Synthesis of optically active γ-lactones and dopants for ferroelectric liquid crystals possessing a trifluoromethyl group

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Abstract

A series of *trans*- and *cis*-γ-lactones with high optical purity have been prepared from the lactonization of (*S*)-(−)-2-(trifluoromethyl)-4-pentenoic acid (>94% *ee*) under acidic conditions. These materials have been transformed into new types of dopant for ferroelectric liquid crystals possessing a trifluoromethyl group.

Introduction

The utility of optically active heterocycles with a trifluoromethyl group as bioactive materials and synthetic intermediates of functionalized materials has received extensive attention in recent years [1, 2]. In the field of ferroelectric liquid crystals (FLCs) and/or chiral dopants for FLCs, we have reported that a fluoroalkyl group attached to the stereo-genic center may increase the polarization and decrease the viscosity [3–6].

We report herein the synthesis of optically active γ-lactones with a trifluoromethyl group based on heterocyclization and the synthesis of new dopants for ferroelectric liquid crystal derived from these γ-lactones. Measurements of spontaneous polarization and phase-transition temperatures for these dopants are also reported.

To achieve the desired synthesis, we investigated direct lactonization (Scheme 1). First, we prepared (*S*)-(−)-2-(trifluoromethyl)-4-pentenoic acid (**1**) [lit. values [7]: $[\alpha]_D^{21}$ −9.77° (*c* 1.13, MeOH), >94% *ee*] and (*R*)-(+)-ethyl 2-(trifluoromethyl)-4-pentenate [lit. values [7]: $[\alpha]_D^{21}$ +9.34° (*c* 1.10, MeOH), >94% *ee*) from the enzymatic resolution of the corresponding acetate derivative. Lactonization [8–10] mediated by acid catalysis (conc. H_2SO_4) of (*S*)-(−)-2-(trifluoromethyl)-4-pentenoic acid (**1**) [lit. value [7]: $[\alpha]_D^{21}$ −9.77° (*c* 1.13, MeOH), >94% *ee*] proceeded via exocyclic ring closure, producing *trans*- [$[\alpha]_D^{21}$ +15.07° (*c* 0.726, $CHCl_3$), >94% *ee*, >98% *de*] and *cis*-γ-lactone [$[\alpha]_D^{21}$ −6.14° (*c* 0.934, $CHCl_3$), >94% *ee*, >97% *de*] (*trans*/*cis* = 35:65) and in 40% yield. It was possible to separate these stereoisomers by column chromatography on silica gel. The resulting γ-lactones **2** were then converted to the target furanose **3**, the core unit of the dopants for ferroelectric liquid crystals. The configuration of the γ-lactones was determined from the ^{1}H NMR coupling constants and molecular mechanics calculations.

PM 3 calculations employing multiconformer analysis of the lactones gave the global minimum conformations for *trans*- and *cis*-γ-lactones as shown in Fig. 1*. Comparison of the conformations gave the calculated coupling constants for the *cis* ($J_{Ha,Hb} < J_{Ha,Hc}$; $J_{Hb,Hd} < J_{Hc,Hd}$) and *trans* isomer ($J_{Ha,Hb} > J_{Ha,Hc}$; $J_{Hb,Hd} < J_{Hc,Hd}$). The ^{1}H NMR spectrum indicates a *cis* configuration for the major product ($J_{Ha,Hb}$ = 9.18 Hz, $J_{Ha,Hc}$ = 11.9 Hz; $J_{Hb,Hd}$ = 6.04 Hz, $J_{Hc,Hd}$ = 9.89 Hz) and *trans* for the minor product ($J_{Ha,Hb}$ = 10.0 Hz, $J_{Ha,Hc}$ = 6.20 Hz; $J_{Hb,Hd}$ = 6.28 Hz, $H_{Hc,Hd}$ = 7.23 Hz); are in accord with the calculated results.

