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Five series of 3β-hydroxy-5-cholenic acid derived steryl benzoates and cinnamates were synthesized and their phase transition properties were characterized by differential scanning calorimetry and polarizing optical microscopy. Their thermal phase behavior is significantly different from that of the cholesterol-based analogues because of the polar side chain. The effects of the fluorination pattern of the phenyl group, the trans-double bond in the acyl moiety, the unsaturated or saturated B-ring, and the length of the terminal alkoxy group are discussed. Two cholesterol-derived cinnamate series were also prepared for comparison.

Keywords 3β-Hydroxy-5-cholenic acid; liquid crystals; mesomorphic; steroids

Introduction

Steroid derivatives belong to the first subfamily of liquid crystals (LCs) discovered in the 19th century [1]. Since then, numerous steroidal LCs have been synthesized [2,3]. Steroidal LCs are widely used as chiral dopants for industrial liquid-crystal mixtures in order to induce chirality in an achiral nematic phase [4]. Furthermore, as a newly emerged research area, steryl-containing hetero-dimers are found rich in novel mesogenic phases, for example, blue phases (BPs) and twist grain boundary (TGB) phases, presumably because of the strong chirality and the bulkiness of the steroidal moiety [5].

In contrast to the popular choice of esterification and etherification of the 3β-hydroxy group of commercial available cholesterol [3b,6] and other natural product sterols, for example, campesterol [7] and diosgenin [8], the structure–property relationship study on the steroidal moiety has attracted much less attention due to the difficulty of the chemical synthesis. There were only several reports on the modification of the 3β-substituent [3c,9] and structural features of the steroidal nucleus [10]. In particular for structure–property relationships of the alkyl side chain

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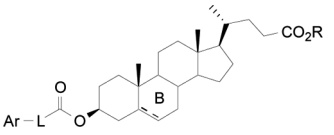


R = *n*-alkyl; Ar = fluorinated phenyl;
L = bond or -CH=CH-; B-ring: ¦¤5 or 5α-H

Scheme 1. Design of target compounds.

at C-17, most of the current knowledge came from Pohlmann *et al.*'s reports [7,11,12], dating back to 1971.

During our previous work on steroidal LCs, we noticed that the research on steroids with 24-carboxylate, that is, derivatives of 3β-hydroxy-5-cholenic acid is very limited [13]. Unlike sterols with a hydrocarbon side chain, 3β-hydroxy-5-cholenic acid can be structurally modified at both ends, which offers opportunities for design of new rod-like LCs. In addition, the 24-carboxyl group makes this template potentially useful in hetero-dimer synthesis [14].

To explore the mesogenic properties of this steroidal subfamily, we synthesized five representative derivative series from 3β-hydroxy-5-cholenic acid and characterized their phase transition behavior (Scheme 1). Benzoate and cinnamate were introduced as a part of the core structure. Effects of the terminal ester group, fluorine substitution on the phenyl group, the unsaturated or saturated B-ring, and the length of the terminal alkoxy group were investigated. Cholesteryl and cholestanyl polyfluoro-cinnamates were also synthesized and characterized for comparison.

