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An Expedient Synthesis of 6α-Fluoroursodeoxycholic Acid

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Abstract:

Optimization of the synthesis of 6α-fluoroursodeoxycholic acid 1 is described starting from the commercially available 2. The penultimate intermediate 16 was made in eight synthetic steps but in only four operations in an overall yield of 57%. The highlights are flourination of hydroxyketo acid 11 using Selectfluor through the intermediacy of silyl enol ether 12, conversion of 13 to 14 via equilibration of fluoroketone, esterification, and acylation. The drug substance 1 was prepared from mesylate 16 using potassium superoxide followed by a mild reductive workup using methoxydiethylborane.

Bile acids are amphiphilic compounds synthesized in the liver from cholesterol. They play an important role in solubilizing cholesterol in bile and in the overall digestive process through formation of micelles. Deconjugation and dehydroxylation of these bile acids leads to the formation of secondary bile acids that were implicated in colonic carcinogenesis. Fluorination of these bile acids at the 6α-position prevents bacterial dehydroxylation, and this concept led to the identification of 6α-fluoroursodeoxycholic acid **1**, as a potential agent for the prevention and treatment of colorectal cancer.[1,2]

The original synthesis by Italian chemists[3] (Scheme 1), starting from **2**, involves a sequence of esterification, oxidation, bromination, hydrolysis to the keto alcohol, protection of the 3α-hydroxyl as a *tert*-butyldimethylsilyl ether, and exchange with diethylaminosulfurtrifluoride (DAST), yielding **9** in 10% overall yield. Fluoroketone **9** was then hydrolyzed to **10**, followed by reduction with $NaBH_4$ in methanol/THF to yield **1** in 41% yield. In this synthesis every intermediate was purified by chromatography. Preliminary screening of this synthesis revealed low-yielding steps and the need for chromatographic purification of every step. In addition, the reported direct reduction of ketone **10** to **1** has not been achieved, despite our extensive effort. As we needed a reliable and well-defined synthesis for the preparation of pure drug substance, we evaluated our synthetic options. We followed a two-pronged approach, that is, one for satisfying the immediate needs for the drug substance and another to find a more direct method for long-term requirements. Intermediate **15** served as a common point for these two requirements.

The key step we envisoned was to fluorinate the silyl enol ether **12** with an electrophilic fluorinating reagent yielding fluoroketone **13**, which in turn could be isomerized to the thermodynamically more stable 6α form by treatment with a base. Initial execution of this strategy using methyl 3α-acetoxy-7-oxocholanoate gave encouraging results. Thus, methyl 3α-acetoxy-7-oxocholanoate **5** was treated with $TMSOTf/NEt_3$ in toluene at 50 °C to afford the crude silyl enol ether, which was taken up in acetonitrile and reacted with Selectfluor to yield a mixture of 6α- and 6β-fluorinated ketoesters. Partial hydrolysis of the methyl ester was observed in the subsequent C-6 epimerization with NaOMe/MeOH. To overcome the complication of partial deprotection of the methyl ester during epimerization at C-6, the fluorination was performed before esterification of free acid with very good success. The expensive triflate was replaced with TMSCl/NaI[4] to form the silyl enol ether **12** in a mixture of toluene and acetonitrile at 50 °C. After aqueous workup, the crude solution was added to a suspension of Selectfluor, and **13** was isolated by precipitation in 93% yield (from **11**).

Equilibration at C-6 of **13** was performed with NaOMe/MeOH to afford **10** with a C-6 α:β ratio of 98:2. When TMSCl was added to the reaction mixture, methyl ester **9** was obtained as a solution in toluene after aqueous workup, and **9** was further protected as the acetate with Ac_2O/NEt_3/DMAP/CH_3CN. After another aqueous workup, at elevated temperature (60−70 °C), dilution of the toluene layer with heptane gave **14** in 87% yield based on **13**.

