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The synthesis of enantiomerically pure novel liquid crystal compounds containing the bis(trifluoromethyl)alkanediol moiety

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Abstract—The synthesis of two types of novel liquid crystals, which possess the optically active bis(trifluoromethyl)alkanediol moiety has been accomplished using the lipase-catalyzed reaction and the Wittig reaction as key reactions.

1. Introduction

Anti-ferroelectric liquid crystal compounds (AFLCs), which possess a chiral 1,1,1-trifluoromethyl-2-alkanol moiety, have been acknowledged as important sources for high-speed switching devices.[1] Hiyama et al. reported unique AFLC molecules, which contain optically active bis(trifluoromethyl)alkanediols as the chiral core units.[2] It was shown that the anti-ferroelectric properties of the compounds is dependent on the alkyl chain length between the two hydroxyl groups. We were interested by this report and hence decided to synthesize novel analogues of the Hiyama-type AFLC compounds. We anticipated that it might be possible to modify the liquid crystalline property by the introduction of an aromatic group in the middle of the alkyl chain of the bis(trifluoromethyl)alkanediol core, because aromatic groups sometimes play an important role in the arrangement of molecules by both the π–π interactions and the planarity between the aromatic rings. We hence planned to synthesise two types of such compounds as shown in Scheme 1. We herein report the successful preparation of enantiomerically pure novel bis(trifluoromethyl)-alkanediols units using lipase technology and the synthesis of novel Hiyama-type liquid crystalline compounds.

2. Result and discussion

Since a cumbersome resolution technique using HPLC with a chiral column was employed for the preparation of the bis(trifluoromethyl)alkanediols by Hiyama et al.,[2] we decided to refine the process of preparing the bis(trifluoromethyl)alkanediols in their enantiomerically pure forms using lipase technology. The lipase-catalyzed reaction is well recognized as a useful method for preparing optically active compounds in organic synthesis while the value of the reaction has recently been increased by its environmentally friendly nature.[3] In fact, we accomplished the synthesis of various types of 1,1,1-trifluoro-2-alkanols in their enantiomerically pure forms using the lipase-catalyzed reaction.[4,5]

The results of the retro-synthetic analysis for our target molecules are shown in Scheme 1. There are two key points for our synthesis; the first is realizing the practical resolution of the racemic 1,1,1-trifluoromethylalkanediol via the lipase-catalyzed reaction while the second is the synthesis of a bis(trifluoromethyl)alkanediol that possesses an aromatic ring in the center of the alkyl chain using the Wittig reaction protocol.

Our synthesis started with the preparation of 1-benzyloxy-8-bromooctane **5**, which was easily prepared from the partially benzyl protected 1,8-octanediol. Alcohol **5** was first converted to the corresponding mesylate and

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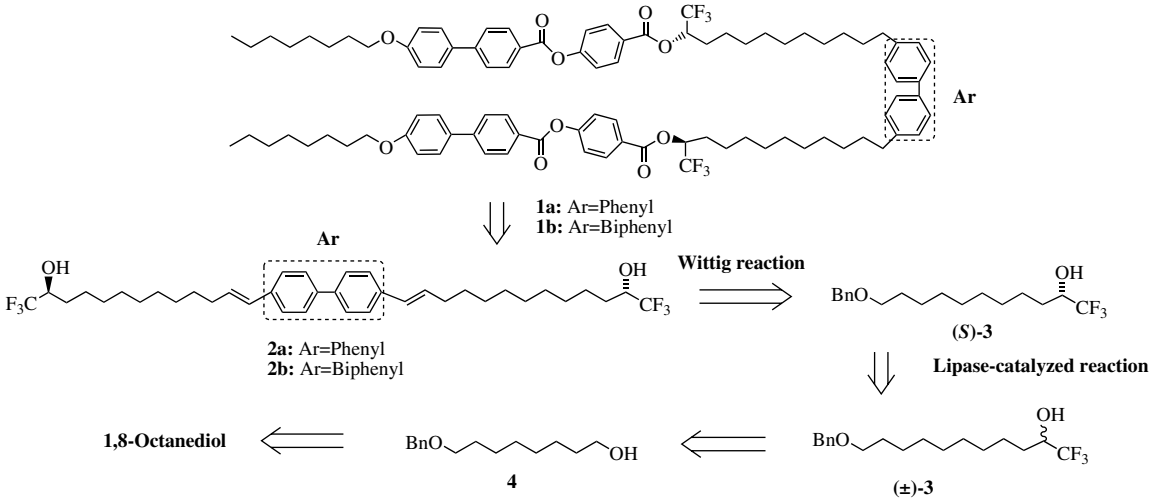


