Pd-C Assisted Synthesis of cis-2,4-Disubstituted γ-Butyrolactones and their Properties for Ferroelectric Liquid Crystals

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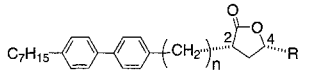
Abstract: *Cis* isomers of optically active 2,4-disubstituted γ-butyrolactone, **1 - 4**, as chiral dopants for ferroelectric liquid crystals (FLCs) are synthesized in a stereoselective manner via a Pd-C catalyzed hydrogenation of the *endo* CC double bond isomers of (4*R*)-2,4-disubstituted γ-butyrolactone, **23**, **19**, **20**, and **21**, respectively. The synthesis involved a novel *exo* to *endo* isomerization of the CC double bond effected by Pd-C in the absence of hydrogen.

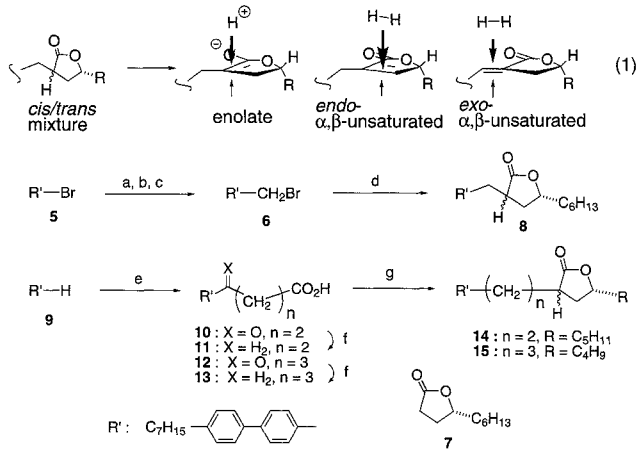
With increasing interest in the electro-optical devices using ferroelectric liquid crystals (FLCs), many materials have been developed to elucidate the switching mechanism of FLC and to achieve its high speed response.[1] In the previous paper, we reported that optically active *cis*-2,4-disubstituted γ-butyrolactone **1** was an excellent chiral dopant for FLC possessing larger spontaneous polarization (Ps)[1] which had higher speed response than its *trans* isomer.[2] In an extension of the previous study, we found the derivatives of **1** with a different chain length between the core part and the chiral lactone part were of interest in view of the structure and the FLC property relationship. Furthermore, an efficient method for the synthesis of *cis*-2,4-disubstituted γ-butyrolactones remained to be developed. In this paper, we wish to report a highly stereoselective route towards the syntheses of optically active *cis*-2,4-disubstituted γ-butyrolactones **1 - 4**. The key to the present study was a regioselective CC double bond isomerization (*exo* to *endo*) effected by Pd-C. Their FLC properties are briefly described.



1 : *cis*-(2*R*, 4*R*), n = 0, R = *n*-C_7H_{15}
2 : *cis*-(2*S*, 4*R*), n = 1, R = *n*-C_6H_{13}
3 : *cis*-(2*S*, 4*R*), n = 2, R = *n*-C_5H_{11}
4 : *cis*-(2*S*, 4*R*), n = 3, R = *n*-C_4H_9

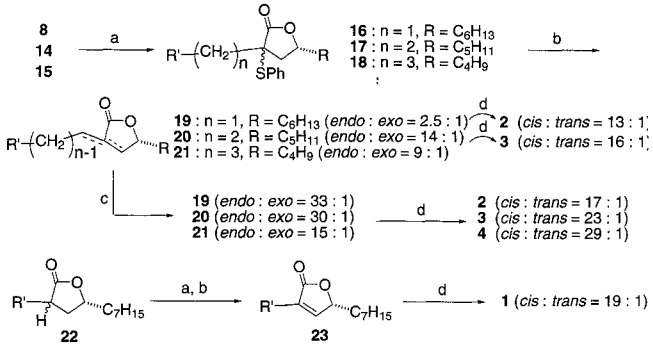
Our synthetic plan was an initial preparation of a mixture of *cis* and *trans* γ-butyrolactones, and subsequent conversion of the mixture into the *cis*-isomer. In this process, it seemed to be possible to trap the lactone enolate under kinetic conditions or a hydrogenation of an *endo*/*exo* mixture of the α,β-unsaturated derivative (eq 1). A high *cis*-selectivity would be obtained by a hydrogenation of the *endo*-isomer where the sterically bulky C4 substituent hindered the α-face. The *cis* and *trans* mixture **8** having one methylene group between the core part and the chiral part was synthesized by coupling of the bromide **6**, prepared from 4-*n*-heptyl-4'-bromobiphenyl (**5**), with the carbanion of (*R*)-4-*n*-hexyl-4-butanolide (**7**)[3] (Scheme 1). The mixture **14** with a two-methylene linkage was synthesized starting from the carboxylic acid **10**, prepared by Friedel-Crafts acylation of 4-*n*-heptylbiphenyl **9** with succinic anhydride. The carboxylic acid **11**, afforded by the reduction of **10** with Et_3SiH[4], was coupled with (*R*)-1,2-epoxyheptane[5] to give **14**. The mixture **15** with a three-methylene linkage was prepared in the same manner as that of **14**.

