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A new route for synthesizing cholesterol analogs with fluorocarbon side chains and their liquid-crystalline aliphatic esters

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Abstract

A new and efficient route has been developed to synthesize 17β-(1-methyl-3-perfluoroalkyl)propyl-3β-androsterol (**1**) in nine steps from hyodeoxycholic acid via selective addition of 1-perfluoroalkyl iodide to 24-norchola-5,22-dien-3β-ol. From (**1**), the first series of steroidal liquid crystalline aliphatic esters (smectic **A**) with fluorocarbon side chains has been prepared.

Keywords: Steroid; Perfluoroalkyl; Free radical; Liquid crystals

Besides their physiological and pharmaceutical activities (for example, 9α-fluorohydrocortisone) [1], fluorinated steroids also exhibit interesting thermotropic liquid crystalline properties (for a review on the liquid crystals derived from non-fluorinated steroids, see [2]; for our work on fluorinated liquid crystals, see [3,4]). To study the structure–property relationships of fluorinated steroidal liquid crystals, efficient synthetic strategies are, therefore, in high demand to synthesize target compounds with various fluorine-substituents. Herein, we report an improved route for the synthesis of 17β-(1-methyl-3-perfluoroalkyl)propyl-3β-androsterols (**1**). Retrosynthetically, (**1**) was traced back to an olefin intermediate (**2**) and further hyodeoxycholic acid (**3**) (Fig. 1). From sterol (**1**), the first series of steroid liquid crystals with fluoro-carbon side chain has been obtained.

By the reaction of a steroidal terminal olefin (**A**) with a perfluoroalkyl radical (for a review on reaction of perfluoroalkyl halides with olefins, see [5–8]) and subsequent modification of the A,B-*cis*-fusion [9], Huang et al. have prepared the sterol (**1**) bearing an *iso*-perfluorobutyl terminal group (Fig. 2) [10,12,13].[1] However, for the general preparation of steroids with *different* perfluoroalkyl appendages, this strategy proved to be inefficient and costly due to the early introduction of different perfluoroalkyl groups needing repetitive and tedious experimental operations, as well as the precious fluorinated materials being consumed heavily by undesired side reactions in the following steps.

To address the aforementioned issues, a new strategy was developed, in which the $\Delta^{5,22}$-steroid (**2**) was selected as the substrate for perfluoroalkyl radical addition (Fig. 1). From literature precedent, chemoselective addition to the Δ^{22}-double bond was expected. Selective dihydroxylation [14] and borohydrogenation [15] at this position have been reported. Furthermore, the Δ^{5}-double bond has been found to be inert to perfluoroalkyl radicals [16].

This new route was summarized in Scheme 1. Compound (**4**) was prepared from hyodeoxycholic acid (**3**) in four steps according to a reported method [9]. This procedure could be carried out in large scale without separation. The crude mixture of (**4**) and a $\Delta^{3,5}$-diene acid by-product (comes from the substitution–elimination step (KOAc, DMF–H_2O, 110 °C)) was easily purified by recrystallization from hot ethyl acetate to give pure material in 56% yield. After protecting hydroxy as acetate, a decarboxylation ($Pb(OAc)_4$, $Cu(OAc)_2$, Py-PhH, reflux) produced $\Delta^{5,22}$-steroid (**5**) in 90% yield based on recovered starting material. For ease of purification by flash chromatography and recrystallization from ethanol, the acetate (**5**) was then hydrolyzed to alcohol (**6**). Using sodium dithionite as an initiator in a chloroform–water system, the terminal double bond of the alcohol (**6**) was selectively reacted with 1-perfluorobutyl and perfluorohexyl iodides, respectively. Due to the low reactivity of the steroid substrate, these radical reactions proceeded slowly

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[1] G.J. Schroepfer et al. synthesized steroids with an *iso*-perfluoropropyl terminal group by a similar strategy, see [12,13].

