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The application of diethylaminosulfur trifluoride in the synthesis of fluorinated sterols and bile acids

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Abstract—Methyl 3,3-(ethylenedioxy)-6β-fluoro-5β-cholan-24-oate has been prepared starting from hyodeoxycholic acid and 3,3-(ethylenedioxy)-7(α and β)-fluorocholestan-22-al starting from stigmasterol, using diethylaminosulfur trifluoride as the fluorinating agent. These molecules will be used to synthesize analogs of the aminosterol antibiotic squalamine.

Our laboratory has been probing the structure–function relationships of squalamine (see Fig. 1 for structure), an aminosterol isolated from the dogfish shark.[1–4] We have used diethylaminosulfur trifluoride (DAST) to prepare fluorinated analogs of aminosterols based upon bile acids, replacing the B-ring hydroxyl substituent with fluorine. DAST has been shown to substitute for hydroxyl substituents on sterol rings, largely with inversion of configuration.[5,6] Three fluorinated sterols were synthesized (Fig. 1): methyl 3,3-(ethylenedioxy)-6β-fluoro-5β-cholan-24-oate (**2**), 3,3-(ethylenedioxy)-7α-fluorocholestan-22-al (**3**), and 3,3-(ethylenedioxy)-7β-fluorocholestan-22-al (**4**). The latter two sterols will be used to synthesize the 7α- and 7β-fluoro analogs of squalamine.

Intermediate **6** (Scheme 1) was prepared in three steps from hyodeoxycholic acid (**5**), using conditions optimized previously.[1,2] The saturated 6α-alcohol **6** was reacted with DAST in *n*-pentane/dichloromethane (50/3) to give the 6β-fluorinated sterol **2** in 28% yield after purification by column chromatography.[†] Remarkable about this reaction is the relatively high yield of fluorinated product with absolute inversion of stereochemistry at C-6. Previous fluorinations of steroidal rings with DAST[5,6] have indicated that allylic hydroxyl groups are most amenable to reaction with DAST, and significant amounts of both isomers are often obtained. Also, the reaction of saturated sterol alcohols with DAST typically results in elimination rather than substitution. The nearby protected ketone, along with its

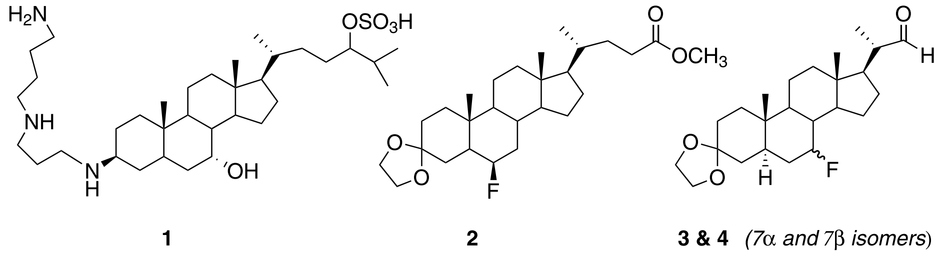

Figure 1. The structures of the fluorinated sterols synthesized in this study. The structure of the target molecule squalamine (**1**) is shown for comparison.

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[†] ^{13}C NMR (75.4 MHz, $CDCl_3$, ref. to TMS): δ 174.6, 109.2, 90.5 (d, $J=174$ Hz), 64.2, 64.1, 56.0, 55.8, 51.4, 45.5, 42.8, 39.8, 39.2, 36.1, 36.0, 35.3, 34.3, 34.1, 32.2, 32.0, 31.0, 30.2, 28.8, 28.0, 24.1, 24.0, 23.0, 20.9, 18.2, 11.9; ^{19}F NMR (282.2 MHz, $CDCl_3$, ref. to Freon 11): δ −183.5 (d, $J=47$ Hz).