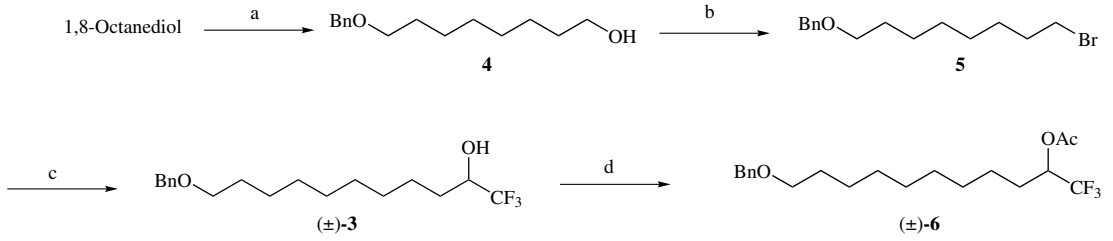
Scheme 1. Retrosynthetic analysis.

subsequent treatment with sodium bromide in a mixed solvent of acetone with dimethylformamide (1:1) gave **5** in 85% yield (two steps). Bromide **5** was then converted to the Grignard reagent, which was immediately subjected to a reaction with 2-trifluoromethyloxirane in the presence of 2 mol% of copper iodide in THF at 0 °C to form racemic 8-benzyloxy-1,1,1-trifluoromethyl-2-octanol **3**, which was finally acetylated to provide acetate (±)-**6** in 84% yield (three steps) (Scheme 2).

With the substrate of the enzymatic reaction in hand, we investigated the lipase-catalyzed hydrolysis reaction of (±)-**6**. We previously reported that *Candida antarctica* lipase (CAL) catalyzed the *trans*-esterification of racemic 1,1,1-trifluoro-2-alkanols with perfect enantioselectivity,[4,5] although the reaction required a long time to go to completion. Therefore, we tested the hydrolysis of acetate **6** using two types of commercial *Candida antarctica* lipases, Novozym 435[6] and CAL-B. These were immobilized using different supporting materials but from the same origin of the enzyme. Typically, the reaction was carried out as follows: to a mixture of (±)-**6** (from 1,8-octanediol, 235 mg, 0.68 mmol) in a mixed solvent of 6.8 mL of 0.1 M phosphate buffer (pH 7.2) and acetone (10:1) was added the Novozym (50 wt% vs substrate). The mixture was then stirred at rt. Extraction with ethyl acetate and subsequent purification using silica gel flash chromatography gave (*S*)-**3** and acetate (*R*)-**6** unreacted in 32% and 41%, respectively (entry 1). The enantiomeric excess of the product alcohol and unreacted acetate was determined by capillary GC using a chiral column (Chiraldex). As seen in Table 1, both Novozym 435 and CAL-B worked nicely with an excellent enantioselectivity being recorded. Also, remarkably high *E* values[7] were obtained for all the reactions.