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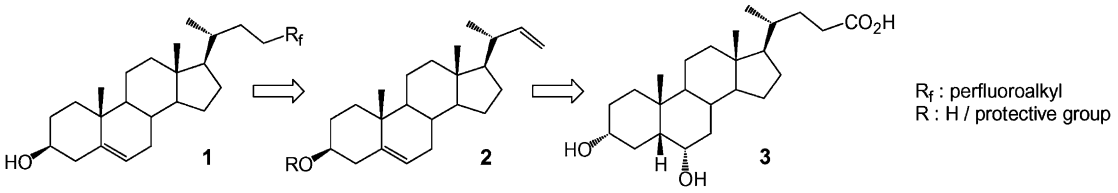


Fig. 1.

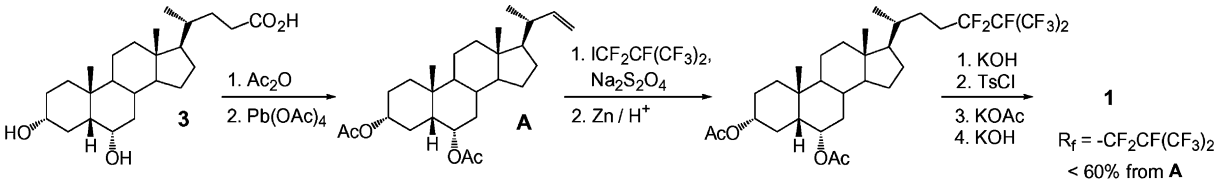
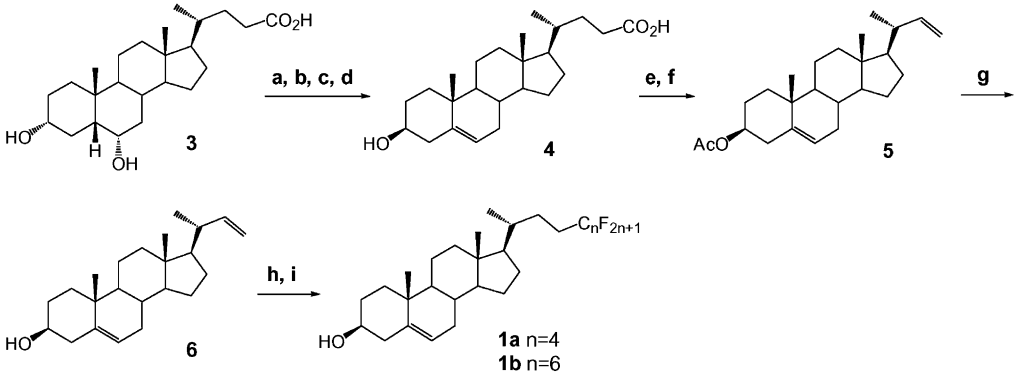


Fig. 2.



Scheme 1. Reagents and conditions: (a) MeOH, cat. H_2SO_4; (b) TsCl, Py; (c) KOAc, DMF–H_2O, 110 °C; (d) KOH, MeOH, 56% (four steps); (e) Ac_2O, Py, 100%; (f) $Pb(OAc)_4$, $Cu(OAc)_2$, Py-PhH, reflux, 71% (90%); (g) KOH, MeOH, 98%; (h) $F(CF_2)_nI$, $Na_2S_2O_4$–$NaHCO_3$, $CHCl_3$–H_2O, 40 °C; (i) $LiAlH_4$, THF, 75% (two steps for $n = 4$), 74% (two steps for $n = 6$).

and the yields varied depending on the amount of perfluoroalkyl iodides. Under optimized conditions, two equivalents of perfluoroalkyl iodide were added in four portions over 24 h to give about 80% yield of the desired iodides, which were then reduced to afford the perfluoroalkylated sterols (**1a**) and (**1b**). They were identified by comparing the data with those in literature [11].

The high efficiency of this strategy is worth highlighting. Due to the perfluoroalkylation at a later stage in the synthesis, only *two* steps were required to obtain the sterol (**1**) in high yield (~75%) from the terminal olefin (**6**). Whereas *six* steps were required to obtain (**1**) in lower yield (<60%) from the substrate (**A**) by the previous route [10].

