malonates *(General procedure)*
Monoethyl malonate[13] (1.0 g 7.6 mmol) and compound **3a**, **3b** or **3c** (7.6 mmol) was solved in dry dichloromethane (7 ml) and the solution was cooled to 0 °C. Dimethylaminopyridine catalyst (0.01 g) and dicyclohexylcarbodiimide (1.56 g, 7.6 mmol) were added to the stirred solution After 10 minutes stirring at 0 °C the cooling bath was removed and the mixture was stirred at 25 °C for an hour. The solid byproduct was filtered off, the solution was washed with 10 % hydrochloric acid solution (1 x 10 ml) then with distilled water (2 x 10 ml). The organic solution was dried over sodium sulfate before evaporating of the solvent in vacuo. The oily residue was finally purified on Silicagel column.

Ethyl-((*E*)-3-trifluoromethyl-2-butene)-1-yl malonate (4a): 93 %,
^{1}H-NMR: δ 6.18 (1H, t like m, *J* 6.5), 4.80 (2H, d like m, *J* 6.5), 4.21 (2H, q, *J* 6.7), 3.41 (2H, s), 1.83 (2H, s), 1.25 (3H, t, *J* 6.7). - ^{19}F-NMR: δ -70.1 (3F). - Ms m/z: 255 (M^{+}+1), 209, 123 , 115 (100 %), 87. Anal. calcd. for $C_{10}H_{13}F_3O_4$: C 47.25, H 5.15, found C 47.01, H 5.23.

Ethyl-((*E*)-4-trifluormethyl-3-pentene)-2-yl malonate (4b): 89 %,

^{1}H-NMR: δ 5.99 (1H, d like m, *J* 8.4), 5.63 (1H, sym.m), 4.21 (2H, q, *J* 7.2), 3.35 (2H, s), 1.87 (3H, d, *J* 1.1), 1. 37 (3H, d, *J* 6.4), 1.26 (3H, t, *J* 7.2). - ^{19}F-NMR: δ -70.1 (3F). - Ms m/z: 269 (M^++1), 223, 137, 115 (100 %), 87. Anal. calcd. for $C_{11}H_{15}F_3O_4$: C 49.26, H 5.64, found C 48.97, H 5.58.

Ethyl-((*E*)-1-phenyl-3-trifluormethyl-2-butene)-1-yl malonate (4c): 69 %,

^{1}H-NMR: δ 7.4 (5H, m), 6.56 (1H, d, *J* 9.0), 6.29 (1H, d, *J* 9.0), 4.21 (2H, q, *J* 7.0), 3.42 (2H, s), 1.96 (3H, s), 1.25 (3H, t, *J* 7.0). - ^{19}F-NMR: δ 70.1 (3F). - Ms m/z: 330 (M^+), 215, 199, 115 (100 %), 77. Anal. calcd. for $C_{16}H_{17}F_3O_4$: C 58.18, H 5.19, found C 57.89, H 5.08.

Preparation of cyclopropane lactone derivatives (5) *(General procedure)*

Compound **4a**, **4b** or **4c** (2.0 mmol) was solved in dry benzene and dry potassium carbonate (1.5 g 11 mmol) powder and TCMC catalyst (0.02 g) were poured into it then it was heated to reflux temperature. A solution of iodine (0.54 g 2.0 mmol) in benzene (20 ml) was added dropwise during 5 hours to the intensively stirred, boiling reaction mixture. The rate of addition has to be set on a way as the colour of the iodine disappears in the reaction mixture. The reaction can be monitored by TLC. After a further 30 minutes heating the mixture was cooled, the solid was filtered off, the filtrate was washed with 10 % sodium thiosulfate solution (3 x 15 ml) and with water (2 x 15 ml) and dried over sodium sulfate. The solution was concentrated in vacuo and the residue was purified by column chromathography after monitoring the composition (isomeric ratio) of the crude products by gas chromathography and spectroscopic methods.

6-Methyl-6-trifluormethyl-3-oxa-bicyclo[3,1,0]hexan-2-one-1-carboxylic acid ethyl ester (5a): 46 % (*exo-CF_3/endo-CF_3* = 37/63).

^{1}H-NMR: δ *exo-CF_3*: 4.46 (2H, dd, *J* 10.0, 6.0), 4.21 (2H, q, *J* 7.1), 2.75 (1H, d like m, *J* 6.0), 1.38 (3H, s), 1.20 (3H, t, *J* 7.1); *endo-CF_3*: 4.55 (2H, dd, *J* 10.0, 5.1), 4.22 (2H, q, *J* 7.1), 2,90 (1H, d, *J* 5.1), 1.33 (3H, s), 1.21 (3H, t, *J* 7.1). - ^{19}F-NMR: δ *exo-CF_3*: -66.5 (3F); *endo-CF_3*: -69.5 (3F). - Ms m/z: 252 (M^+), 207, 176 (100 %), 157, 132. Anal. calcd. for $C_{10}H_{11}F_3O_4$: C 47.63, H 4.40, found C 47.48, H 4.28.

4,6-Dimethyl-6-trifluormethyl-3-oxa-bicyclo[3,1,0]hexan-2-one-1-carboxylic acid ethyl ester (5b): 41 % (*exo-CF_3/endo-CF_3* = 65/35).

^{1}H-NMR: δ *exo-CF_3*: 4.69 (1H, q, *J* 6.3), 4.21 (2H, q, *J* 7.0), 2.47 (1H, t, *J* 0.8), 1.57 (3H, d, *J* 6.3), 1.41 (3H, s), 1.33 (3H, t, *J* 7.0); *endo-CF_3*: 4.48 (1H, q, *J* 6.4), 4.20 (2H, q *J* 7.0), 2.68 (1H, s), 1.59 (3H, d, *J* 6.4), 1.43 (3H, s), 1.33 (3H, t, *J* 7.0). - ^{19}F-NMR: δ *exo-CF_3*: -66.2 (3F); *endo-CF_3*: -69.6 (3F). - Ms m/z: 266 (M^+), 221, 193, 176 (100 %), 148. Anal. calcd. for $C_{11}H_{13}F_3O_4$: C 49.63, H 4.92, found C 49.31, H 4.84.

4-Phenyl-6-methyl-6-trifluormethyl-3-oxa-bicyclo[3,1,0]hexan-2-one-1-carboxylic acid ethyl ester (5c): 47 % (*exo-CF_3/endo-CF_3* = 73/27).

^{1}H-NMR: δ *exo-CF_3*: 7.38 (5H, m), 5.48 (1H, s), 4.38 (2H, q, *J* 7.0), 2.73 (1H, t like m, *J* 0.7), 1.43 (3H, s), 1.34 (3H, t, *J* 7.0); *endo-CF_3*: 7.45 (5H, m), 5.24 (1H, s), 4.38 (2H, q, *J* 7.0), 2.96 (1H, s), 1.40 (3H, s), 1.34

(3H, t, *J* 7.0). - ^{19}F-NMR: δ *exo-CF$_3$*: -66.0 (3F); *endo-CF$_3$*: -69.5 (3F). - Ms m/z: 328 (M^+), 283, 255, 141, 77 (100 %). Anal. calcd. for $C_{16}H_{15}F_3O_4$: C 58.54, H 4.61, found C 58.28, H 4.70.

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16. For the possible elemental steps leading to the transition state showed in Scheme 5 see our previous work published in *Tetrahedron* (references 6 and 7).

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