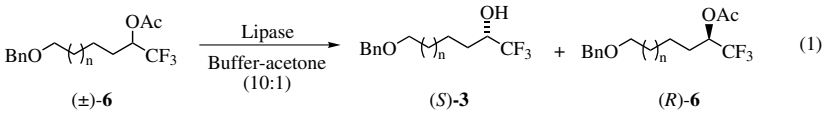
Conversion to the bis(trifluoromethyl)alkanediol **10** was accomplished using the Wittig reaction protocol (Scheme 3): The benzyl protecting group of (*S*)-**3** was first converted to the tertiary butyl dimethylsilyl group with the 2-hydroxyl group was protected as a benzyl ether (94%), which was then converted to aldehyde (*S*)-**7** by Swern oxidation in 85% yield. Aldehyde (*S*)-**7** was subjected to the Wittig reaction by treatment with bisphosphoniumylide **8** to give the corresponding diene (*S*,*S*)-**10a** in 62% yield. Diene (*R*,*R*)-**10b** was also prepared using the same sequence in a 46% overall yield.

The syntheses of the optically active liquid crystals **1a** and **1b** were accomplished following by Scheme 4. The benzyl protecting group of the 2-hydroxyl group of **10a** was first deprotected by hydrogenolysis and subjected to the esterification with *p*-benzyloxybenzoic acid to afford **11a** in 89% yield. The 4-benzyloxy group of **11a** was deprotected with the final esterification with octyloxyphenylbenzoic acid using EDC in the presence of DMAP as the base in CH_2Cl_2 giving **1a** in 67% yield (two steps).[8] Compound



Scheme 2. Reagents and conditions: (a) NaH, THF; BnBr, DMF; 54%; (b) MsCl, pyridine, CH_2Cl_2; NaBr, acetone–DMF; 84% (two steps); (c) Mg, THF; 2-(trifluoromethyl)oxirane, CuI, THF; 84% (two steps); (d) AcCl, pyridine, CH_2Cl_2; quant.

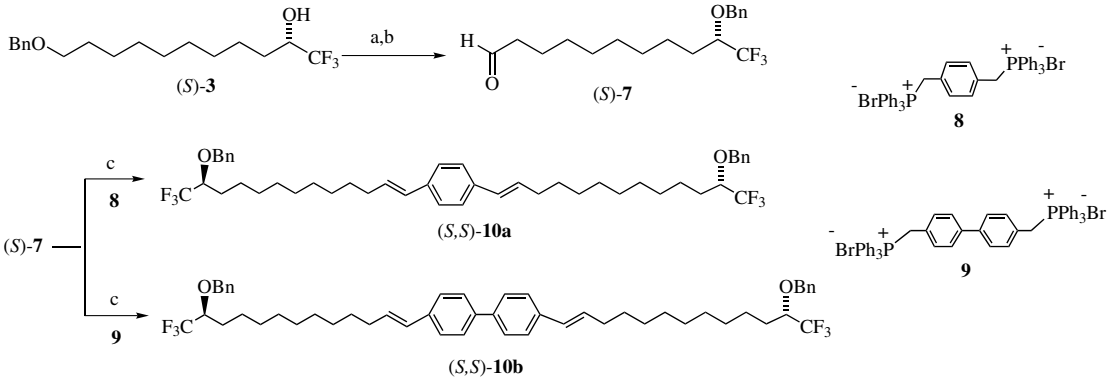
Table 1. Resolution of 1,1,1-trifluoro-2-undecanol by CAL-catalyzed hydrolysis reaction



