Preparation of β-Trifluoromethyl-γ-butyrolactones via Claisen Rearrangement

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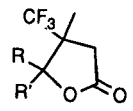
The Claisen rearrangement of allylic alcohol **2** provided the β-trifluoromethyl γ,δ-ethylenic ester **3** which gave access to a series of β-trifluoromethyl-γ-butyrolactones **1**.

Fluorinated organic compounds have received increased attention during the past years[1] due to the enhancement of activity when an hydrogen atom or a methyl group are replaced by a fluorine atom or a trifluoromethyl group in a biological molecule[2]. Especially, the advance in the preparation and use in total synthesis of trifluoromethyl synthetic intermediates has been remarkable.[3]

γ-Butyrolactones (dihydro-2(3*H*)-furanones) are a highly important class of compounds owing to their presence in many natural products and other biologically active molecules.[4] In particular, β,β-disubstituted γ-butyrolactones show strong convulsant or anticonvulsant activity.[5] They are also versatile intermediates in the synthesis of other important classes of compounds (e.g. cyclopentenones, furans).[6]

There are few reports on the synthesis of trifluoromethylated γ-butyrolactones, and none of them are related to a β,β-disubstituted one.[7] Here, we describe the preparation of β-methyl-β-trifluoromethyl-γ-butyrolactones of type **1**.

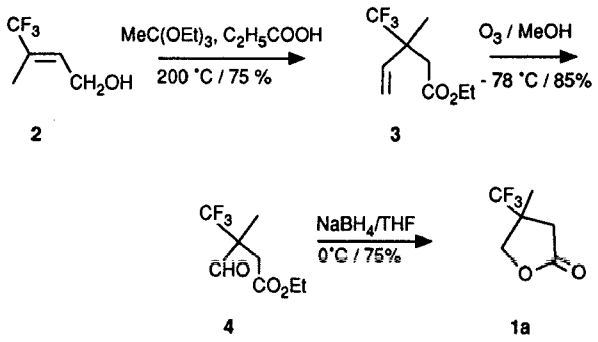


1

	R	R'
a	H	H
b	H	OEt
c	H	OMe
d	-S(CH$_2$)$_3$S-	

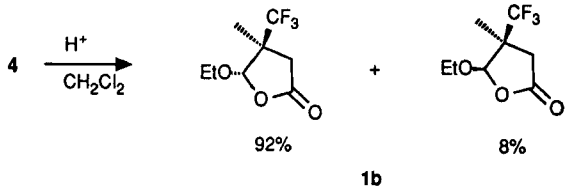
Our strategy for their preparation was based on the Claisen rearrangement of the trifluoromethylated allylic alcohol **2** easily obtained from commercially available trifluoroacetone.[8] The reaction was conducted under ortho-ester conditions[9] at 200 °C for 30 hours and afforded ethyl 3-methyl-3-trifluoromethyl-4-pentenoate (**3**) in 75 % yield. With prenyl alcohol, the Claisen rearrangement was complete in only 3.5 hours[9] to give ethyl 3,3-dimethyl-4-pentenoate, and could even be conducted at 140 °C.[10] With the trifluoromethylated analog, only a very small amount of **3** was detected under the same conditions. Ozonolysis of the double bond afforded the new aldehyde ester **4** in 85 % yield. This 1,4-dicarbonyl compound was the intermediate in the synthesis of lactones of type **1**. Treatment of **4** with sodium borohydride in tetrahydrofuran gave lactone **1a** in 75 % yield (Scheme 1).

Another lactonisation was observed when compound **4** was stirred in dichloromethane with a few drops of concentrated hydrochloric acid (Scheme 2). The ethoxy lactone **1b** was obtained as a mixture of two diastereomers in a 92:8 ratio. If one considers the ^{19}F NMR chemical