The α,β-unsaturated derivatives of **1 - 4** were prepared by sulfination of the lactones and desulfoxide (Scheme 2). The elimination step was non-stereoselective to give a mixture of α,β-unsaturated γ-butyrolactones **19**, **20**, and **21** and their *endo*/*exo*[6] ratios were 2.5/1, 14/1, and 9/1, respectively. The α,β-unsaturated γ-butyrolactone **23** was prepared



Scheme 1. a) *n*-BuLi, *N*-formyl pipelidine, THF, -78 °C to room temperature, 12 h (67 %). b) $NaBH_4$, MeOH, room temperature, 12 h (97 %). c) PBr_3, Et_2O, room temperature, 24 h (quant). d) LDA, **7**, HMPA, THF, -78 °C to room temperature, 2 (58 %). e) Succinic anhydride for **10**, glutaric anhydride for **12**, $AlCl_3$, CH_2Cl_2, 0 °C 3 h (95 %). f) Et_3SiH, TFA, room temperature, 48 h (82 - 84 %). g) i) LDA (2 eq.), (*R*)-1,2-epoxyheptane for **14**, (*R*)-1,2-epoxyhexane for **15** , THF, -78 °C to room temperature, 2 h. ii) conc. H_2SO_4 (cat), reflux, 2 h (59 - 60 %).

from **22**[2c] in a similar manner as above. Initial attempts to hydrogenate the mixture **19** (*endo*/*exo* = 2.5/1) with Pd-C (10 mol%) in AcOEt at room temperature gave the *cis*/*trans* mixture **2** in 13/1 ratio, much better *cis*-selectivity than that achieved with the trap of the lactone enolate.[7] The *cis*-selectivity decreased when pure *exo*-**19** was hydrogenated (*cis*/*trans* = 7/1). These results suggest that the hydrogenation of the *endo* isomer provides higher *cis*-selectivity (1,2-stereocontrol by the C4 substituent) than that of the *exo* isomers (1,3-stereocontrol). Therefore, we turned our attention to the conversion of the mixtures **19-21** into the corresponding *endo* isomers.



Scheme 2. a) LDA, PhSSPh, THF, 0 °C, 3 h (80 - 95 %). b) *m*CPBA, toluene, reflux, 2 h (94 - 95 %). c) Ar, Pd-C (50 mol%), AcOEt, room temperature, 120 - 192 h (quant) d) H_2, Pd-C (10 mol%), AcOEt, room temperature, 30 min (85 - 96 %).

***Exo* to *endo* isomerization of α,β-unsaturated γ-butyrolactones and the synthesis of *cis*-γ-butyrolactones 1 - 4.** Attempts to isomerize the mixture **19** (*endo*/*exo* = 2/1) using several bases (1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), *endo*/*exo* = 1/1.7; $NaHCO_3$, 1/1.5) were unsuccessful. We, unexpectedly, found that Pd-C[8] under Ar in the absence of hydrogen catalyzed the conversion of the mixture **19** (*endo*/*exo* = 2.5/1) to the endo-rich mixture **19** (*endo*/*exo* = 33/1) (Table