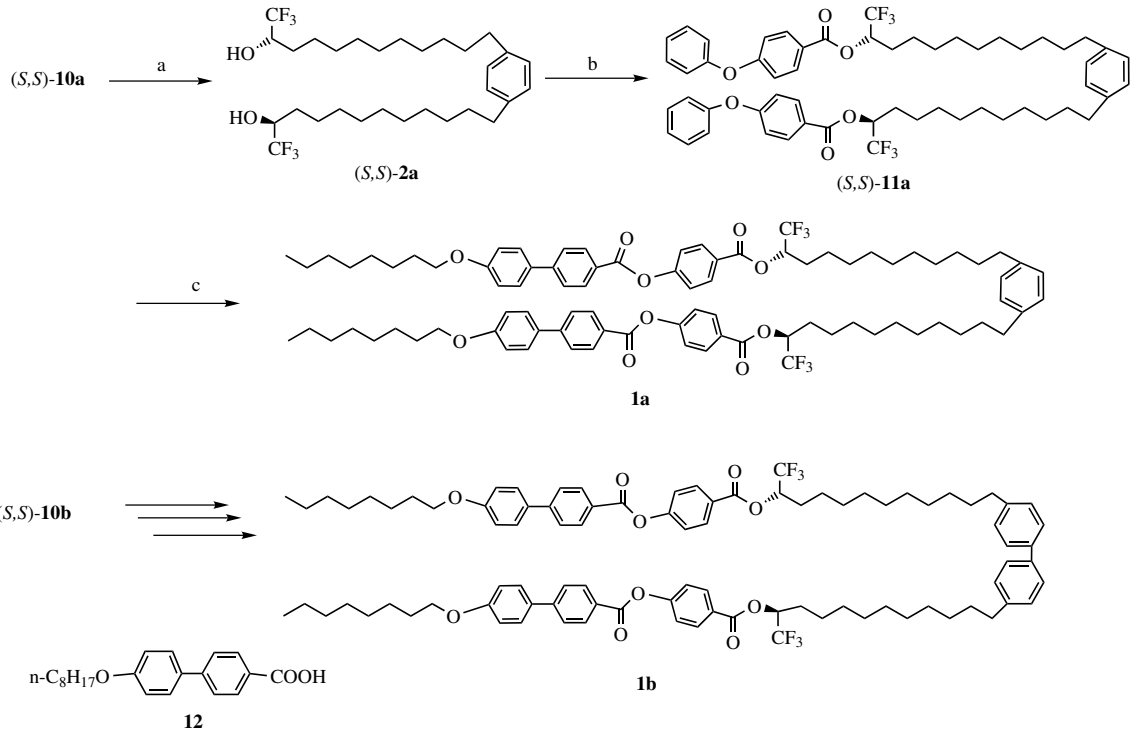
(±)-**6** (*S*)-**3** (*R*)-**6**

Entry	*n* (substrate)	Lipase[a]	Time (h)	Conv. (%)	Ee of (*S*)-**3**	Ee of (*R*)-**6**	*E*
1	*n* = 8 (from 1,8-octanediol)	Novozym 435	6	26	>99	69	>990
2		CAL B	18	45	>99	84	>530
3	*n* = 6 (from 1,6-hexanediol)	Novozym 435	6	40	>99	84	>530
4		CAL B	4	44	>99	45	>260

[a] Candida antarctica lipase.



Scheme 3. Reagents and conditions: (a) H_2, Pd/C, ethanol; TBSCl, imidazole, DMAP, CH_2Cl_2; 94% (two steps); (b) 1, NaH, THF; BnBr, DMF; 2, TBAF, THF; 3, Swern Oxi. 85% (three steps); (c) *n*-BuLi, THF; then **8** or **9**; **10a** 62%, **10b** 58%.



Scheme 4. Reagent and conditions: (a) H_2, Pd/C, ethanol; BCl_3, THF; 90% (two steps); (b) $BnOC_6H_4COOH$, DCC, DMAP, CH_2Cl_2 89%; (c) H_2, Pd/C, ethanol; EDC, DMAP, CH_2Cl_2; 67% (two steps).

1a showed only the SmA phase at 135 °C; unfortunately, no desired anti-ferroelectric property was observed. Compound **1b** was also synthesized from **10b** through the same reaction sequences as illustrated in Scheme 4.

Compound **1b** also showed no desired anti-ferroelectric property, though it showed the SmA phase at 170 °C.[9] Since our molecules, **1a** and **1b**, should be less flexible, due to the existing aromatic ring at the center part of the core molecule, than the Hiyama-type liquid crystal molecules, it was concluded that the flexibility of the core part contributed causing antiferroelectric property of this type of liquid crystal molecule.