Another problem we faced was reproducing the reported selective reduction of compound **10** to **1**. Numerous reduction conditions were tested to achieve this transformation but to no avail; typically, 7α-hydroxyl-elimination, or -defluorination products or both were obtained. Selective reduction of C7-keto steroids has been achieved in the literature[5] with 7α-hydroxysteroid dehydrogenase. However, the 6α-fluorosteroid **10** was found not to be a substrate for this enzyme. The bottom face of 5β-7-oxo steroids is very crowded. Modelling (MM2) revealed that the bottom access to the C-7 carbonyl is guarded by protons on C-4α, C-9, and C-14. This means that a hydride reduction would only be possible by flipping the steroid B-ring into a twist or boat conformation via complexation of the ketone or through enolization. Indeed, hydrogenation of the enolate of **10** with Raney-nickel gave predominantly the 7β-alcohol. This approach could not be used, however, because of the consequent inversion of

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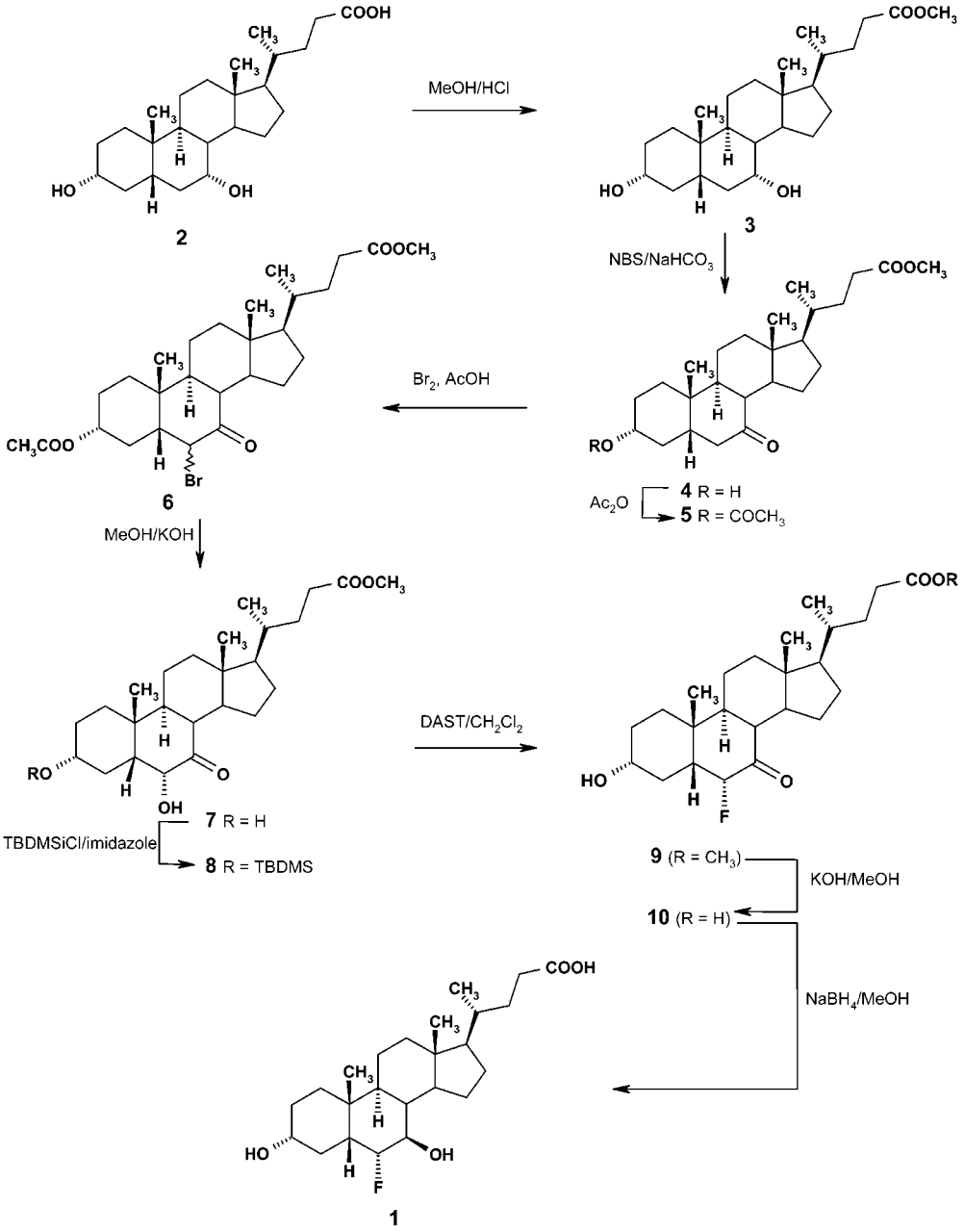
Scheme 1



