Supporting Information

pH Sensitive Tubules of a Bile Acid Derivative: a Tubule Opening by Release of Wall Leaves

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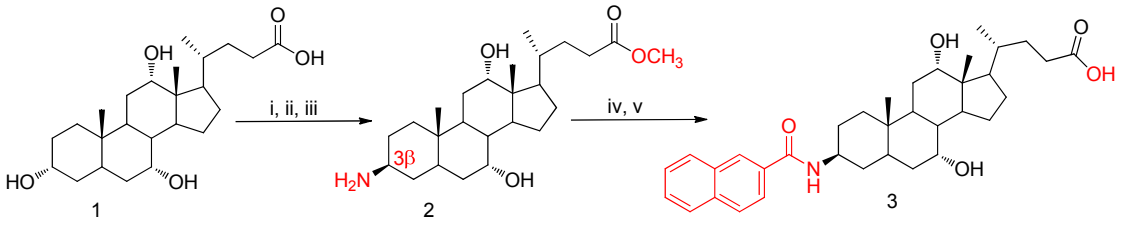
Supporting Information Contents:

Materials and Methods

Synthesis of HNaphC

The naphtoyl derivative 3, was obtained by the reaction of naphtoyl chloride with the 3β - amino derivative of cholic acid 2, according to a modified procedure by Gouin, Zhu[1] and Anelli et al.[2] All the chemicals were from Aldrich, and purified before use.



Scheme 1: Reaction sequence for the synthesis of HNaphC 3: i: MeOH/HCl, ii: DIAD, DPPA, PPh_3, THF, iii: PPh_3, H_2O, iv: naphtoyl chloride CHCl3, TEA, v: a) NaOH/MeOH: 1M, Δ, b) H_2O/H+

Synthesis of product 3. In a 5 mL one necked (14/20) round bottom flask with a reflux condenser with $CaCl_2$ trap, was added, β-Naphtoic acid (1.03 g, 6 mmol), and thionyl chloride (1 mL, 14 mmol). The mixture was refluxed for 1 hour and the excess of thionyl chloride was eliminated in vacuo. The acyl chloride was used without further purification in the next step. Coupling of compound 2 with Naphtoyl chloride: In a three necked round bottom flask with a reflux condenser, under dry nitrogen, compound 2 (2.28 g; 5.4 mmol) was dissolved in $CHCl_3$(20 mL; 246 mmol). Dry triethylamine (2 mL; 14 mmol) was added and the mixture cooled to 0 °C, and naphtoyl chloride (5 mL; 61.6 mmol) in $CHCl_3$ was added dropwise over 20 minutes. The cooling bath was removed and the reaction mixture was stirred over 12 hours. Solvent was removed in vacuo and the reaction mixture was purified by column chromatography (20:1 ethyl acetate/methanol).

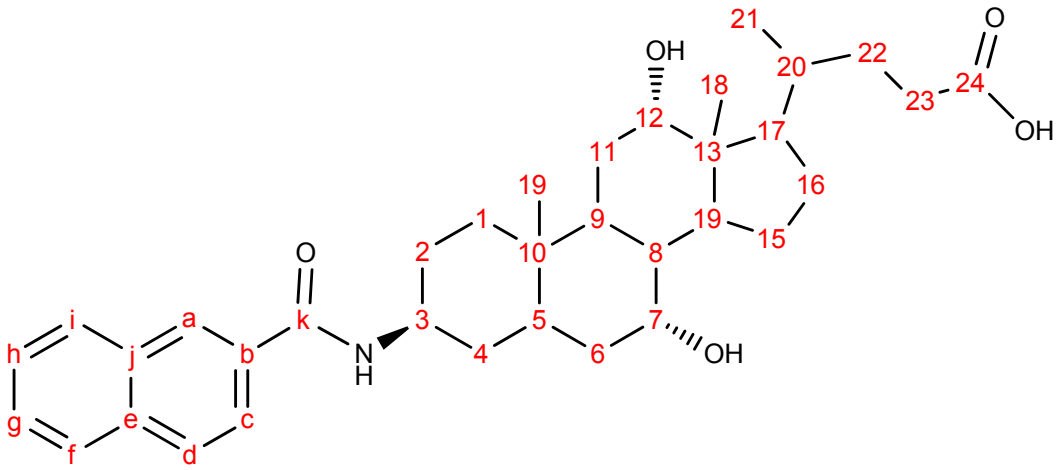
In a one necked round (14/20) bottom flask with a reflux condenser and $CaCl_2$ trap, was dissolved of the aromatic ester (1.15 g; 2 mmol) prepared before in 1M sodium hydroxide in

methanol solution (50 mmol, 50 mL). The solution was refluxed over 1 hour, after cooling the solvent was removed in vacuo and redisolved in water (400 mL; 22.2 mol) and precipitated with HCl (pH 2). The solid was washed several times with water and drying in a vacuum oven overnight.