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*Calculations were performed by MOPAC v 6.10 (PM 3) included in CAChe Worksystem (SONY/Tektronix Corporation) for the conformers obtained from the rigid search method with the key word 'PERCISE' and the eigenvector following minimization (EF) method. The final gradient norm was less than 0.01 kcal Å^{-1}.

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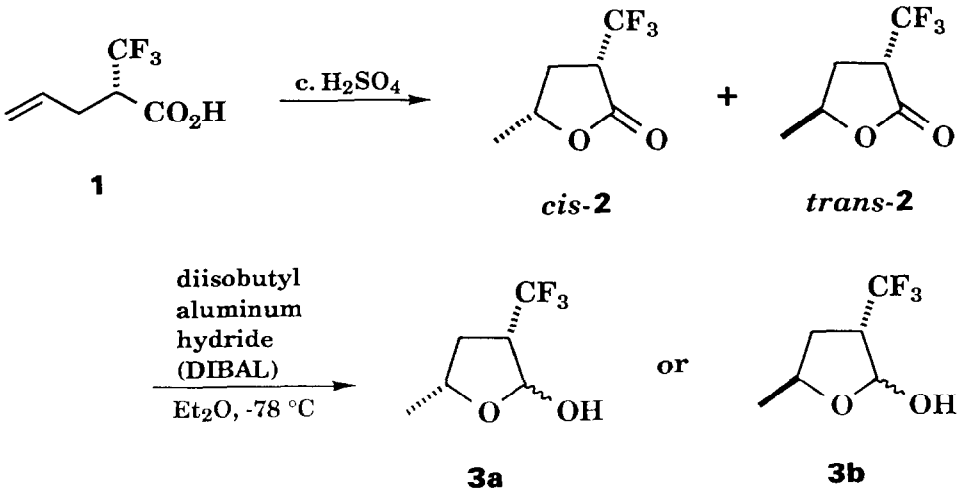


Scheme 1.

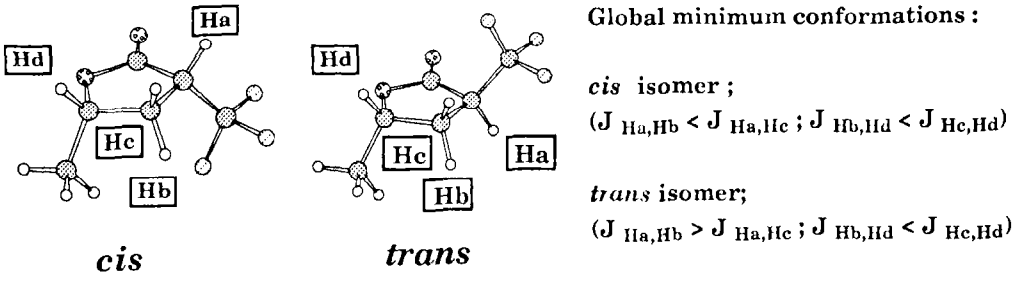
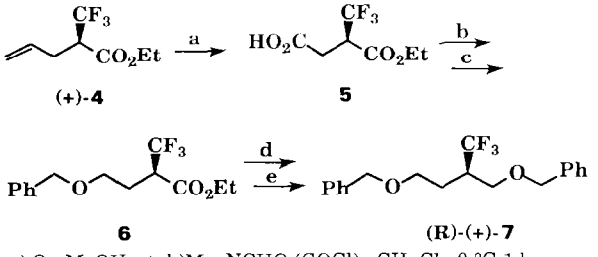


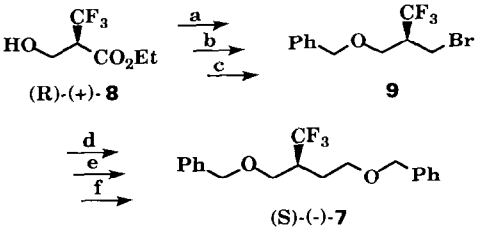
Fig. 1. Global minimum conformations for *trans*- and *cis*-γ-lactones.