the fluorine at C-6. Reduction by Na/liquid NH_3 typically afforded the thermodynamically more stable epimer but with the loss of fluorine atom. Attempts to bring a hydride to the α-face of the ketone by employing a tether from the hydroxyl on C-3α failed as well.

To overcome the lack of a suitable reduction method, a search for a suitable microorganism to perform this reduction was initiated, which is beyond the scope of this publication. To continuously supply the drug substance until a suitable microbial reduction method was found, we attempted a reduction of the C-7 ketone to the undesired 7α-alcohol, followed by an inversion.

Reduction of the ketone **14** to **15** was achieved in 97% yield using $PtO_2/H_2/CH_3COOH$ at 40 psi. The mesylation of **15** with mesyl chloride initially proved to be difficult, and only low yields and complex mixtures requiring chromatography were obtained, using a variety of solvents and bases. An interesting solution was found when DMAP was used as a base in large excess. Thus, in a 24-h reaction, **15** was transformed with Ms_2O (2.5 equiv) and DMAP (4 equiv) in toluene at 75 °C to obtain **16** in 92% yield.

The key step in this sequence, the displacement of the mesylate with a hydroxyl group (**16** to **1**), resisted our efforts because of competing elimination reactions. The axial H on C-6 and the mesylate are ideally lined up for elimination, and this was the product obtained under most conditions. Finally, superoxide anion (KO_2/DMSO),[6] in the presence of the chelator TDA-1, gave the desired displacement product **1**, accompanied by some elimination product in a ratio of 3:1 to 5:1. Problems were encountered initially in reproducing the reaction yields, which ranged from 10 to 50%. Controlled decomposition of the intermediate hydroperoxides