Scheme 1

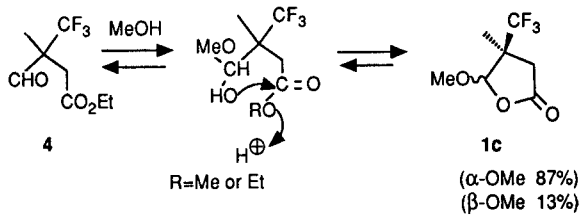
shift, the major isomer has the trifluoromethyl and ethoxy groups in trans position.[11] Indeed the chemical shift of the trifluoromethyl group in cis position relative to the β-ethoxy group is lower (− 71 ppm) than when it is in a trans relationship (− 77 ppm). We have checked that there is no equilibrium between the two isomers: no change in the isomer ratio was observed by stirring an enriched fraction of **1b** (ratio 80:20) under the same conditions. Formation of **1b** could involve the initial hydrolysis of the ethyl ester giving ethanol and a carboxylic acid which could lead to a γ-hydroxylactone by cyclisation. However, it is surprising that only one mole of ethanol in wet dichloromethane could transform the γ-hydroxylactone to **1b** in 90 % yield. Alternatively, **1b** could be formed by an unknown intramolecular acidic rearrangement.



Scheme 2

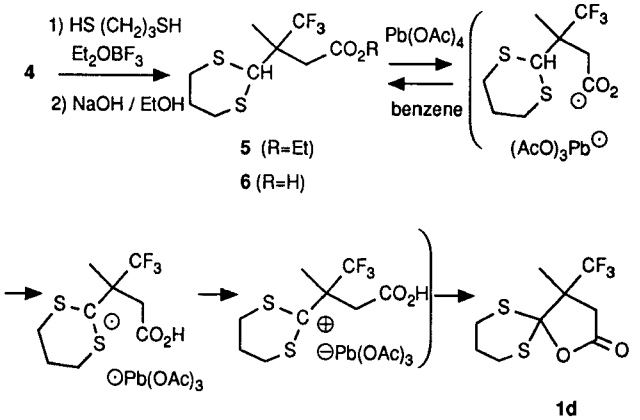
The methoxy analog **1c** was formed by stirring **4** in methanol in the presence of a few drops of concentrated hydrochloric acid. Here, the diastereomeric excess was a little lower (87:13). Compound **1b** is not an intermediate as it was not detected by monitoring the reaction with capillary GC. We also checked independently that the transformation of **1b** to **1c** under the same conditions was slow (8 hours). An hemiketal is the most likely intermediate, which further cyclised to afford the diastereomeric mixture of **1c** as shown in Scheme 3.

Another lactone derivative was obtained by a radical process. Treatment of **4** with 1,3-propanedithiol in dichloromethane in presence of boron trifluoride etherate[12] afforded the ester **5** in 70 % yield, saponification of which gave the corresponding acid **6**. From this acid, we at-



Scheme 3

tempted a cyclisation using lead tetraacetate by analogy with the formation of tetrahydrofurans from alcohols having a proton in δ-position.[13] Indeed, **1d** was obtained from **6** in 60% yield following probably the mechanism shown in Scheme 4.



Scheme 4

Thus, we have shown that a Claisen rearrangement of a fluorinated allylic alcohol gives a γ,δ-ethylenic ester which serves as a synthon for the preparation of a variety of β-trifluoromethyl-γ-butyrolactones.

Melting points were determined on a Mettler FP-61 apparatus. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. NMR spectra were taken, in $CDCl_3$, on a Bruker AC-200 E spectrometer. Chemical shifts are expressed in ppm from internal TMS (^1H and ^{13}C) and $CFCl_3$ (^{19}F). Preparative chromatography was performed on silica gel column (Merck 70–230 Mesh). Preparative GC was performed on a Shimadzu GC-8A equipped with a 2.5 m SE-30 column operating at 150°C. Analytical GC was performed on a Shimadzu GC-14A equipped with a 10 m CP-Sil 19 column. Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr apparatus. Ozonolysis was performed using an ozone generator (Fisher, Modell 502). For new compounds satisfactory microanalyses obtained: C ± 0.36, H ± 0.17.