We investigated the absolute configuration of (+)-ethyl 2-(trifluoromethyl)-4-pentenoate (**4**) recovered from the enzymatic hydrolysis of racemic ester as shown in Schemes 2 and 3. (+)-Ethyl 2-(trifluoromethyl)-4-pentenoate [$[\alpha]_D^{21}$ +9.34° (*c* 1.10, MeOH), >94% *ee*] was oxidized with O_3 and then reduced with $NaBH_4$ to give the corresponding hydroxy ester. After protection of the hydroxy group by conversion to the benzyl ether **6**, compound **6** was reduced with $LiAlH_4$ to give the corresponding alcohol. Protection of this alcohol with a benzyl group gave (+)-**7**, $[\alpha]_D^{21}$ +7.65° (*c* 1.04, MeOH). In addition, the results based on (*R*)-(+)-ethyl 2-(trifluoromethyl)-3-hydroxypropanoate with a known absolute configuration [lit. value [11]: $[\alpha]_D^{21}$ +3.65° (*c* 1.16, MeOH), >93% *ee*] in Scheme 3 support the absolute configuration of (−)-**7** as the (*S*)-isomer. These results establish that the absolute configuration of (−)-2-(trifluoromethyl)-4-pentenoic acid (**1**) is the (*S*)-configuration.



a) O_3,MeOH,r.t. b)Me_2NCHO,$(COCl)_2$,CH_2Cl_2,0 °C,1 h ; 2.3 equiv of $NaBH_4$,MeCN-THF,-20 °C c)$PhCH_2Br$,pyr.,Et_2O d) $LiAlH_4$,Et_2O e)$PhCH_2Br$,pyr.,Et_2O

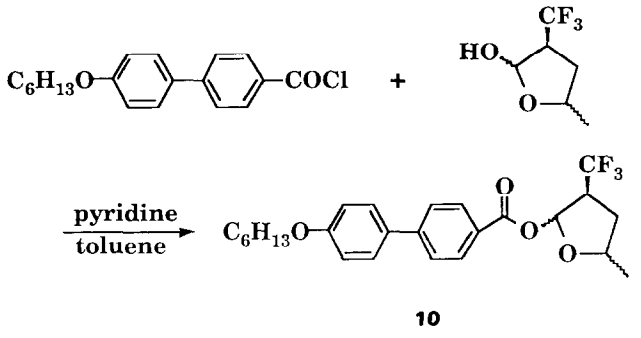
Scheme 2.



a) DHP, cat.p-TsOH, Et_2O; $LiAlH_4$, Et_2O b) NaH, $PhCH_2Br$, THF; cat.p-TsOH, MeOH c) CBr_4, Ph_3P, THF d) Mg, THF; $ClCO_2Et$ e) $LiAlH_4$, Et_2O f) $PhCH_2Br$, pyr., Et_2O

Scheme 3.

The next step was the preparation of dopants for ferroelectric liquid crystals possessing furanose **3**. Condensation of furanose **3** and 4'-hexyloxy-4-biphenyl carboxylic acid chloride in toluene was undertaken to give the dopant **10** for ferroelectric liquid crystals (Scheme 4).



10

Scheme 4.

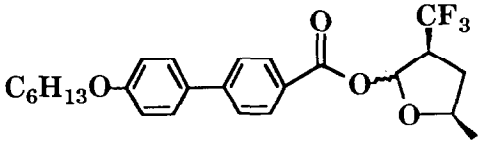
TABLE 1. Physical properties of liquid crystals

No.	Transition temp. (°C)				Response time (μs)	Tilt angle (°)
	S_C	S_A[a]	N[a]	I		
10a	43	65	69		665	11
10b	42	64	68		193	13

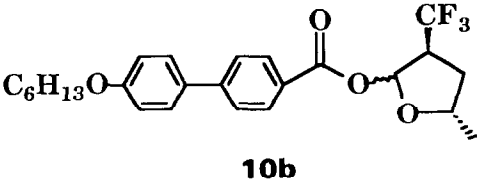
[a]Host LC: S_C, 51; S_A, 63; N, 69; I (°C). Cell thickness: 2 μm. Response time: $V_{p-p}=10$ V μm^{-1}, 30 °C, 0→50% transmittance change.