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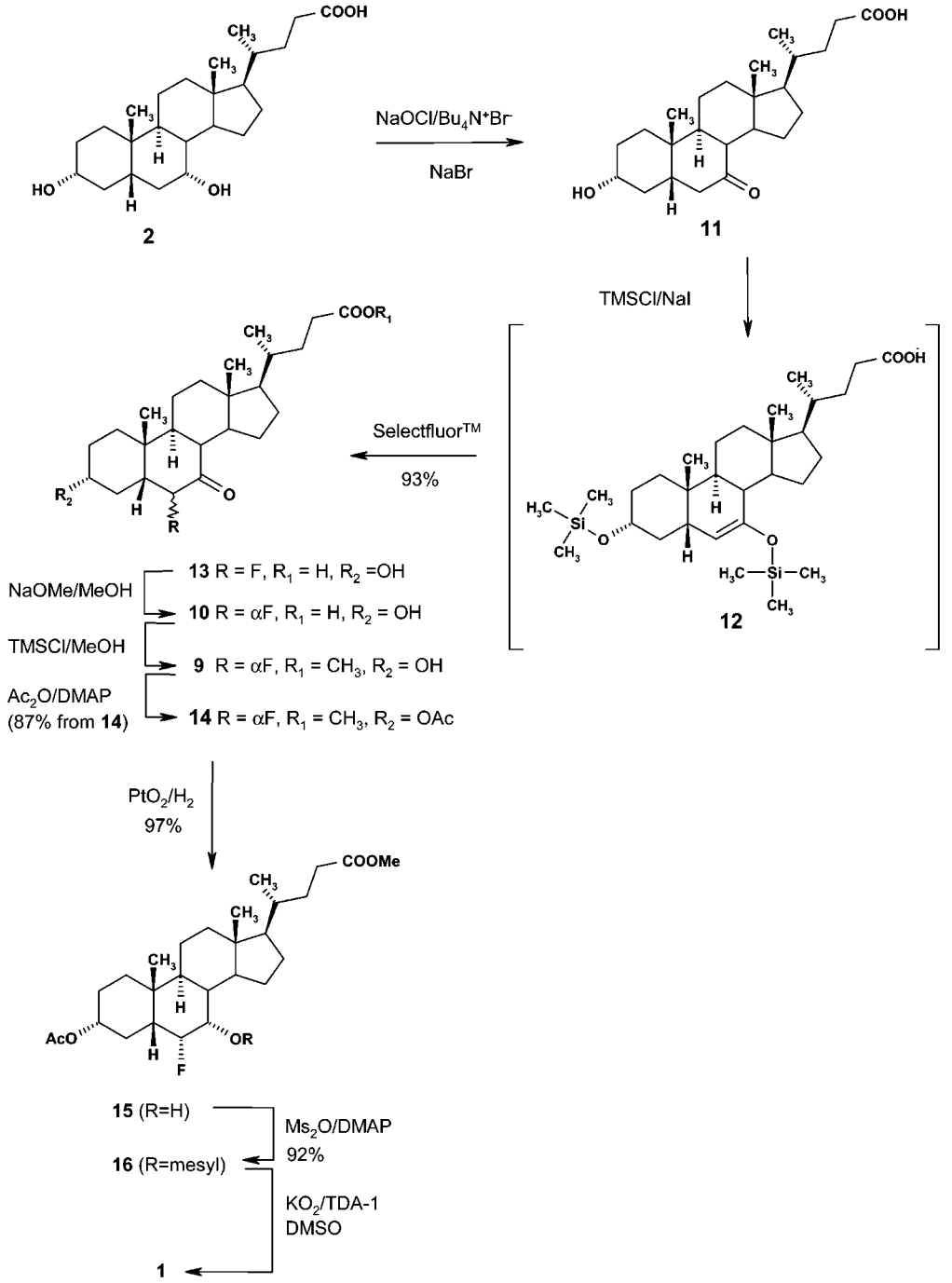
Scheme 2



and excess superoxide with diethylmethoxyborane, followed by complete hydrolysis of all esters with $NaOH/H_2O/DMSO$ gave **1** reproducibly in 50% yield, after chromatography on reversed-phase silica (Scheme 2).

In conclusion, the original synthesis was significantly improved by a judicious choice of reagents, avoiding the isolation of intermediates wherever possible by combining different synthetic steps, and developing simple isolation procedures. The displacement of the mesyl group in **16** using KO_2 was optimized and made reproducible with a better defined workup conditions. Ultimately, we believe, a suitable microorganism will be found to reduce compound **10** to **1** selectively, thus reducing the number of synthetic steps from ten to five.

Experimental Section

General Remarks. Chenodeoxycholic acid **2** was obtained from TCI America. All reagents were of commercial grade and have been used without further purification. Purities of products were determined by HPLC using refractive index detection and area normalization. ^1H NMR was measured at 300 MHz, calibrated to TMS (0.0 ppm) as internal standard, ^{13}C NMR was obtained at 75 MHz, calibrated to $CDCl_3$ (77 ppm, middle line), ^{19}F NMR was obtained at 282 MHz, calibrated to trifluorotoluene as an internal standard (−64.0 ppm).

3-Hydroxy-7-oxo-(3α,5β)-cholan-24-oic acid (11). An inerted 5-L, four-necked flask with mechanical stirrer was charged with chenodeoxycholic acid (**2**, 190 g, 0.474 mol),