Ethyl 3-Methyl-3-trifluoromethyl-4-pentenoate (3):
A solution of the alcohol **2** (6 g, 0.043 mmol), triethyl orthoacetate (27.8 g, 0.172 mol) and propionic acid (0.19 g, 0.0025 mol) was heated in a heavy-walled Pyrex tube equipped with a Teflon stopper at 200°C for 30 h. After cooling, the mixture was diluted with Et_2O (50 mL) and washed with ice cold 50% HCl (3 × 40 mL). The combined aqueous layers were washed with Et_2O (50 mL) and the combined organic layers washed successively with H_2O (50 mL) sat. $NaHCO_3$ solution (50 mL), brine (50 mL) and dried ($MgSO_4$). After filtration, the solvent was removed in vacuo to give a residue which was distilled to afford **3**; yield: 6.8 g (75%); bp 55–56°C/13 Torr.

IR ($CHCl_3$): ν = 1720, 1640 cm^{-1}.

^1H NMR: δ = 1.21 (t, 3H, J = 7.1 Hz), 1.40 (s, 3H), 2.58 (AB system, 2H, J = 14 Hz), 4.08 (q, 2H, J = 7.1 Hz), 5.25–5.33 (m, 2H), 5.89 (dd, 1H, J = 10.9, 17.4 Hz).

^{13}C NMR: δ = 13.5, 16, 38.6, 45.07 (C_{quat}, $J_{C,F}$ = 25 Hz), 60.17 (OCH_2), 117.8 (CH_2=), 127 (CF_3, $J_{C,F}$ = 282 Hz), 134.8 (CH=), 169 (CO).

^{19}F NMR: δ = −77 (s).

Ethyl 3-Formyl-3-trifluoromethylbutanoate (4):
A solution of the unsaturated ester **3** (6 g, 0.028 mol) in MeOH (50 mL) was treated with O_3 (4 g/h) at −78°C until a slight blue color persisted. The solution was degassed with N_2 and brought to 0°C whereupon Me_2S (7.3 mL, 0.085 mol) was added. The mixture was stirred at this temperature for 1 h. MeOH was evaporated at reduced pressure and the residue was taken up in H_2O (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with brine and dried ($MgSO_4$). Filtration and removal of the solvent under vacuum gave a crude product which was distilled to afford the aldehyde **4**; yield: 5.1 g (85%); bp 72°C/15 Torr.

IR (CCl_4): ν = 1735 cm^{-1}.

^1H NMR: δ = 1.22 (t, 3H, J = 7 Hz), 1.42 (s, 3H), 2.85 (AB system, 2H, J = 16.2 Hz), 4.11 (q, 2H, J = 7 Hz), 9.67 (m, 1H).

^{19}F NMR: δ = −72.6 (s).

Dihydro-4-methyl-4-trifluoromethyl-2(3*H*)-furanone (1a):
To a solution of **4** (1 g, 4.7 mmol) in THF (20 mL) at 0°C was added in small portions $NaBH_4$ (90 mg, 2.35 mmol). The mixture was stirred for 4 h at r.t. After acidification with a 5% aq HCl solution and addition of H_2O (30 mL), the mixture was extracted with CH_2Cl_2 (2 × 30 mL) the organic layer was dried ($MgSO_4$), filtered, and the solvent removed under vacuum to afford the crude product which was distilled using a Kugelrohr apparatus to give the lactone **1a**; yield: 0.6 g (75%); bp 140°C/17 Torr.

IR (CCl_4): ν = 1795 cm^{-1}.

^1H NMR: δ = 1.37 (s, 3H), 2.6 (AB system, 2H, J = 18 Hz), 4.22 (AB system, 2H, J = 9.9 Hz).

^{19}F NMR: δ = −78.1 (s).

Dihydro-5-ethoxy-4-methyl-4-trifluoromethyl-2(3*H*)-furanone (1b):
A solution of the aldehyde **4** (1 g, 4.7 mmol) in CH_2Cl_2 (30 mL) containing a few drops of conc. HCl was stirred overnight (the reaction could be easily monitored by GC). The solution was washed with sat. $NaHCO_3$ solution (30 mL), brine (30 mL), dried ($MgSO_4$) and filtered. The solvent was evaporated under vacuum. Purification was effected by distillation using a Kugelrohr apparatus affording the lactone **1b** as a mixture of diastereomers in a ratio 92:8; yield: 0.9 g (90%); bp 125–130°C/16 Torr.