1). The other Pd catalysts such as Pd-black, $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ were not effective for the present isomerization. Charcoal was also tested and found to be similarly ineffective. The reaction using methanol-*d* as the solvent gave the 15/1 mixture in which no deuterium atom was incorporated. This indicates that neither enolization of the lactone nor generation of an anionic species was involved in the reaction. The reaction was assumed to proceed via a 1,3-hydride migration from the β hydrogen of the *exo* isomer. The treatment of the other substrates, **20** (*endo/exo* = 14/1) and **21** (*endo/exo* = 9/1), also gave the *endo*-rich mixtures, **20** (30/1) and **21** (15/1), respectively. Hydrogenation of the resulting *endo*-rich mixture **19** (*endo/exo* = 33/1) with H_2/Pd-C afforded the *cis*-γ-butyrolactone **2**[9] in 85% yield (*cis/trans* = 17/1). That no *endo/exo* isomerization took place under the hydrogenation reaction conditions was ascertained by the fact that hydrogenation of the *exo*-isomer (the reaction completed within 9 min) is much faster than that of the *endo*-isomer (31 min), and that no isomerized product was detected by ^1H NMR during the hydrogenation of both the *exo*- and *endo*-isomers. Therefore, the products ratio clearly reflects the results from the hydrogenation of the *endo*-isomer. Finally, the *cis*-γ-butyrolactones **3**[10] (*cis/trans* = 23/1) and **4**[11] (*cis/trans* = 29/1) were prepared stereoselectively from **20** and **21** in a similar manner to that of **19**. The *cis*-γ-butyrolactone **1** (*cis/trans* = 19/1) was also prepared stereoselectively from **23**. The minor isomer was completely removed by a single recrystallization to give a pure *cis* isomer.[12]

Table 1. The Pd-C catalyzed *exo/endo* olefin isomerization of **19**, **20**, and **21**

	Substrate	Catalyst	Solvent	Temp.	Time	*endo/exo*[a]
1	**19**[b]	Pd-C (50 mol%)	AcOEt	rt	21 h	9 : 1
2	**19**[b]	Pd-C (50 mol%)	AcOEt	rt	63 h	17 : 1
3	**19**[b]	Pd-C (50 mol%)	AcOEt	rt	192 h	33 : 1
4	**19**[b]	Pd-C (50 mol%)	AcOEt	60°C	17 h	17 : 1
5	**19**[b]	Pd-C (50 mol%)	toluene	rt	63 h	8 : 1
6	**19**[b]	Pd-C (50 mol%)	MeOH	rt	63 h	15 : 1
7	**19**[c]	charcoal	AcOEt	rt	72 h	2 : 1
8	**19**[c]	Pd-black(50 mol%)	AcOEt	rt	96 h	2 : 1
9	**19**[c]	$Pd(OAc)_2$ (770 mol%)	AcOEt	rt	168 h	2 : 1
10	**19**[c]	$PdCl_2$ (270 mol%)	AcOEt	rt	264 h	2 : 1
11	**19**[c]	$PdCl_2(PPh_3)_2$ (300 mol%)	toluene	rt	240 h	2.6 : 1
12	**19**[c]	$Pd(PPh_3)_4$ (200 mol%)	toluene	rt	240 h	2.7 : 1
13	**20**[d]	Pd-C (50 mol%)	AcOEt	rt	63 h	30 : 1
14	**21**[e]	Pd-C (200 mol%)	AcOEt	rt	120 h	15 : 1

[a]The ratios were determined by ^1H NMR. [b]*Endo/exo* = 2.5/1. [c]*Endo/exo* = 2/1. [d]*Endo/exo* = 14/1. [e]*Endo/exo* = 9/1.

Table 2. Characteristics and electro-optical properties of FLC mixtures containing 2 wt% of the γ-butyrolactone and 98wt% of mixture A[a] at 25°C

		Transition temp. /°C				Ps[b]	Tilt angle	Response[c]
	mp[d]	S_C*	S_A	N*	Iso	/nC cm^{-2}	/deg	/μs
1	107	66.2	77.7	88.0		+4.0	21.2	91.5
2	98	58.3	76.9	86.3		+1.6	18.9	100.0
3	121	64.4	77.2	87.9		+3.1	19.7	89.0
4	94	61.1	77.9	88.2		+2.1	21.0	109.0

[a]The host liquid crystalline mixture A is composed of 2-(4-hexyloxyphenyl)-5-octylpyrimidine (35wt%), 2-(4-nonyloxyphenyl)-5-heptylpyrimidine (10wt%), 2-(4-nonyloxyphenyl)-5-octylpyrimidine (20wt%), 2-(4'-pentylbiphenyl)-5-hexylpyrimidine (20wt%), and 2-(4'-heptylbiphenyl)-5-hexylpyrimidine (15wt%). Cr 4 S_C 65 S_A 79 N 90 I (°C). Cr: crystalline phase, S_C: smectic C phase, S_A: smectic A phase, N: nematic phase, I: isotropic liquid phase. [b]Ps was measured by the triangular wave method. [c]Response time was defined as the 0 to 90% change of transmission of light under the voltage of 10 $V_{p\text{-}p}\mu m^{-1}$. Cells were coated with polyimide rubbed in the same direction and their thickness was 2 μm. [d]Melting point of the γ-butyrolactone.