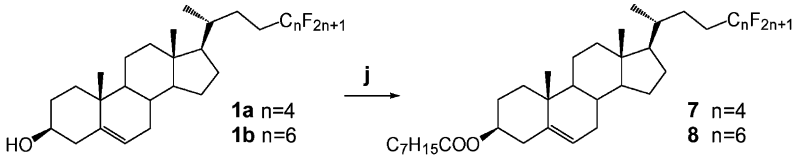
Lastly, the condensation of (**1a**) and (**1b**) with octanoic acid gave two corresponding aliphatic esters (**7** and **8**) (Scheme 2).[2] Their phase transition properties were investigated by differential scanning calorimetry (DSC) and polarizing optical microscopy. The esters are enantiotropic smectic (Table 1, entry 1 and 2). To the best of our knowledge, this is the first series of steroid liquid crystals that

Table 1
The phase transition temperatures[a]

Entry	Compounds	Phase transition temperatures (°C)
1	**7**	Cr 132.3 S_A 134.0 I 133.0 S_A 102.3 Cr
2	**8**	Cr 124.6 S_A 159.3 I 156.4 S_A 103.2 Cr
3	**1a**	Cr 138.6 I
4	**1b**	Cr 161.0 I 151.5 Ch 150.3 Cr

[a] The phase transition temperatures were the peak values of the curves recorded by DSC (with a heating and cooling rate of 5 °C/min). Cr: crystalline; S_A: smectic **A**; Ch: cholesteric; I: isotropic liquid.

[2] The structures of compounds (**7**) and (**8**) are supported by MS, IR, ^1H and ^{19}F NMR spectra and elemental analyses. Compound (**7**): MS (*m*/*z*) 530 ($M^+ - C_7H_{15}CO_2H$), 408, 255, 213, 147; IR (KBr) υ (cm^{-1}) 1736 (C=O, ester); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ (ppm) 5.41 (d, 1H, $J = 4.8$ Hz), 4.68 (m, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz, TFA) δ (ppm) 3.5 (m, 3F), 37.2 (m, 2F), 46.9 (m, 2F), 48.6 (m, 2F); analysis calcd. for $C_{35}H_{51}F_9O_2$, C 62.30, H 7.62; found C 62.69, H 7.65. Compound (**8**): MS (*m*/*z*) 632 ($M^+ - C_7H_{15}CO_2H + 2H$), 631 ($M^+ - C_7H_{15}CO_2H + 1H$), 509, 255, 213, 147; IR (KBr) υ (cm^{-1}) 1737 (C=O, ester); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ (ppm) 5.37 (d, 1H, $J = 4.8$ Hz), 4.61 (m, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz, TFA) δ (ppm) 3.82 (m, 3F), 37.58 (s, 2F), 45.05 (s, 2F), 45.99 (s, 2F), 46.51 (s, 2F), 49.24 (s, 2F); analysis calcd. for $C_{38}H_{53}F_{13}O_2$, C 57.36, H 6.64; found C 57.25, H 6.71.



Scheme 2. Reagents and conditions: (j) $C_7H_{13}CO_2H$, DCC, cat. DMAP, CH_2Cl_2, 92% for (**7**), 69% for (**8**).

incorporate a perfluorinated side chain. In comparison with cholesteryl octanoate, which is enantiotropic cholesteric and monotropic smectic [2], the esters (**7**) and (**8**) displayed only a smectic phase, conceivable due to the fluorocarbon chain increasing intermolecular lateral interactions. Compound (**8**), with a longer fluorocarbon chain than (**7**), showed higher thermal mesomorphic stability. Interestingly, the fluorinated sterol (**1b**) also showed a monotropic cholesteric phase (Table 1, entry 3).

In conclusion, a new and efficient route has been established for the preparation of cholesterol analogs bearing a perfluoroalkylated side chain. These fluorinated sterols and their corresponding aliphatic esters display interesting thermotropic liquid crystalline phases. Further work in this direction is currently under investigation.

Acknowledgements

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