IR ($CHCl_3$): ν = 1780 cm^{-1}.

^1H NMR Mixture of the two diasteromers D_1 (92%) and D_2 (8%): δ = 1.14 (t, 3H, J = 7 Hz, $D_1 + D_2$), 1.24 (s, 3H, D_1), 1.26 (s, 3H, D_2), 2.55 (AB system, 2H, J = 18 Hz, D_1), 2.82 (AB system, 2H, J = 17.3 Hz, D_2), 3.52–3.89 (m, 2H, OCH_2, $D_1 + D_2$), 5.1 (s, 1H, D_2), 5.35 (s, 1H, D_1).

^{19}F NMR: δ = −77.1 (s, D_1) and −71.7 (s, D_2).

Dihydro-5-methoxy-4-methyl-4-trifluoromethyl-3(2*H*)-furanone (1c):
A solution of the aldehyde **4** (1 g, 4.7 mmol) in MeOH (30 mL) containing a few drops of conc. HCl was stirred overnight. H_2O (50 mL) was added and the solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with sat. $NaHCO_3$ solution (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. A part of the crude product was purified by preparative GC giving a pure sample of **1c** as a mixture of diastereomers in ratio of 87:13.

IR ($CHCl_3$): ν = 1780 cm^{-1}.

^1H NMR, mixture of the diastereomers D_1 (87%) and D_2 (13%): δ = 1.26 (s, 3H, D_1), 1.30 (s, 3H, D_2), 2.58 (AB system D_1, 2H, J = 18 Hz), 2.61 (AB system D_2, 2H, J = 17.3 Hz), 3.45 (s, 3H, D_2), 3.47 (s, 3H, D_1), 5.26 (s, 1H, D_2), 5.28 (s, 1H, D_1).

^{19}F NMR: δ = −77.1 (s, D_1) and −71.7 (s, D_2).

Ethyl 3-(1,3-Dithian-2-yl)-3-trifluoromethylbutanoate (5):
A solution of the aldehyde **4** (3 g, 14 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C. 1,3-propanedithiol (1.6 g, 14.8 mmol) was added and the resulting mixture was stirred 10 min before $BF_3 \cdot OEt_2$ (0.9 mL, 7 mmol) was added dropwise via a syringe. The ice bath was removed and the reaction allowed to stir for 1 h at r.t. and refluxed for 4 h. After cooling, the solution was poured in 10% aq NaOH (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL) and dried ($MgSO_4$). After filtration, the solvent was removed at reduced pressure to give a crude oil which was distilled (Kugelrohr) to yield **5**; 3 g (70%); bp 190 °C/0.3 Torr.

IR (CCl_4): ν = 1720 cm^{-1}.

^1H NMR: δ = 1.23 (t, 3H, J = 7.1 Hz), 1.43 (s, 3H), 1.74–2.12 (m, 2H), 2.61–3.03 (m, 6H with AB system at 2.76, 2H, J = 15.7 Hz), 4.11 (q, 2H, J = 7.1 Hz), 4.75 (s, 1H).

^{19}F NMR: δ = −70 (s).

3-(1,3-Dithian-2-yl)-3-trifluoromethylbutanoic Acid (6):
A solution of the ester **5** (3 g, 9.9 mmol) in EtOH (40 mL) and H_2O (10 mL) containing KOH (1.6 g, 28.5 mmol) was refluxed for 6 h. After cooling, H_2O (50 mL) was added and the solution was washed with Et_2O. Aqueous layer was acidified with 10% HCl and extracted with $CHCl_3$ (2 × 40 mL) and the organic layer was dried ($MgSO_4$). After filtration, the solvent was evaporated at reduced pressure to afford the crude material which was purified by chromatography on silica gel using CH_2Cl_2/Et_2O (90:10) as eluent to give the acid **6** as white crystals; yield: 2.3 g (84.5 %); mp 115–116 °C.

IR (CCl_4): ν = 1700 cm^{-1}.

^1H NMR: δ = 1.47 (s, 3H), 1.78–2.14 (m, 2H), 2.83–2.99 (m, 6H with AB system at 2.86, 2H, J = 16.1 Hz), 4.71 (s, 1H).