FLC Properties. Table 2 shows the characteristics and the electro-optical properties of the FLC mixtures containing **1** - **4**. Apparently, an odd-even effect of the methylene chain between the γ-butyrolactone group and the biphenyl group towards phase transition, the Ps and the response time was observed. Both compounds **1** and **3** comparatively showed large Ps's and high speed responses. The compound **2** showed a lower transition point, a smaller Ps, and a lower speed response than **1** and **3**. Values of phase transitions and ferroelectric properties of **4** were almost in-between **2** and **3**.

References and Notes

1 The response time of an FLC device depends on the Ps, the tilt angle, and the rotational viscosity. Goodby, J. W.; Blinc, R.; Clark, N. A.; Lagerwall, S. T.; Osipov, M. A.; Pikin, S. A.; Sakurai, T.; Yoshino, K.; Zenks, B. In *Ferroelectricity and Related Phenomena*; Taylor, G. W.; Shuvalov, L. A., Ed.; Gordon and Breach Science: Philadelphia, 1991; Vol. 7.

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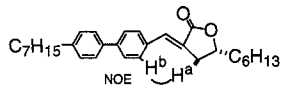
3 Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 381. The compound **7** were prepared as follows: (i) (*R*)-1,2-epoxyoctane,[5] dimethylmalonate, MeONa, MeOH, 40 °C, 4 h (80 %). (ii) $MgCl_2$, DMA, H_2O (1 drop), 140 °C, 3.5 h (quant.).

4 West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* 1973, *38*, 2675.

5 (*R*)-1,2-epoxyalkanes were prepared from (*R*)-epichlorohydrin (>98%ee).[2c] We thank Daiso Co., Ltd., for kindly providing (*R*)-epichlorohydrin.

6 The olefin geometry of *exo*-**19** was assigned to be *Z* by the NOE experiments. Strong NOEs between H^a and H^b were observed.



7 We first examined the enolate trap experiments of the lactones **1-3**. Under both thermodynamic (DBU, toluene, 80 °C; *t*-BuOK, *t*-BuOH, 80 °C) and kinetic (lithium diisopropylamide (LDA), THF, -78 °C then HCl; LDA, THF, -78 °C then 2,6-di-*t*-butylphenol) conditions, satisfactory *cis*-selectivity was not observed (thermodynamic: *cis/trans* = 2.3-1/1, kinetic: *cis/trans* = 4.9-2.9/1) due to a flexible five-membered ring structure.[13]

8 Commercially available 10% Pd-C (Aldrich, 20,569-9) was used. Nakarai (259-28) and Merck (807104) were also effective for this transformation.

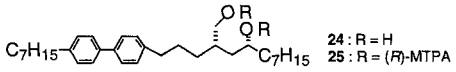
9 **2**: Colorless crystals, mp 98 °C; $[\alpha]^D_{19}$ +91.3° (*c* 0.4, $CHCl_3$).

10 **3**: Colorless crystals, mp 121 °C; $[\alpha]^D_{19}$ +21.9° (*c* 0.5, $CHCl_3$).

11 **4**: Colorless crystals, mp 94 °C; $[\alpha]^D_{26}$ +26.7° (*c* 0.6, $CHCl_3$).

12 Optical purity of the resulting *cis*-γ-butyrolactone **4** was estimated by Mosher's method[14] as follows. Reduction of *cis*-**4** with lithium aluminum hydride (LAH) and subsequent esterification of the resulting diol **24** with (*S*)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) chloride gave the di-(*R*)-MTPA-ester **25**. Enantiomeric excess of **25** was estimated to be 97% by ^1H NMR. This result shows that no epimerization at the γ-position of

the resulting *cis*-γ-butyrolactones occurred under the reaction conditions.



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