sodium bromide (2.5 g, 0.024 mol), tetrabutylammonium bromide (0.5 g, 1.55 mmol), methanol (616 mL), acetic acid (200 mL), water (49 mL), and ethyl acetate (1330 mL). The mixture was stirred at room temperature until a homogeneous solution formed (15 min) and then cooled to 0 °C. Sodium hypochlorite solution (5.23%, 756 g, 0.531 mol) was added over 1 h at 1−2 °C (exothermic), and the yellow suspension was stirred at 1−2 °C for 0.5 h, then warmed slowly to 5 °C over 0.5 h to give a pale-yellow slurry. If a test for hypochlorite (peroxide test paper) at this point was negative, 37 g of bleach was added and stirred at 4−5 °C for an additional 30 min and then checked for excess hypochlorite again. Aqueous sodium hydrosulfite (3.3%, 83 g, 0.0135 mol) was added to afford a white suspension (negative test for peroxide). Water (2113 mL) was added at 7−15 °C and the mixture stirred at 14−15 °C for 5 min. The slurry was cooled back to 10 °C and most of the clear bottom aqueous layer removed. The remaining suspension was filtered and the cake washed with a precooled (5 °C) mixture of water (200 mL) and ethyl acetate (100 mL). The solid was dried at 60 °C and 150 mbar for 16 h to afford **11** (149 g, 79.2%) as a white solid. Purity: 96.6% **11**; 1.0% (5β)-3,7-dioxocholan-24-oic acid; 1.9% (5β,7α)-7-hydroxy-3-oxocholan-24-oic acid (by HPLC peak area normalization); mp 196−198 °C.

(3α,5β)-6-Fluoro-3-hydroxy-7-oxocholan-24-oic acid (13). A 5-L, four-necked flask equipped with a mechanical stirrer was purged with nitrogen. Keto acid **11** (144.9 g, 0.371 mol), sodium iodide (278.0 g, 1.855 mol), toluene (750 mL), acetonitrile (750 mL), and triethylamine (310 mL, 2.22 mol) were charged. Chlorotrimethylsilane (235 mL, 1.85 mol) was added over 15 min to the stirred suspension, causing the temperature to rise to approximately 40 °C (from room temperature). Stirring at 40 °C was continued for 30 min, and then the reaction mixture was heated at 50 °C for 6 h. The mixture was cooled to room temperature, and water (1500 mL) was added while stirring vigorously. After stirring for 3−5 min, the bottom aqueous layer was removed, and the organic layer was washed with three portions of phosphate buffer (pH 6, 0.2 M, 1541 g each) and brine (1800 g). Meanwhile, a 5-L round-bottomed flask equipped with a mechanical stirrer was purged with nitrogen and charged with Selectfluor (164.3 g, 0.464 mol) and acetonitrile (1500 mL). The mixture was stirred vigorously at 20 °C for 1−1.5 h, and then the solution of **13** was added over ca. 2 h while cooling to maintain a temperature of 17−20 °C. Stirring was continued at 20 °C for at least 6 h. While stirring vigorously, solvent (1700 mL) was distilled off at a vacuum of 400 mbar. Cold (rt) water (1500 mL) and heptane (500 mL) were added to the hot reaction mixture, which was then cooled to 5 °C over 1 h, stirred for 15−30 min, and filtered. The cake was washed with acetonitrile/water (400 mL, 1:2.5) in two portions, and dried at ≤50 °C and 150 mbar for 16 h to obtain **13** (141.0 g, 0.345 mol, 93%). Purity: 96%, by HPLC peak area normalization; ratio of α/β-isomers: 87/13; mp 225−235 °C dec. ^{1}H NMR (isomeric mixture, 300 MHz, $CDCl_3$/ CD_3OD) 5.35 (0.87 H, dd, J = 49.6, 6.4), 4.26 (0.13 H, dd, J = 52.0, 3.0), 3.54 (1 H, m), 3.00 (0.13 H, m), 2.52 (0.87 H, t, J = 11.2 Hz), 2.42 (30 H, m), 0.8−0.68 (3 H, m). ^{1}H NMR (α-isomer, 300 MHz, $CDCl_3/CD_3OD$) 5.35 (1 H, dd, J = 49.6, 6.4), 4.2 (2H, broad), 3.54 (1 H, m), 2.5−0.85 (30 H, m), 0.68 (3 H, s). ^{13}C NMR (α-isomer, 75 MHz, $CDCl_3/CD_3OD$) 206.9 (d, 13.5 Hz), 176.8, 91.8 (d, J = 191), 60.4, 54.5, 50.7 (d, J = 15 Hz), 48.2, 47.5, 42.5, 42.4, 38.4, 35.7 (d, J = 7 Hz), 35.0, 34.0, 30.8, 30.7, 29.4 (d, J = 5 Hz), 28.9, 27.9, 24.1, 23.0, 21.4, 18.0, 11.7. ^{19}F NMR (α-isomer, $CDCl_3/CD_3OD$) −203.1 (d, J = 50 Hz).