IR (KBr): ν = 3448 cm-1 (OH), ν = 2869, 2953 cm-1(-C-H) , ν = 1710 cm-1 (C=O acid), ν = 1638 cm-1 (amide I C=O), ν = 1528 cm-1 (amide II N-H), ν = 1497, 1458 cm-1 (C=C aromatic), ν = 820, 773, 713 cm-1 (=C-H).

Mass spectra: C35H46NNaO5 theoretical: 561.35 g/mol. Found [M+1] 562.40 g/mol.

The structure elucidation of the new compound 3, was performed by NMR (1H, 13C) and (COSY, HSQC edited, HMBC, NOESY, and TOCSY).



Scheme 2. Structure of new compound 3.

1H NMR (600 MHz, CDCl3): δ = 8.25 (Ha), 7.92 (Hi, J = 7.46 Hz), 7.86, (Hd, Hf), 7.80, (Hc, J = 8.41 Hz), 7.52, (Hg, Hh), 6.58, (N-H, J = 5.71Hz), 4.34 (H3), 3.99 (H12), 3.86 (H7), 2.68 (H4), 2.37(H22), 2.27 (H22, H9), 1.97 (H6, H14), 1.88 (H16), 1.79 (H17, H23, H2), 1.69 (H15, H4, H2,H1), 1.55 (H5, H11), 1.52 (H6, H8), 1.40 (H23, H20), 1.26 (H16), 1.18 (H1), 1.09(H15), 0.98 (H21), 0.97 (H19), 0.67 (H18).

13C NMR (151 MHz, CDCl3): δ = 178.4 (C24), 167.3 (Ck), 134.6 (Ce), 132.6 (Cj), 132.3 (Cb), 128.9 (Ci), 128.4 (Cd), 127.7 (Cg), 127.5 (Cf), 127.3 (Ca), 126.7 (Ch), 123.6 (Cc), 73.1 (C12), 68.4 (C7), 46.9 (C17), 46.5 (C13), 46.2 (C3), 41.7 (C14), 39.4 (C8), 37.7 (C5), 35.4 (C20), 35.3 (C10), 34.3 (C6), 33.5(C4), 31.5 (C1), 31.1 (C22), 30.8 (C23), 28.4 (C11), 27.6 (C16), 27.0 (C9), 24.7 (C2), 23.2 (C19, C15), 17.3 (C21), 12.5 (C18).

References

(1) S. Gouin, X. X. Zhu *Steroids* **1996**, *61*, 664-669.

(2) P. L. Anelli, L. Lattuada, F. Uggeri *Synthetic Commun*. **1998**, *28*, 109-117.

Supporting figures

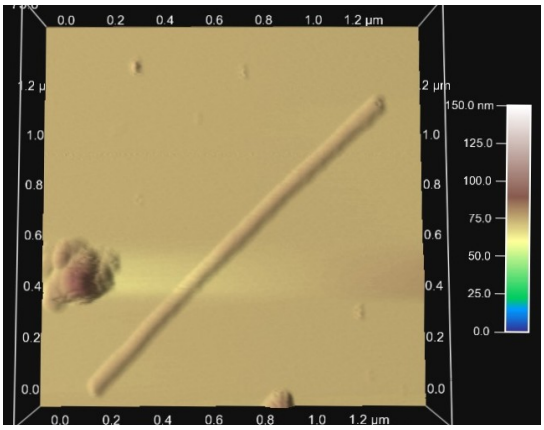


Figure S1. AFM images of HNaphC tubules at pH=8.5

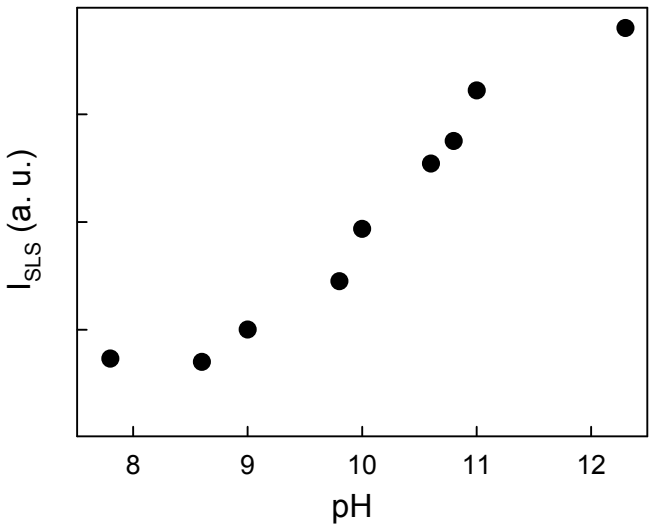


Figure S2. Light scattering intensity (I_{SLS}) as a function of pH for a 1.0 mM HNaphC solution in water. The measurements were performed by a Malvern Zetasizer unit, Nano ZS series HT at 25.0 ± 0.1 °C.