Supporting Information for

Synthesis of Modified Bile Acids via Palladium-Catalyzed C(sp³)-H (Hetero)arylation

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Contents

1. Preparation of Starting Materials............................................................................................................. S02
2. Original ¹H & ¹³C NMR Spectra of 1b, 3 & 4ba .................................................................................. S04
3. Competitive Experiment.............................................................................................................................. S39
4. Characterization Data of Intermediate Complex (Crude)........................................................................... S39
5. HPLC Profiles of 3 ...................................................................................................................................... S39
6. X-Ray Crystallographic Study of 3aa ....................................................................................................... S44
7. References.................................................................................................................................................. S45
1. Preparation of starting materials

General procedure for the synthesis of O-methylated cholic acid (CA) and deoxycholic acid (DCA) (1A-B)

To a suspension of NaH [(4.40 g, 183.5 mmol, 15 equiv, 55 % dispersion in mineral oil for cholic acid A)/(4.58 g, 191.0 mmol, 15 equiv for deoxycholic acid B)] in dry THF (100 mL) at 0 °C, a solution of A (5.0 g, 12.23 mmol, 1 equiv)/B (5.0 g, 12.73 mmol, 1 equiv) in THF (30 mL) was added. After allowing the reaction mixture to stir at room temperature for 1 h, it was cooled to 0 °C. After this, MeI [(7.61 mL, 122.3 mmol, 10 equiv for A) and (7.92 mL, 127.3 mmol, 10 equiv for B)] was slowly added to the mixture, and it was allowed to stir for 24 h at 40 °C. A second portion of NaH [(4.40 g for A and (4.58 g for B)] and MeI [(7.61 mL, 122.3 mmol, for A) and (7.92 mL, 127.3 mmol for B)] were added to the reaction mixture, and the reaction mixture was allowed to stir for another 24 h at 40 °C. Thereafter, the reaction mixture was quenched by slow addition of saturated aqueous NH₄Cl (50 mL) at 0 °C. Tetrahydrofuran were removed under reduced pressure. To the resulting suspension, ethyl acetate (100 mL) was added and the mixture was washed with water (3 × 50 mL). The organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (Hexanes/EtOAc, 70:30) to afford 4.63 g (84%) of compound 1A and 4.71 g (88%) of compound 1B as a white solid. TLC R_f = 0.36 (Hexanes/EtOAc, 70:30).

(4R)-4-((3R,7R,10S,12S,13R,17R)-3,7,12-trimethoxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoic acid (1A). Compound 1A was prepared by literature reported procedure¹ as a white solid; 5.01 g (91%); m.p. 64-68 °C (Lit. m.p. 65-70 °C).

(4R)-4-((3R,10S,12S,13R,17R)-3,12-dimethoxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoic acid (1B). Compound 1B was prepared by literature reported procedure² as a white solid; 4.71 g (88%); m.p. 140-144 °C (Lit. m.p. not reported).
General procedure for the synthesis of O-methylated $N$-(quinolin-8-yl)cholyl/deoxylcholyl amides (1a-b)

To a stirred solution of O-methylated cholic acid (1A) [or deoxycholic acid (1B)] [3.0 g, 1 equiv] in dry DCM (100 mL), thionyl chloride (3 equiv) was added at room temperature. The reaction mixture was stirred under reflux conditions at 55 °C for 6 h and was monitored by TLC. After the completion of the reaction, DCM and excess of thionyl chloride was removed under reduced pressure. To the resulting dry crude O-methylated cholyl/deoxylcholyl chloride, freshly distilled DCM (100 mL) and 8-aminoquinoline (1.2 equiv) were added and the mixture was stir at room temperature for 10 h. Thereafter, the resulting reaction mixture was washed with 1 M HCl (3 × 50 mL) solution to remove unreacted 8-aminoquinoline. The organic layer were separated, dried to afford crude product, which was purified by flash column chromatography (Hexanes/EtOAc, 90:10) to afford pure O-methylated $N$-(quinolin-8-yl)cholyl/deoxylcholyl amide (1a-b).


Compound 1a was prepared by literature reported procedure$^3$ as a white solid; 3.56 gm (93%); (Lit. m.p. 158-160 °C).