Methyl (3α,5β,6α)-3-Acetoxy-6-fluoro-7-oxocholan-24-oate (14). Keto acid **13** (140.6 g) and methanol (650 mL) were charged into an inerted, four-necked round-bottomed flask equipped with a mechanical stirrer, and sodium methoxide solution (25 wt %, 92.9 g) was added. The mixture was heated at reflux for 3 h and cooled to 10 °C, and chlorotrimethylsilane (66.3 g) was added over 15 min. The mixture was heated at reflux for 3 h. After cooling to room temperature, toluene (780 mL) and aqueous Na_2HPO_4 solution (3.8%, 811 g) were added and stirred for 5−10 min. After removal of the aqueous bottom layer, the organic layer was washed with brine (775 g) before toluene (600 mL) was added. Solvent (950 mL) was distilled off at a pressure of 275 mbar. After cooling to room temperature, acetonitrile (260 mL), triethylamine (65 mL), and 4-(*N*,*N*-dimethylamino)pyridine (880 mg) were added. The mixture was heated to 60 °C, and acetic anhydride (37 mL) was added over 10−20 min at a rate to keep the temperature of the reaction at 55−60 °C. The mixture was stirred at 55−60 °C for 3 h and cooled to room temperature. Aqueous phosphoric acid (3.45%, 813 g) was added, the mixture was heated to 60−65 °C, stirred for 3−5 min, and the bottom aqueous layer was removed at this temperature. The organic layer was washed with water (680 mL) and brine (600 g); both phase separations were performed at 60−65 °C. Solvent (460 mL) was distilled off at a pressure of 275 mbar. Without cooling the residue, toluene (150 mL) was added to the distillation residue, and the mixture was heated to 70 °C. Heptane (900 mL) was added over 30 min at 70 °C. The mixture was cooled to 5 °C over 90 min, stirred for 30 min, and filtered. The filter cake was washed with toluene/heptane (ratio 1:2, 250 mL) and dried in a vacuum oven at 50 °C and 150 mbar to obtain **14 (**139.3 g, 0.300 mol, 87%). Purity: 98% (by HPLC peak area normalization); 0.8−1% of *desfluoro-17* (by HPLC and ^{1}H NMR); mp 173−175 °C. ^{1}H NMR ($CDCl_3$) 5.35 (1 H, dd, J = 49.5, 6.4), 4.68 (1H, m), 3.67 (3H, s), 2.45−2.15 (5 H, m), 1.70−2.08 (10H, m), 0.85−1.63 (18 H, m), 0.68 (3 H, s). ^{13}C NMR ($CDCl_3$) 205.45 (d, 13.5 Hz), 174.5, 170.2, 91.5 (d, J = 192 Hz), 72.0, 54.6, 51.4, 50.6 (d, J = 15 Hz), 48.3, 47.5, 42.55, 42.51, 38.5, 35.8 (d, J = 7 Hz), 35.1, 33.8, 30.9, 30.8, 28.1, 26.1 (d, J = 6 Hz), 25.8, 24.3, 23.2, 21.5, 21.1, 18.2, 11.9. ^{19}F NMR ($CDCl_3$) −203.2 (d, J = 50 Hz).