Ferroelectric liquid crystal properties

The preparation of homogeneously aligned liquid crystals of 2 μm thickness between conducting glass plates was achieved using a temperature gradient method [12]. The spontaneous polarization was measured by the triangular wave voltage method [13]. It was found that the spontaneous polarization increases monotonically as a function of T_{AC}–T without any irregularities. The phase sequence was determined by means of a polarization optical microscope with a hot stage (Mettler FP-82). The results of the chiral dopants for FLCs are listed in Table 1.



10a



10b

Experimental

General procedure

All commercially available reagents were used without further purification. Infrared (IR) spectra were obtained using a JASCO A-102 spectrometer and KBr pellets. The ^{1}H (200 or 500 MHz; internal Me_4Si) and ^{19}F (470 MHz; external C_6F_6) NMR spectra were recorded in $CDCl_3$ using Varian Gemini 200 or VXR 500 instruments. Specific rotations were recorded using a JASCO DIP-140 digital polarimeter. Yields quoted are those of the products actually isolated.

2-Trifluoromethyl-4-methyl-γ-lactone (2) (nc)

A solution consisting of (*S*)-(−)-(2-trifluoromethyl)-4-pentenoic acid, $[\alpha]_D^{21}$ −9.81 [(*c* 1.09, MeOH], >94% *ee*, 0.79 g, 4.7 mmol] and conc. H_2SO_4 (8 ml) was refluxed under a nitrogen atmosphere. After 5 h refluxing, the mixture was poured into ice–water (10 ml) and the oily materials generated extracted with diisopropyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and the solvent removed. The γ-lactone was separated in 40% yield by column chromatography on silica gel using a mixture of n-hexane ethyl acetate as eluent.

trans Isomer: $[\alpha]_D^{21}$ +15.07° (*c* 0.726, $CHCl_3$) >94% *ee*, >98% *de* ^{19}F NMR ($CDCl_3$) δ: 75.9 (d, $J_{F,H}=9.7$ Hz) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, d, $J_{H,H}=6.33$ Hz); 2.18 (1H, ddd, $J_{gem}=13.8$, $J_{H,H}=10.0$, 6.28 Hz); 2.62 (1H, ddd, $J_{gem}=13.8$, $J_{H,H}=7.23$, 6.19 Hz); 3.44 (1H, qdd, $J_{H,F}=9.50$, $J_{H,H}=10.0$, 6.20 Hz); 4.81 (1H, qdd, $J_{H,H}=6.34$, 6.27, 7.25 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 20.71 (s), 30.33 (s); 45.94 (q, $J=30.0$ Hz); 75.79 (s); 124.0 (q, $J=279$ Hz); 169.2 (s) ppm. Analysis: Calc. for $C_6H_7O_2F_3$: C, 42.87; H, 4.20%. Found: C, 42.61; H, 4.52%. HRMS: Calc. for $C_6H_7O_2F_3$: 168.0398. Found: 168.0405.