(4R)-4-((3R,10S,12S,13R,17R)-3,12-dimethoxy-10,13-dimethylhexadecahydro-1H cyclopenta[a]phenanthren-17-yl)-$N$-(quinolin-8-yl)pentanamide (1b). White solid, 3.51 gm (90%); m.p. 150-152 °C; $^1$H NMR (400 MHz, CDCl$_3$, ppm) δ 9.84 (s, 1H), 8.87 - 8.77 (m, 2H), 8.18 (d, $J$ = 8.0 Hz, 1H), 7.58 - 7.45 (m, 3H), 3.45 - 3.40 (m, 1H), 3.63 (s, 3H), 3.29 (s, 3H), 3.22 - 3.11 (m, 1H), 2.70 - 2.61 (m, 1H), 2.54 - 2.44 (m, 1H), 2.06 - 1.88 (m, 4H), 1.86 - 1.70 (m, 8H), 1.64 - 1.51 (m, 6H), 1.44 - 1.31 (m, 3H), 1.25 - 1.13 (m, 3H), 1.02 (d, $J$ = 6.0 Hz, 3H), 0.93 (s, 3H), 0.69 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, ppm) δ 172.4, 148.1, 138.4, 136.3, 134.7, 128.0, 127.5, 121.6, 121.2, 116.4, 82.3, 80.5, 55.7, 55.5, 48.9, 46.5, 46.4, 42.1, 36.1, 35.4, 35.2, 34.9, 34.9, 33.6, 32.6, 31.5, 27.5, 27.4, 26.8, 26.1, 23.7, 23.3, 22.0, 17.6, 12.8; HRMS (ESI) $m/z$ Calcd for C$_{35}$H$_{53}$N$_2$O$_3$+ (M+H)$^+$ : 547.3894, found 547.3885.
2. Original $^1$H & $^{13}$C NMR Spectra of 1b, 3 & 4ba

$^1$H NMR of 1b (400 MHz, CDCl$_3$)

$^{13}$C NMR of 1b (400 MHz, CDCl$_3$)
$^1$H NMR of 3aa (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3aa (400 MHz, CDCl$_3$)
$^1$H NMR of 3ab (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ab (400 MHz, CDCl$_3$)
$^1$H NMR of 3ac (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ac (400 MHz, CDCl$_3$)
$^1$H NMR of 3ad (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ad (400 MHz, CDCl$_3$)
$^1$H NMR of 3ae (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ae (400 MHz, CDCl$_3$)
$^1$H NMR of 3af (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3af (400 MHz, CDCl$_3$)
$^1$H NMR of 3ah (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ah (400 MHz, CDCl$_3$)
$^1$H NMR of 3ai (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ai (400 MHz, CDCl$_3$)
$^1$H NMR of 3aj (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3aj (400 MHz, CDCl$_3$)
$^1$H NMR of 3ak (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ak (400 MHz, CDCl$_3$)
$^1$H NMR of 3al (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3al (400 MHz, CDCl$_3$)
$^1$H NMR of 3aq (400 MHz, CDCl$_3$)

13C NMR of 3aq (400 MHz, CDCl$_3$)
$^1$H NMR of 3ar (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ar (400 MHz, CDCl$_3$)
$^1$H NMR of 3as (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3as (400 MHz, CDCl$_3$)
$^1$H NMR of 3ax (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ax (400 MHz, CDCl$_3$)
$^1$H NMR of 3ba (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3ba (400 MHz, CDCl$_3$)
$^1$H NMR of 3bb (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bb (400 MHz, CDCl$_3$)
$^1$H NMR of 3bc (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bc (400 MHz, CDCl$_3$)
$^1$H NMR of 3be (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3be (400 MHz, CDCl$_3$)
$^1$H NMR of 3bg (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bg (400 MHz, CDCl$_3$)
$^1$H NMR of 3bh (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bh (400 MHz, CDCl$_3$)
$^1$H NMR of 3bk (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bk (400 MHz, CDCl$_3$)
$^1$H NMR of 3bl (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bl (400 MHz, CDCl$_3$)
$^1$H NMR of 3bm (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bm (400 MHz, CDCl$_3$)
$^{1}$H NMR of 3bn (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bn (400 MHz, CDCl$_3$)
$^1$H NMR of 3bo (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bo (400 MHz, CDCl$_3$)
$^1$H NMR of 3bp (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bp (400 MHz, CDCl$_3$)
$^1$H NMR of 3bq (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bq (400 MHz, CDCl$_3$)
$^1$H NMR of 3bs (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bs (400 MHz, CDCl$_3$)
\(^{1}\)H NMR of 3bt (400 MHz, CDCl\(_3\))

\[^{13}\)C NMR of 3bt (400 MHz, CDCl\(_3\))
$^1$H NMR of 3bu (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bu (400 MHz, CDCl$_3$)
$^1$H NMR of 3bv (400 MHz, CDCl$_3$)