3. Conclusion

In summary, we have synthesized two novel types of liquid crystalline compounds using lipase technology and the Wittig reaction as the key steps. Although the products showed only the SmA phase, we are still expecting that unique properties might be obtained by modification of the central aromatic group and proper combination of the side chain part. Further investigation into the synthesis of compounds, which possess the spirobicyclobutane moiety at the center of the molecules, are currently underway.

Acknowledgements

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8. Selected spectra data for **1a**: $[\alpha]_D^{25} = -30.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ) 0.82 (6H, t, $J = 6.1$ Hz), 1.17–1.22 (44H, m), 1.33–1.40 (4H, m), 1.50 (4H, d, $J = 2.44$ Hz), 1.70–1.83 (8H, m), 2.47 (4H, t, $J = 7.8$ Hz), 3.94 (4H, t, $J = 6.3$ Hz), 5.45–5.50 (2H, m), 6.93 (4H, d, $J = 8.3$ Hz), 7.00 (4H, s), 7.28 (4H, d, $J = 8.3$ Hz), 7.52 (8H, d, $J = 8.3$ Hz), 7.62 (4H, d, $J = 8.3$ Hz), 8.10 (4H, d, $J = 8.3$ Hz), 8.15 (4H, d, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 14.08, 22.64, 24.53, 26.03, 28.00, 29.07, 29.22, 29.35, 29.41, 29.45, 31.55, 31.80, 35.54, 70.07, 115.00, 122.07, 126.64, 128.19, 128.37, 130.81, 131.68, 140.02, 146.34, 155.31, 159.67, 164.34, 164.50; ^{19}F NMR (188 MHz, $CDCl_3$, δ) 84.76 (s); IR (neat, NaCl) 3860, 2920, 1730, 1600, 1160 and 890 cm^{-1}. Anal. Calcd for $C_{86}H_{104}F_6O_{10}$: C, 73.17; H, 7.43. Found: C, 73.20; H, 7.49. HRMS (FABMS): 1411.7612 (calcd for $C_{86}H_{104}F_6O_{10}$ 1411.730).
9. Selected spectra data for **1b**: $[\alpha]_D^{25} = -45.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ) 0.82 (6H, t, $J = 6.5$ Hz), 1.19–1.23 (48H, m), 1.51–1.57 (4H, m), 1.71–1.76 (4H, m), 1.78–1.84 (4H, m), 2.54 (4H, t, $J = 7.8$ Hz), 3.94 (4H, t, $J = 6.6$ Hz), 5.46–5.41 (2H, m), 6.93 (4H, d, $J = 8.3$ Hz) 7.14 (4H, d, $J = 7.8$ Hz), 7.41 (8H, d, $J = 8.3$ Hz), 7.52 (4H, d, $J = 8.8$ Hz), 8.10 (4H, d, $J = 8.8$ Hz), 8.15 (4H, d, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 14.10, 22.65, 24.53, 26.04, 27.07, 29.23, 29.35, 29.41, 29.46, 31.49, 31.82, 35.59, 68.16, 70.40, 115.01, 122,07, 126.31, 126.64, 126,77, 128.39, 128.72, 130.82, 131.69, 131.76, 138.46, 141.72, 146.39, 155.32, 159.67, 164.36, 164.52; ^{19}F NMR (188 MHz, $CDCl_3$, δ) 84.71 (s); IR (neat, NaCl) 3390, 2930, 1730, 1600, 1160 and 880 cm^{-1}. Anal. Calcd for $C_{92}H_{108}F_6O_{10}\cdot 2H_2O$: C, 72.51; H, 7.41. Found: C, 74.10; H, 7.66. HRMS (FABMS): 1487.7973 (calcd for $C_{86}H_{104}F_6O_{10}$ 1487.826).