Results and Discussion

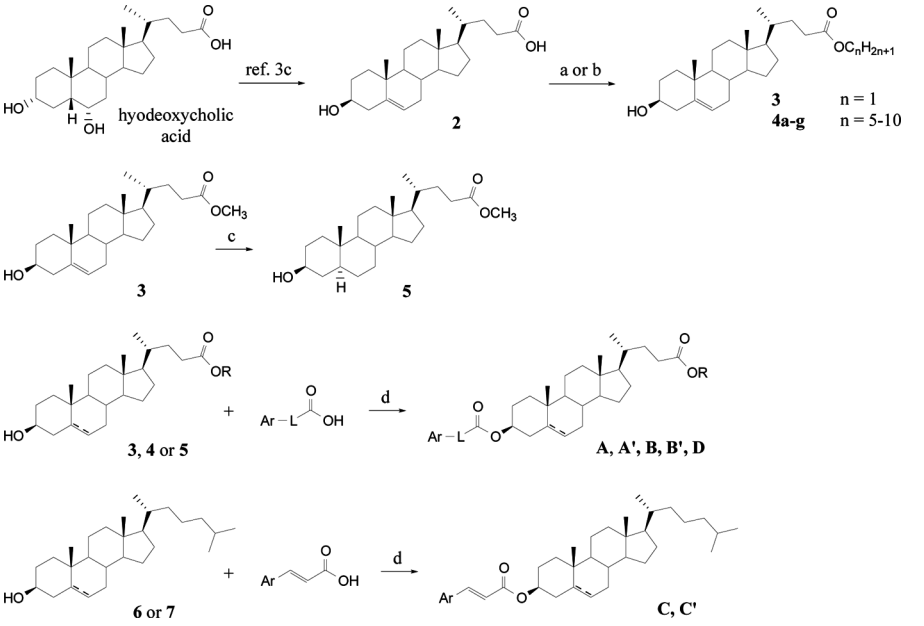
Compound Synthesis

The syntheses of target compounds are summarized in Scheme 2. 3β-Hydroxy-5-cholenic acid (**1**), prepared from hyodeoxycholic acid *via* an established method [3b], was converted to the methyl ester intermediate **2** under an acid-catalyzed condition. For ester intermediates containing a homologous alkoxy chain (**3a–g**), a nucleophilic substitution approach was proved suitable. Hydrogenation of Δ^5-ester **2** afforded the saturated methyl ester **4**. The above-obtained alkylated 3β-sterols **2, 3,** and **4** were reacted with polyfluoro-benzoic and cinnamic acids [15] to deliver the corresponding target series **A, A′, B, B′**, and **D**. In addition, cholesterol (**5**) and cholestanol (**6**) were reacted with polyfluoro-cinnamic acids to give the series **C** and **C′**, respectively.

Mesomorphic Properties

The phase transition temperatures of the target series are summarized in Tables 1, 2, and 3. All of the compounds are chiral nematic (N^*) mesogens.

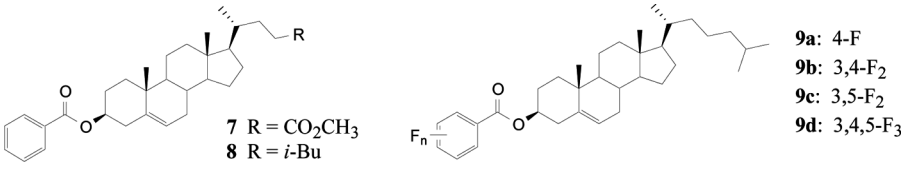
The compounds in series **A** exhibit enantiotropic or monotropic N^* phases (Table 1). As expected, *para*-fluorination is favorable for the mesophase formation and *meta*-fluorination is unfavorable. A comparison between series **A** and their cholesteryl benzoate analogues [13,16] reveals the unique effects of the side-chain methyl ester group. All of the compounds in series **A** have higher melting points than



Scheme 2. Synthesis of target series. *Reagents and conditions*: (a) MeOH, cat. H_2SO_4; (b) $C_nH_{2n+1}Br$ (n = 5–10), K_2CO_3, cat. 18-Crown-6, DMF; (c) H_2, Pd/C, MeOH; (d) DCC, cat. DMAP, THF.

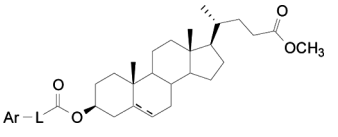
cholesteryl benzoates. Furthermore, the fluorination pattern of the benzoate moiety has a magnified impact on the mesomorphic properties of series **A**. Methyl 3β-benzoyloxy-5-cholenate (**7**, Cr 167–169 N* 171 I) [13] displays an enantiotropic N* phase in a much narrower temperature range than cholesteryl benzoate does (**8**, Cr 145.5 N* 178.5 I) [1]. However, the introduction of a *para*-fluorine surprisingly expands the mesomorphic temperature range to 70°C (Table 1, **A4**), comparable with that of cholesteryl 4-fluorobenzoate (**9a**, Scheme 3) (Cr 152–154 Ch 227 I) [13] (Figure 1). On the other hand, lateral fluoro-substitution in series **A** significantly reduces the mesomorphic temperature ranges. Although **A34, A35,** and **A345** have similar N*-I transition temperatures to that of cholesteryl benzoate LCs [16], their melting points are much higher, resulting in monotropic mesophases of **A35** and **A345**.