Methyl (3α,5β,6α,7α)-3-Acetoxy-6-fluoro-7-hydroxycholan-24-oate (15). A 1000-mL stirred pressure reactor was charged with ketone **14** (50.0 g, 107.2 mmol), platinum(IV) oxide (2.0 g, 8.8 mmol), and acetic acid (250 mL). The vessel was closed and inerted with nitrogen. While stirring moderately, the mixture was heated to 45 °C. Stirring was stopped, and the headspace was purged with hydrogen at 40

psi (2.7 bar). The agitation was started, and after 5 min the mixture was heated to 55 °C and held for 18 h. After TLC showed complete reduction, the vessel was purged with nitrogen, the mixture was filtered over Celite, and the residue was rinsed with acetic acid (250 mL). The filtrate was concentrated to a volume of 300 mL in vacuo and then added dropwise into vigorously stirred water at 0 °C. The mixture was stirred at room temperature for at least 1 h and filtered. The cake was washed with cold water (3−5 °C, 500 mL) and dried under N_2-sweep at 32 (±2) °C and 100−150 mbar for 12 h, then at 50 (±2) °C for at least 12 h to obtain **15** as a white powder (48.7 g, 103.9 mmol 97%). Purity: 97%; mp 121−123 °C. ^{1}H NMR ($CDCl_3$) 4.7 (1 H, ddd, J = 45, 5.6, 3.5), 4.55 (1H, m), 4.03 (1H, m), 3.67 (3H, s), 2.45−2.10 (3 H, m), 1.05−2.07 (25H, m), 0.85−1.0 (6 H, m), 0.66 (3 H, s). ^{13}C NMR ($CDCl_3$) 174.7, 170.6, 91.5 (d, J = 176 Hz), 73.6, 69.9 (d, J = 17 Hz), 55.6, 51.4, 49.7, 45.9 (d, J = 17 Hz), 42.6, 39.2, 37.9 (d, J = 5 Hz), 36.2 (d, J = 7 Hz), 35.3, 35.1, 32.6, 30.95, 30.90, 28.3 (d, J = 5 Hz), 28.0, 26.6, 23.4, 22.9, 21.3, 20.5, 18.2, 11.6. ^{19}F NMR ($CDCl_3$) − 198.5 (dm, J = 45 Hz).

Methyl (3α,5*β*,6α,7α)-3-Acetoxy-6-fluoro-7-(methylsulfonyloxy)cholan-24-oate (16). A 3-L, four-necked round-bottom flask equipped with a mechanical stirrer was charged with **15** (81.93 g 0.1756 mol), methanesulfonic anhydride (76.4 g, 0.439 mol), 4-(*N*,*N*-dimethylamino)pyridine (86.0 g, 0.704 mol), and toluene (1100 mL). The mixture was heated at 75 °C for 20−24 h. After TLC indicated complete reaction, the reaction mixture was cooled to room temperature and filtered, and the cake was washed with toluene (400 mL). The filtrate was washed with water (300 mL), twice with saturated aqueous ammonium chloride (195 g each), and then with water (150 mL). The organic layer was concentrated to a minimum volume at a bath temperature of 45 °C and a vacuum of up to 25 mbar. While stirring vigorously, the thick brown oil was diluted with heptane (900 mL) and then cooled to 3−5 °C for 2 h. The slurry was filtered, the filter cake was rinsed with precooled heptane (150 mL) and dried at 50 °C and 100 mbar to obtain **16** (87.9 g, 161.4 mmol, 92%). Purity 98.2%; mp 174−176 °C. ^{1}H NMR ($CDCl_3$) 5.08 (m, 1H), 4.8 (1H, ddd, J = 45, 4.5, 3.5), 4.57 (1H, m), 3.67 (3H, s), 3.10 (s, 3H), 2.36 (1H, ddd, J = 15, 10, 5.4 Hz), 2.22 (1H, ddd, J = 15, 8.5, 6.7 Hz), 2.10−0.85 (31 H, m), 0.6 (3H, s). ^{13}C NMR ($CDCl_3$) 174.5, 170.4, 89.3 (d, J = 184 Hz), 81.55 (d, J = 15 Hz), 73.1, 55.2, 51.4, 49.3, 45.9 (d, J = 16 Hz), 42.8, 38.9 (d, J = 9 Hz), 38.5, 36.65 (d, J = 4.5 Hz), 36.07 (d, J = 8 Hz), 35.1, 34.8, 33.1, 30.85, 30.73, 28.0 (d, J = 4 Hz), 27.7, 26.5, 23.1, 22.9, 21.3, 20.3, 18.2, 11.8. ^{19}F NMR ($CDCl_3$) −191.75 (dm, J = 45 Hz).