cis Isomer: $[\alpha]_D^{21}$ −6.14° (*c* 0.934, $CHCl_3$) >94% *ee*, >97% *de*. ^{19}F NMR ($CDCl_3$) δ: 76.2 (d, $J_{HF}=8.3$ Hz ppm). ^{1}H NMR ($CDCl_3$) δ: 1.49 (3H, d, $J_{H,H}=6.15$ Hz); 2.03 (1H, ddd, $J_{gem}=13.0$; $J_{H,H}=9.18$, 6.04 Hz); 2.68 (1H, dd, $J_{H,H}=11.9$; 9.89 Hz); 3.50 (1H, qdd, $J_{H,F}=8.6$, $J_{H,H}=11.9$, 9.18 Hz); 4.63 (1H, qdd, $J_{H,H}=6.19$, 9.85, 6.04 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 20.70 (s); 31.32 (s); 46.00 (q, $J=30.7$ Hz); 75.12 (s); 123.8 (q, $J=277$ Hz); 169.1 (s) ppm. Analysis: Calc. for $C_6H_7O_2F_3$: C, 42.87; H, 4.20%. Found: C, 42.97%; H, 4.11%. HRMS: Calc. for $C_6H_7O_2F_3$: 168.0398. Found: 168.0387.

(3S, 5R)-2-Hydroxy-5-methyl-3-trifluoromethyltetrahydrofuran (3a) (nc)

To a solution of *cis*-γ-lactone (1.07 g, 6.36 mmol) and diethyl ether (20 ml) under a nitrogen atmosphere was added diisobutyl aluminum hydride in hexane (0.93

M, 7 ml, 6.51 mmol) at −78 °C. After 6 h stirring, the reaction was quenched with H_2O and then 1 N HCl (50 ml) was added to the mixture. The oily materials formed were extracted with diethyl ether, and then the extract was washed with saturated aq. $NaHCO_3$ and brine. On removal of the solvent, the title material was separated in 80% yield by column chromatography on silica gel; $[\alpha]_D^{21}$ −23.38° (*c* 0.011, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.32 (3H, d, $J_{H,H}$=6.10 Hz); 1.60 (2H, ddd, $J_{H,H}$=8.48; 9.85, 12.88 Hz); 2.32 (2H, ddd, $J_{H,H}$=5.49, 7.90, 12.8 Hz); 2.85–3.00 (1H, m); 3.10–4.00 (1H); 4.43 (1H, ddq, $J_{H,H}$=5.87, 9.85, 5.87 Hz); 5.61 (1H, d, $J_{H,H}$=2.20 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 19.70 (s); 33.08 (q, *J*=2.13 Hz); 52.10 (q, *J*=27.5 Hz); 74.57 (s); 97.52 (q, *J*=3.81 Hz); 126.5 (q, *J*=277 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 92.5 (d, $J_{F,H}$=10.7 Hz) ppm. Analysis: Calc. for $C_6H_9O_2F_3$: C, 42.36; H, 5.33%. Found: C, 42.64; H, 5.17% HRMS: Calc. for $C_6H_9O_2F_3$: 170.0555. Found: 170.0561.

*(3S, 5S)-2-Hydroxy-5-methyl-3-trifluoromethyltetrahydrofuran (**3b**) (nc)*

In the above reaction, *trans*-γ-lactone (0.57 g, 3.37 mol) and DIBAL in hexane (0.93 M, 3.8 ml, 3.53 mmol) were used, and then worked-up similarly to give the title material in 77% yield; $[\alpha]_D^{21}$ −17.67° (*c* 0.010, $CHCl_3$) ^1H NMR ($CDCl_3$) δ: 1.37 (3H, d, $J_{H,H}$=6.35 Hz); 1.99 (1H, ddd, $J_{H,H}$=7.67; 9.16, 13.43 Hz); 2.24 (1H, ddd, $J_{H,H}$=3.66, 6.84, 13.43 Hz); 2.88–2.98 (1H, m); 3.10–4.00 (1H); 4.58 (1H, tq, $J_{H,H}$=6.69, 6.10 Hz); 5.54 (1H, d, $J_{H,H}$=1.95 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ: 22.78 (s); 31.75 (q, *J*=1.96 Hz); 51.43 (q, *J*=27.1 Hz); 76.53 (s); 97.85 (q, *J*=3.61 Hz); 126.5 (q, *J*=278 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 91.7 (d, $J_{F,H}$=10.7 Hz) ppm. Analysis: Calc. for $C_6H_9O_2F_3$: C, 42.36; H, 5.33%. Found: C, 42.61; H, 5.59%.