Likewise, the aromatic fluorination pattern of cinnamate moiety shows the same effects (series **B** and **C**, Figure 2). For methyl 3β-cholenate/cholesteryl 3,5- and 3,4-difluorocinnamates, moving a *meta*-fluorine to a *para*-position expands the mesogenic temperature range more for 3β-cholenate cinnamates. In the case of



Scheme 3. Structures of compounds **7, 8,** and **9**.

Table 1. Phase transition temperatures of series **A, A′, B** and **B′**



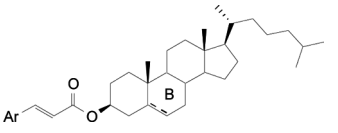
Entry	Ar	L	B-ring	Phase transition temperatures (°C)
A4	4-F	Bond	Δ^5	Cr 157.5 N* 232.0 I 227.7 N* 85.7 Recr
A34	3,4-F_2	Bond	Δ^5	Cr 189.8 N* 216.1 I 212.4 N* 136.0 Recr
A35	3,5-F_2	Bond	Δ^5	Cr 206.8 I 162.0 N* 92.2 Recr
A345	3,4,5-F_3	Bond	Δ^5	Cr 194.8 I 188.2 N* 149.3 Recr
A′4	4-F	Bond	5α-H	Cr 160.4 N* 215.8 I 210.5 N* 106.8 Recr
B34	3,4-F_2	−CH=CH−	Δ^5	Cr 172.7 N* 241.3 I 239.8 N* 130.6 Recr
B35	3,5-F_2	−CH=CH−	Δ^5	Cr 161.8 N* 180.2 I 175.2 N* 102.8 Recr
B345	3,4,5-F_3	−CH=CH−	Δ^5	Cr 196.7 N* 222.3 I 220.3 N* 145.8 Recr
B′34	3,4-F_2	−CH=CH−	5α-H	Cr 158.7 N* 224.6 I 222.6 N* 105.6 Recr
B′345	3,4,5-F_3	−CH=CH−	5α-H	Cr 170.1 N* 208.0 I 203.7 N* 116.2 Recr

Cr = crystal; N* = chiral nematic; I = isotropic.

3,4-difluoro- and 3,4,5-trifluorocinnamates, adding a *meta*-fluorine narrows the mesogenic temperature range of methyl 3β-cholenate cinnamates sharply but only slightly for cholesteryl cinnamates. The melting points of series **B** are higher than those of series **C** as well.

In contrast to the alkyl side chain of cholesteryl, the ester-tethered side chain of methyl cholenate is much more polar. Pohlmann *et al.* reported that replacing the terminal *iso*-propyl of cholesteryl acetate with a polar acetyl group significantly increases the melting point [11]. Similarly, the terminal ester group of benzoate **7** results in a higher melting point than its nonpolar analog **8**, most likely due to the increased

Table 2. Phase transition temperatures of series **C** and **C′**



Entry	Ar	B-ring	Phase transition temperatures (°C)
C34	3,4-F_2	Δ^5	Cr 148.4 N* 229.7 I 227.6 N* 104.3 Recr
C35	3,5-F_2	Δ^5	Cr 143.4 N* 188.1 I 186.3 N* 103.0 Recr
C345	3,4,5-F_3	Δ^5	Cr 149.4 N* 222.1 I 220.6 N* 112.2 Recr
C′34	3,4-F_2	5α-H	Cr 153.1 N* 222.8 I 220.9 N* 102.3 Recr
C′35	3,5-F_2	5α-H	Cr 154.4 N* 174.3 I 173.8 N* 121.5 Recr
C′345	3,4,5-F_3	5α-H	Cr 164.6 N* 209.8 I 209.5 N* 144.3 Recr

Cr = crystal; N* = chiral nematic; I = isotropic.