(3α,5*β*,6α,7*β*)-6-Fluoro-3,7-dihydroxycholan-24-oic acid (1). An oven-dried 250-mL, four-necked round-bottomed flask equipped with a mechanical stirrer was charged with molecular sieves (4Å, 10 g), anhydrous DMSO (54 mL), and potassium superoxide (5.4 g). TDA-1 (9.0 g) was added, and the mixture was stirred for 10−15 min. At the same time, under anhydrous conditions, mesylate **16** (10.0 g) was dissolved in anhydrous DMSO (48 mL) (heated if necessary), and the solution was added slowly over 1.5 h to the reagent mixture while cooling in a water bath to maintain a temperature of 15−20 °C. The mixture was stirred at 20 °C for at least 48 h (check for complete reaction by ^{1}H NMR). When the mesylate had reacted completely, diethylmethoxyborane (10 mL) was added while cooling in an ice bath to keep the temperature at 15−20 °C. The mixture was stirred for 1 h at 20 °C and then heated to 50 °C; aqueous sodium hydroxide (1 M, 100 mL) was added over 15 min, allowing the mixture temperature to rise to 60 °C. The mixture was held at 55−60 °C for 2 h and filtered hot through a pad of Celite. The filter residue was rinsed with DMSO/sodium hydroxide solution (DMSO/1 M NaOH, 50/50, 50 mL). The combined filtrates were washed with *tert*-butyl methyl ether (80 mL), acidified to pH 3−4 with concentrated HCl, and extracted twice with *tert*-butyl methyl ether (2 × 80 mL). The combined organic layers were washed with water (80 mL). The solution was concentrated to a minimum volume in vacuo, then flushed three times with methanol (80 mL each) and concentrated to a minimum volume using 40−50 °C bath temperature and a vacuum of up to 100 mbar, affording a final volume of approximately 25 mL. NaOH (1 **N**, 20 mL) was added, and the mixture was stirred and heated to 50 °C to dissolve the acid. After cooling to room temperature, the pH was brought to 7.5 ± 0.5 by addition of phosphoric acid (85%, approximately 1 g). The solution was chromatographed over RP-18 silica gel, eluting with sodium phosphate buffer (0.05 M, pH 6.8)/methanol (45−60% methanol), collecting 100-mL fractions. Clean fractions were combined, and methanol was distilled in vacuo. The aqueous residue was acidified to pH 3 with 85% H_3PO_4 (8 g) and extracted twice with *tert*-butyl methyl ether (60 mL each). The combined organic layers were washed with water (40 mL) and concentrated to dryness to afford **1** as a solidified foam (4.15 g, 9.25 mmol, 50.3%). ^{1}H NMR ($CDCl_3$/CD_3OD) 4.60 (1H, ddd, J = 49, 8.5, 6.2 Hz), 3.45−4.0 (5H, m), 2.36 (1H, ddd, J = 15, 10, 5.4 Hz), 2.22 (1H, ddd, J = 15, 8.5, 6.7 Hz), 2.10−0.85 (28 H, m), 0.67 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD) 177.27, 95.31 (d, J = 173 Hz), 73.12 (dd, J = 17 Hz), 70.44, 55.75, 54.84, 46.13 (d, J = 15 Hz), 43.62, 40.93 (d, J = 7 Hz), 39.77, 39.08, 35.40 (d, J = 8 Hz), 35.19, 35.01, 30.92, 30.82, 30.18 (d, J = 5 Hz), 29.54, 28.36, 26.37, 23.21, 20.98, 18.21, 11.98. ^{19}F NMR ($CDCl_3$/CD_3OD) −196.67 (dd, J = 48,14 Hz).

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