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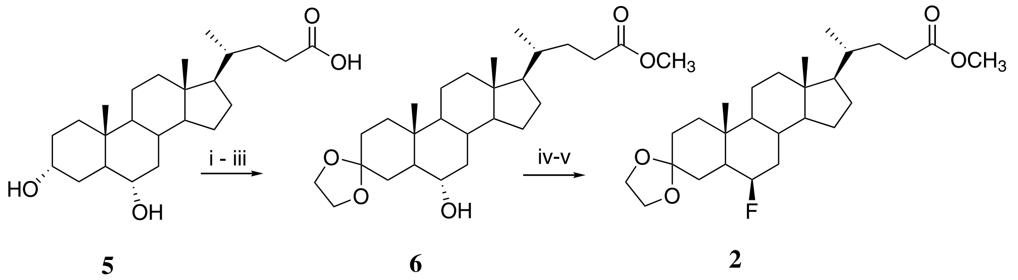
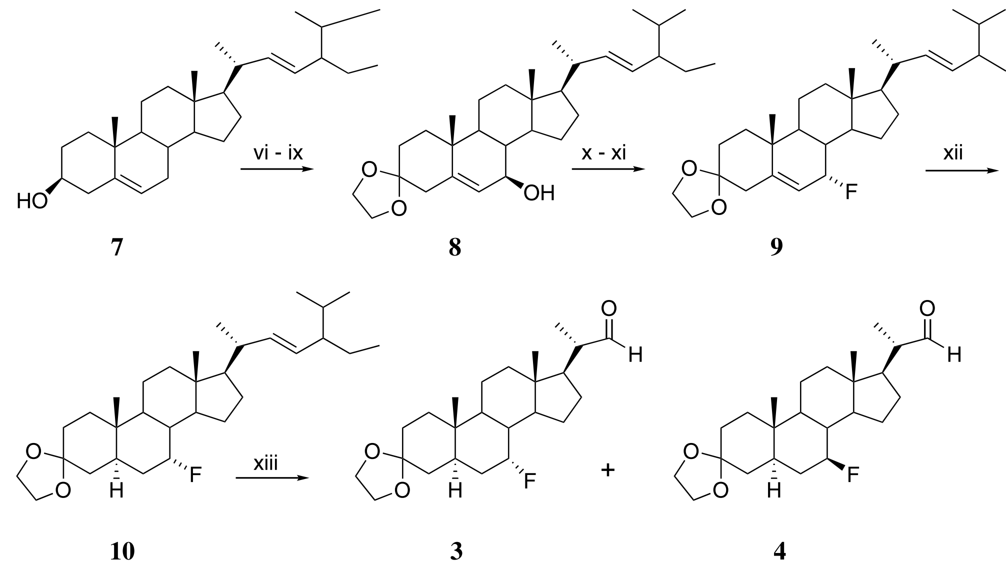


5 **6** **2**

Scheme 1. *Reagents and conditions*: (i) HCl, MeOH, 25°C, 16 h, 96%; (ii) $AgCO_3$/Celite, toluene, 8 h reflux, 99%; (iii) ethylene glycol, PTSA, toluene, 2 h reflux, 100%; (iv) DAST, *n*-pentane/dichloromethane (50/3), argon, 2 h, 25°C; (v) PTSA, acetone/water (85/15), 15 min, 25°C, 28%. PTSA=*p*-toluenesulfonic acid.



7 **8** **9**

10 **3** **4**

Scheme 2. *Reagents and conditions*: (vi) ClCOCOCl, Me_2SO, CH_2Cl_2, −60°C, 20 min, 90%; (vii) $HOCH_2$–CH_2OH, PTSA, benzene, 8 h reflux, 75%; (viii) (a) *N*-hydroxyphthalimide, dibenzoyl peroxide, O_2, 55°C, 96 h, (b) $CuCl_2$, pyridine, 0°C, 12 h, 30%; (ix) $CeCl_3$, $NaBH_4$, MeOH/THF (5/3), 25°C, 1.5 h, 99%; (x) DAST, CH_2Cl_2, argon, 25°C, 10 min; (xi) PTSA, acetone/water (85/15), 25°C, 15 min, 88%; (xii) Li/NH_3(l), THF, −78°C, 1 h, quench with NH_4Cl, 56%; (xiii) O_3, CH_2Cl_2/EtOH (2/1), −116°C, 4 h; silica gel chromatography, hexanes/ethyl acetate (9/1), **3** (24%) and **4** (14%).