$^{13}$C NMR of 3bv (400 MHz, CDCl$_3$)
$^1$H NMR of 4ba (400 MHz, CDCl$_3$)

$^{13}$C NMR of 4ba (400 MHz, CDCl$_3$)
3. Competitive Experiment

![Chemical Structures and Spectra](image)

4. Characterization Data of Intermediate Complex (Crude)

**Chemical Formula:**
- Crude Complex: $\text{C}_{38}\text{H}_{54}\text{N}_2\text{O}_6\text{Pd}$
- 1aA: $\text{C}_{38}\text{H}_{54}\text{N}_2\text{O}_6\text{Pd}$
- 1aB: $\text{C}_{38}\text{H}_{54}\text{N}_2\text{O}_6\text{Pd}$

**HRMS of the Intermediate Complex (Crude):**
- Detected in crude complex
- Found: 741.3074 (M+H)$^+$
- Calc.: 741.3094

**Comparison of UV-Vis and IR Spectra of Intermediate Complex with Starting Materials:**

- UV-Vis
- IR

**Crude Complex**
- Confirmed by HRMS and comparison of its UV-Vis and IR spectra with that of 1a
5. HPLC Profiles of 3

HPLC Profiles of 3aa & 3ba

HPLC Profiles of 3ab & 3bb

HPLC Profile of 3ac & 3bc
HPLC Profile of 3ad & 3ae

HPLC Profile of 3be & 3af

HPLC Profile of 3bg & 3ah
HPLC Profile of 3bh & 3bi

HPLC Profile of 3aj & 3ak

HPLC Profile of 3bk & 3al

HPLC Profile of 3bl & 3bm
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<th>HPLC Profile of 3bn &amp; 3bo</th>
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<th>HPLC Profile of 3bp &amp; 3aq</th>
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<th>HPLC Profile of 3bq &amp; 3ar</th>
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HPLC Profile of 3as & 3bs

HPLC Profile of 3bt & 3bu

HPLC Profile of 3bv & 3ax
6. X-Ray Crystallographic Study of 3aa

A transparent block-shaped crystal was cut to obtain a single crystal, which was chosen by using a polarizing microscope. The crystal was immersed in Paratone-N oil and mounted on goniometer head with nylon loop. To obtain the crystal structure data, a Kappa APEX II diffractometer was used. The diffractometer was equipped with CCD detector and a sealed-tube monochromated MoKα radiation which was used for centering and screening the crystal, determining unit cell for primary evaluation and data collection (with crystal to detector distance 50 mm). The temperature at which data collection was done is 298 K. An APEX3 program was used for the data integration, and SAINT program was used to fit the reflections and obtaining F² and σ(F²) values. Lorentz and polarization effects were also corrected. To obtain a final structure solution, space group was decided along with absorption correction (SADABS)⁴, using a subroutine XPREP. The data was merged and required files were generated for proper analysis and refinement. The direct method was used in structure solution using SHELXS program of SHELXTL package followed by refinement using SHELXL.⁵ The anisotropic refinement parameters were used to refine all NHAs (non-hydrogen atoms) and the hydrogen atoms present were refined as riding atoms with individual isotropic displacement parameters. All the figures presented were drawn using MERCURY 2023 1.0⁷

Crystal data for 3aa. C₄₂H₅₆N₂O₄, Mr = 652.88 g/mol, orthorhombic, space group P2₁2₁2₁ (No. 19), a = 9.2466(7) Å, b = 11.7371(8) Å, c = 33.379(3) Å, α = 90°, β = 90°, γ = 90°, V = 3622.6(5) Å³, Z = 4, T = 296.15 K, Dcalcd = 1.197 g/cm³; Full matrix least-square on F²; R₁ = 0.0446, wR₂ = 0.0924 for 5377 observed reflections [I > 2σ(I)] and R₁ = 0.0701, wR₂ = 0.1021 for all 7340 reflections; number of parameters = 443; GOF = 1.024.
Figure S1. ORTEP view of the asymmetric unit in 3aa. Non-hydrogen atoms are depicted as ellipsoids with 30% probability. Hydrogen atoms are represented by spheres with random radius.

7. References
4. APEX2, SADABS and SAINT; Bruker AXS inc: Madison, WI, USA, 2015.