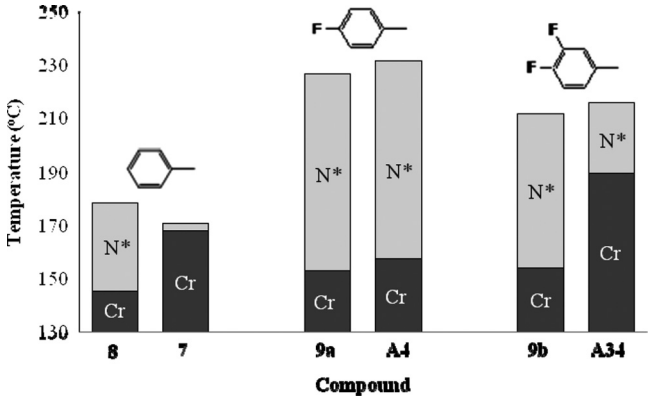


Figure 1. Comparison between phase transition properties of enantiotropic cholesteryl benzoates (**8, 9a, 9b**) and methyl 3β-benzoyloxy-5-cholenates (**7, A4, A34**).

dipole–dipole interactions. For fluorinated benzoates (**A, A′**) and cinnamates (**B, B′**), in addition to the various molecular length–breadth ratios [17,18], this change of the overall molecular polarity may also play an important role in the observed magnified favorable effect of *para*-fluorine and the unfavorable effect of *meta*-fluorine.

The effect of the cinnamic trans-double bond is apparent by comparing series **B** with **A**. Compounds in series **B** are all enantiotropic mesogens and have significantly broader mesogenic temperature ranges because of the extension of the rigid core structure. Cholesteryl cinnamates (series **C**) also have broader mesomorphic temperature ranges than cholesteryl benzoates (**9b–d**, Scheme 3).

Our previous study on cholesteryl/cholestanyl polyfluorobenzoates [16] showed that saturation of the Δ^5-double bond narrows mesomorphic temperature range. This is the case for most of the unsaturated/saturated compound pairs except **B345**/**B345′**. B-ring saturation uniformly reduces clearing points, but in terms of melting points, cholesterol- and methyl 3β-hydroxy-5-cholenate-derived compounds behave differently. In cholesterol-derived series, B-ring saturation reduces the mps of the benzoates and increases the mps of the cinnamates. However, the opposite trend

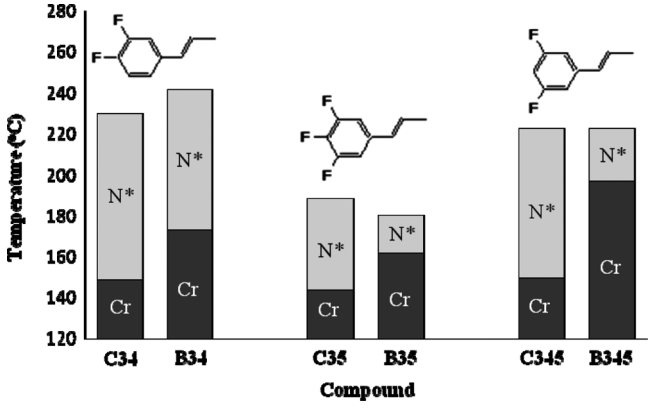
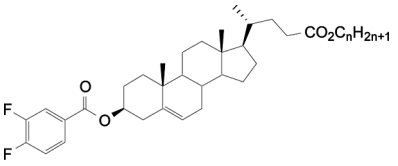


Figure 2. Comparison between phase transition properties of enantiotropic cholesteryl cinnamates (**C34, C35, C345**) and methyl 3β-cinnamoyloxy-5-cholenates (**B34, B35, B345**).