*(3S, 5R)-2-(4‴-Hexyloxybiphenyl)-4″-carbonyloxy]-3-trifluoromethyl-5-methyltetrahydrofuran (**10a**) (nc)*

To a solution of 4′-hexyloxy-4-biphenylcarboxylic acid chloride (0.34 g, 1.1 mmol) and (3*S*, 5*R*)-2-hydroxy-5-methyl-3-trifluoromethyltetrahydrofuran (***3a***) (0.17 g, 1.0 mmol) in toluene (5 ml) was added pyridine (2 ml) and the whole stirred for 10 h at room temperature. After quenching with 3 N HCl, the oily materials generated were extracted with diethyl ether. The extract was washed with saturated aq. $NaHCO_3$ and brine. On removal of the solvent, the title material was isolated by column chromatography on silica gel. ^1H NMR ($CDCl_3$) δ: 0.92 (3H, t, $J_{H,H}$=6.9 Hz); 1.20–1.90 (9H, m); 1.39 (3H, d, $J_{H,H}$=6.1 Hz); 2.47 (1H, ddd, $J_{H,H}$=5.8, 9.1, 13.0 Hz); 3.27 (1H, dtq, $J_{H,H}$=1.9, 9.0, 9.0 Hz); 4.01 (2H, t, $J_{H,H}$=6.5 Hz); 4.48 (1H, ddq, $J_{H,H}$=5.8, 9.8, 5.8 Hz); 6.67 (1H, d, $J_{H,H}$=2.0 Hz); 6.99 (2H, d, $J_{H,H}$=8.7 Hz); 7.56 (2H, d, $J_{H,H}$=8.7 Hz); 7.64 (2H, d, $J_{H,H}$=8.3 Hz); 8.06 (2H, d, $J_{H,H}$=8.4 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ; 92.4 9d, $J_{F,H}$=9.3 Hz) ppm. HRMS: Calc. for $C_{25}H_{29}O_4F_3$ (M^+): 450.2018. Found: 450.2011.

*(3S, 5S)-2-(4‴-Hexyloxybiphenyl-4″-carbonyloxy]-3-trifluoromethyl-5-methyl tetrahydrofuran (**10b**) (nc)*

In the above reaction, 4′-hexyloxy-4-biphenylcarboxylic acid chloride (0.34 g, 1.1 mmol) and (3*S*, 5*S*)-2-hydroxy-5-methyl-3-trifluoromethyltetrahydrofuran (**3b**) (0.17 g, 1.0 mmol) were used and the reaction mixture then worked-up similarly. ^1H NMR ($CDCl_3$) δ: 0.92 (3H, t, $J_{H,H}$=6.9 Hz); 1.00–2.20 (12H, m); 2.42 (1H, ddd, $J_{H,H}$=3.3, 7.0, 13.6 Hz); 3.10–3.40 (1H, m); 4.01 (2H, t, $J_{H,H}$=6.5 Hz); 4.46 (1H, tq, $J_{H,H}$=6.5, 6.5 Hz); 6.65 (1H, s); 6.99 (2H, d, $J_{H,H}$=8.7 Hz); 7.56 (2H, d, $J_{H,H}$=8.8 Hz); 7.63 (2H, d, $J_{H,H}$=8.5 Hz); 8.06 (2H, d, $J_{H,H}$=8.4 Hz) ppm. ^{19}F NMR ($CDCl_3$) δ; 92.4 (d, $J_{H,F}$=9.8 IIz) ppm. HRMS: Calc. for $C_{25}H_{29}O_4F_3$ (M^+): 450.2018. Found: 450.2024.

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