^{19}F NMR: δ = −69.7 (s).

Dihydro-5,5-(1,3-dithian-2-yl)-4-methyl-4-trifluoromethyl-2(3*H*)-furanone (1d):
A solution of the acid **6** (1 g, 3.64 mmol) in anhydr. benzene (30 mL) was placed in a 100 mL 3-necked round-bottomed flask under Ar. $Pb(OAc)_4$ (1.61 g, 3.64 mmol) was added in small portions. The solution was refluxed for 2 h. After cooling, H_2O (50 mL) was added. The organic layer was washed with 10% NaOH (50 mL) and H_2O (30 mL) and dried ($MgSO_4$). After filtration and removal of the solvent under vacuum, the crude product was chromatographed on silica gel using CH_2Cl_2 as eluent to afford the lactone **1d** as white crystals; yield: 0.59 mg (60%); mp 88–89 °C.

IR (CCl_4): ν = 1800 cm^{-1}.

^1H NMR: δ = 1.53 (s, 3H), 1.93–2.22 (m, 2H), 2.79–2.90 (m, 4H with AB system at 2.88, 2H, J = 17.5 Hz), 3.37–3.55 (m, 2H).

^{19}F NMR: δ = −70.5 (s).

(1) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123.
Welch, J.T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.
(2) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha, Ltd., and Elsevier Biomedical Press: Amsterdam, 1982.
(3) Uneyama, K. *J. Synth. Org. Chem.* **1991**, *49*, 612.
(4) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha: Tokyo, 1974.
(5) Weissman, B.A.; Burke, T.R.; Rice, K.C.; Skolnick, P. *European J. Pharmacol.* **1984**, *105*, 195.
Klunk, W.E.; Covey, D.F.; Ferrendelli, J.A. *Mol. Pharmacol.* **1982**, *22*, 444.
Klunk, W.E.; Kalman, B.L.; Ferrendelli, J.A.; Covey, D.F. *Mol. Pharmacol.* **1982**, *23*, 511.
(6) Grimm, E.L.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 242.
Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034.
(7) Andreev, V.G.; Kolomiets, A.F.; Fokin, A.V. *J. Fluor. Chem.* **1992**, *56*, 259.
Hanzawa, Y.; Suzuki, M.; Sekine, T.; Murayama, T.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1991**, 721.
Fujiwara, J.; Arai, S.; Nishida, M.; Oyamada, M. *Jap. Patent* 02115161 (1990); *Chem. Abstr.* **1990**, *113*, 110935.
Kobayashi, Y.; Taguchi, T. *Jap. Patent* 62192329 (1988); *Chem. Abstr.* **1988**, *108*, 204229.
Kubota, T.; Aoyagi, R.; Sando, H.; Kawasumi, M.; Tanaka, T. *Chem. Lett.* **1987**, 1435.
Taguchi, T.; Kawara, A.; Watanabe, S.; Oki, Y.; Fukushima, H.; Kobayashi, Y.; Okada, M.; Ohta, K.; Iitaka, Y. *Tetrahedron Lett.* **1986**, *27*, 5117.
Seebach, D.; Renaud, P. *Helv. Chim. Acta.* **1985**, *68*, 2342.
Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1984**, 1815.
(8) Poulter, C.D.; Satterwhite, D.M. *Biochemistry* **1977**, *16*, 5470.
(9) Carman, L.; Kwart, L.D.; Hudlicky, T. *Synth. Commun.* **1986**, *16*, 169.
(10) Nakada, Y.; Endo, R.; Muramatsu, S.; Ide, J.; Yura, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1511.
(11) Blazejewski, J.C.; Haddad, M.; Wakselman, C. *J. Fluor. Chem.* **1991**, *52*, 353.
(12) Poulter, C.D.; Hughes, J.M. *J. Am. Chem. Soc.* **1977**, *99*, 3830.
(13) Mihailovic, M.L.; Cekovic, Z.; Maksimovic, Z.; Jeremic, D.; Lorenc, L.; Mamuzic, R.I. *Tetrahedron* **1965**, *21*, 2799.