Table 3. Phase transition properties of series **D**



Entry	n	Phase transition temperatures (°C)
D1 (A34)	1	Cr 189.8 N* 216.1 I 212.4 N* 136.0 Recr
D5	5	Cr 158.0 I 152.2 N* 138.0 Recr
D6	6	Cr 131.2 N* 145.2 I 143.6 N* 104.3 Recr
D7	7	Cr 106.4 N* 137.4 I 135.9 N* 74.8 Recr
D8	8	Cr 114.6 N* 130.5 I 128.8 N* 82.1 Recr
D9	9	Cr 117.4 N* 125.3 I 122.5 N* 89.1 Recr
D10	10	Cr 121.4 I 119.3 N* 102.0 Recr

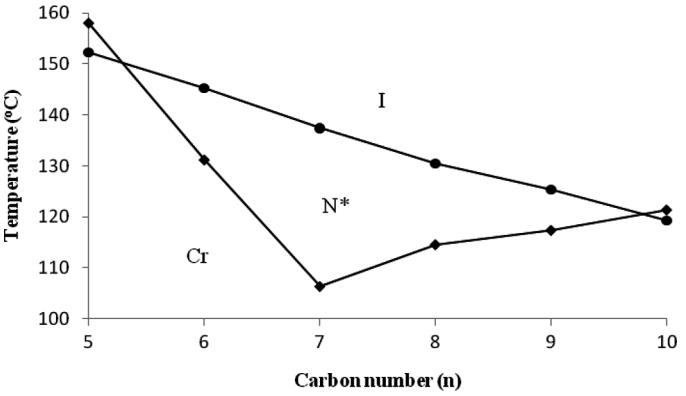


Figure 3. Melting and clearing points versus carbon number (n) of series **D**.

was found in methyl 3β-hydroxy-5-cholenate-derived series. This subtle difference again indicates the effect of the side-chain polarity on the phase transition properties.

To test the feasibility of side-chain modification, the homologous ester series **D** was investigated (Table 3). These compounds exhibit narrower mesogenic temperature ranges than methyl ester **A34** (**D1**). With the increasing carbon number of the alkoxy chain, the N*-I transition temperatures of series **D** decreased gradually without a visible odd–even effect; however, the melting points dropped at first and then increased, pointing to a possible change of the crystal structure lattice (Figure 3). Compared with the only known steroidal series with a homologous alkyl side chain [12], the behavior of series **D** appears less predictable.

Conclusion

As a summary, this study disclosed the unique phase transition properties of 3β-hydroxy-5-cholenic acid-derived liquid crystals. Compared with the cholesterol-based

analogues, the polarity of the terminal ester group has a significant impact on the mesomorphic property of these compounds: (1) the melting points are higher; (2) the change of the fluorination pattern of the phenyl group exhibits magnified favorable or unfavorable effects; and (3) the side-chain homologous esters have narrower mesogenic temperature ranges than the methyl ester parent. The favorable effect of the trans-double bond in the acyl moiety and the unfavorable effect of B-ring saturation were discussed as well. These results indicate that 3β-hydroxy-5-cholenic acid is a useful template for design and synthesis of liquid-crystal compounds.

Experimental

Characterization

The structures of the intermediates and the target compounds were verified by spectrometric methods. Infrared (IR) spectra were recorded on a Perkin Elmer (Waltham, MA, USA) IR-983 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (Billerica, MA, USA). Advance300 spectrometer (300 MHz), Varian (Palo Atlo, CA, USA) EM 360 L spectrometer (60 MHz), or JEOL (Tokyo, Japan) FX-90Q spectrometer (90 MHz) with tetramethylsilane (TMS) as internal standard for ^{1}H-NMR and trifluoroacetic acid (TFA) as external standard for ^{19}F-NMR. The high field was set to be positive in ^{19}F-NMR spectra. Mass spectra were obtained with a Finnigan (Austin, TX, USA) 4021 mass spectrometer using electrical ionization. High-resolution mass spectra were recorded with Kratos (Manchester, UK) Concept 1H mass spectrometer.