close spatial proximity due to the *cis* configuration of the A/B ring junction of the steroid, seems to stabilize the reaction intermediate and allows fluorination to proceed at yields comparable to those obtained with allylic hydroxyls. Attempts to fluorinate the 6-hydroxyl substitutent (either α or β) of 5α-sterols gave primarily the 5-ene elimination product. 6-Fluorocholesterols have been prepared from the reaction of DAST with 6-oxo-cholestanes.[7,8]

The preparation of the 7α- and 7β-fluorosterol aldehydes from stigmasterol is described in Scheme 2. Stigmasterol (**7**) is converted into the allylic 7β-alcohol **8** in four steps, using methods previously optimized.[4] Reaction with DAST resulted in the 7-fluorosterol in 88% yield, with a 2/1 ratio of α to β isomers by ^{19}F NMR. The mixed products gave a single spot by tlc, and were not separable using silica gel chromatography. The fluorination reaction is again highly dependent upon the presence of a protected ketone on C-3. If the analogous acetate-protected hydroxyl compound is used instead, the yield of the fluorinated products is much lower, with significant elimination to the 4,6-diene. Others have successfully fluorinated 3β-acetoxy-7-hydroxyandrost-5-en-17-one to 5-en-7-fluoro products.[6] As expected, if the 5-ene is reduced before reacting with DAST, no fluorinated product can be isolated and only the elimination product is observed.

To separate the two isomers, the 5-ene group was reduced with lithium metal in liquid ammonia. The crude reduction product was chromatographed on silica gel to yield intermediate **10**. This product, which again was a mixture of 7α and 7β isomers, was converted into the 22-aldehyde by ozonolysis. The resulting white solid was chromatographed on silica to yield the 7α-fluorosterol **3** (24%) and the 7β-fluorosterol **4** (14%).[‡]

[‡] **3**: ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 204.8, 108.9, 90.2 (dd, *J*=170, 5 Hz), 52.1, 49.3, 46.3, 39.3, 39.1, 39.0, 37.2, 36.4, 35.4, 34.1, 33.8, 33.7, 31.1, 27.2, 23.6, 20.9, 20.8, 11.5, 10.2; ^{19}F NMR (282.2 MHz, $CDCl_3$): δ −169.4 (m, *J*=49 Hz); **4**: ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.7, 108.9, 95.9 (d, *J*=174 Hz), 54.5, 51.6, 51.3, 51.2, 41.4, 41.2, 40.4, 40.3, 39.5, 39.1, 37.4, 35.6, 34.9, 34.8, 34.6, 31.0, 27.5, 26.1, 26.0, 22.5, 21.1, 14.0, 11.8, 11.5, 11.4; ^{19}F NMR (282.2 MHz, $CDCl_3$): δ −140.9 (d, *J*=47 Hz).

Sterols usually react readily with DAST at room temperature, but the product is highly dependent on the structure of the steroid. When a steroid possesses a 5-ene-3-ol structure, the corresponding 5-ene-3β-fluoro steroid is generally produced in high yield.[6] In this study, the reaction of intermediate **6** with DAST gave only the S_N2 reaction product. However, in the case where intermediate **8** reacted with DAST, a mixture of α and β isomers were obtained, with an approximate ratio of 7/3 indicted by ^{19}F NMR. These compounds will be used to further probe the requirement of substitution at the 7-position on the biological activity of squalamine.

Acknowledgements

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