The transition temperatures of the final liquid-crystalline compounds were measured by an Olympus (Tokyo, Japan) PM-6 polarizing optical microscope fitted with a Mettler (Greifensee, Switzerland) FP-80 heating stage and a FP-82 control unit and by a Shimadzu (Kyoto, Japan) DSC-50 differential scanning calorimeter with a heating/cooling rate 5°C/min. The transition temperatures in this article are the peak values of the transitions on DSC traces. Phase assignment was made by comparing the observed textures with those in the literature [20–22].

Compound Synthesis

Examples of the typical procedures for the preparation of the intermediates and the target compounds are given as follows. All of the target compounds have satisfying elemental analysis and appropriate ^{1}H- and ^{19}F-NMR, IR, and mass spectra data.

*Methyl 3β-Hydroxy-5-cholenate (***2***).* 3β-Hydroxy-5-cholenic acid (2.25 g, 6.02 mmol) was stirred in methanol (50 mL) in the presence of sulfuric acid (2.5 mL) overnight. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried, and concentrated. The crude product was purified by column chromatography on silica gel (hexane-ethyl acetate) to give the product as a white solid (2.29 g, 98%). ^{1}H-NMR ($CDCl_3$) δ 5.34 (d, $J = 4.4$ Hz, 1H), 3.63 (s, 3H), 3.52 (m, 1H) [17].

*n-Octyl 3β-Hydroxy-5-cholenate (***3e***).* 3β-Hydroxy-5-cholenic acid (0.40 g, 1.07 mmol) was stirred with 1-bromooctane (0.50 g, 2.59 mmol), potassium carbonate (0.40 g, 2.89 mmol), and 18-crown-6 (5 mg) in dimethylformamide (3.0 mL) for 2 days. The mixture was poured into water and extracted with ethyl acetate. The

organic layer was separated, washed with brine, dried, and concentrated. The crude product was purified by column chromatography on silica gel (hexane-ethyl acetate) to give a white solid (0.47 g, 91%). ^{1}H-NMR ($CDCl_3$) δ 5.42 (d, $J = 4.4$ Hz, 1H), 4.61 (m, 1H), 4.07 (t, $J = 6.3$ Hz, 2H). MS (m/z): 486 (M^+).

*Methyl 3β-Hydroxy-5α-cholate (**4**).* Methyl 3β-hydroxy-5-cholenate (7.80 g, 20.1 mmol) was dissolved in methanol and stirred with 10% Pd/C (0.30 g) under hydrogen (30 bar). The mixture was filtered through celite and the filtrate was concentrated to give a white solid (7.83 g, 100%). MS (m/z): 390 (M^+).

*Methyl 3β-(4-Fluorobenzoyloxy)-5-cholenate (**A4**).* Methyl 3β-hydroxy-5-cholenate (350 mg, 0.90 mmol) and 4-fluorobenzoic acid (140 mg, 1.00 mmol) were stirred with *N,N′*-dicyclohexylcarbodiimide (250 mg, 1.21 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) in tetrahydrofuran (10 mL) overnight. The resulting slurry was filtered and the filtrate was concentrated. The solid residue was purified by column chromatography on silica gel (hexane-ethyl acetate) to give a white solid (307 mg, 67%). ^{1}H-NMR ($CDCl_3$) δ 8.07 (m, 2H), 7.10 (m, 2H), 5.44 (d, $J = 4.5$ Hz, 1H), 4.89 (m, 1H), 3.72 (s, 3H). ^{19}F NMR ($CDCl_3$) δ 28.3 (m, 1 F). MS (m/z) 370. IR (KBr) υ (cm^{-1}) 1706, 1747. Analysis for $C_{32}H_{43}FO_4$: Calcd. C75.26, H8.49; Found C75.37, H8.51.

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