Electronic Supporting Information for

Highly efficient synthesis of novel methyl 13\(^2\)-methylene mesopyropheophorbide \(a\) by pH-dependent regionselective condensation with formaldehyde and its stereoselective Michael addition reaction

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Table of Contents

1. Supporting Tables and Figures
2. General Information
3. Experimental Procedure and characterization of products
4. NMR (1D, 2D, \(^1\)H, \(^13\)C) and MS (ESI) spectrum of products
5. References
1. Supporting Tables and Figures

**Table S1.** The reaction of methyl mesopyropheophorbide \( \alpha \) 5 with formaldehyde sources (40% formalin or paraformaldehyde) in various conditions.

<table>
<thead>
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<th>entry</th>
<th>reagent 1 (eq.)</th>
<th>reagent 2 (eq.)</th>
<th>time (h)</th>
<th>yield (6) (^a)</th>
<th>yield (6a) (^b)</th>
<th>yield (7) (^c)</th>
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<td>10%</td>
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<tr>
<td>7</td>
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<td>25%</td>
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<td>NaOMe (5.0)</td>
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<tr>
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<td>paraformaldehyde (^b)</td>
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<td>6%</td>
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<tr>
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<td>5%</td>
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<tr>
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<td>combined acid</td>
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</tbody>
</table>

\(^a\) After standard treatment with 5% H\(_2\)SO\(_4\)/MeOH. \(^b\) Equal-weight was used as methyl mesopyropheophorbide \( \alpha \) 5. \(^c\) No product was observed.
Fig. S1. The comparative $^1$H NMR spectra (CDCl$_3$, 400 MHz) in the region $\delta$ 2.8–11.0 ppm of methyl $^{13}_2$-methylene mesopyropheophorbide $a$ 6 and its Michael reaction adducts 8a - 8c.

Fig. S2. NOE interactions (selected) observed in 2D/NOESY $^1$H NMR spectra of Michael reaction adducts 8a - 8c.
2. General Information

All reactions were monitored by TLC using 0.20 mm silica gel plates with or without UV indicator (60F–254). Silica gel 60 (230–400 mesh, Merck) was used for flash column chromatography. $^1$H and $^{13}$C NMR spectra were measured at 400 and 101 MHz, respectively, on a Bruker Advance II spectrometer. COSY and NOESY techniques were used to assign the NMR peak. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS, 0 ppm) unless otherwise indicated. Electronic absorption spectra were measured on a AOE A560 UV–Vis spectrophotometer. The absorption maxima $\lambda_{\text{max}}$ are given in nm and molar absorbance coefficient ($\epsilon$) or relative intensity. MS(ESI) were obtained on a AB SCIEX API 4000 LC/MS System at Yantai University. Materials obtained from commercial suppliers were used without further purification. Methyl mesopyropheophorbide a 5 was prepared according to the procedure described in the literature[1].

3. Experimental Procedure and characterization of products

**Synthesis of methyl 13$^2$-methylene mesopyropheophorbide a 6 and methyl 13$^2$-dihydromethyl mesopyropheophorbide a 6a**

Methyl mesopyropheophorbide a 5 (300 mg, 0.545 mmol) and paraformaldehyde (300 mg) was dissolved in THF (50 mL), and a solution of sodium methoxide in methanol (1mol/L, 5.45mL) was added under N$_2$ atmosphere, then the reaction mixture was stirring at room temperature under N$_2$ atmosphere for 6 h, monitoring the progress spectroscopically. pH value of the reaction mixture was adjusted to 4-6 by adding diluted hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was dissolved in 100 mL methanol containing 5% H$_2$SO$_4$ and allowed to stir at room temperature under N$_2$ atmosphere overnight to recover the 17$^3$-methyl ester structure. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-acetone, gradient 2-4% acetone) to give 261 mg (0.463 mmol, 85%) of the title compound 6 as dark green solid and 20 mg (0.033mmol, 6%) of 6a as a byproduct. 6: UV-VIS (CH$_2$Cl$_2$) $\lambda_{\text{max}}$ 409 (relative intensity, 0.90), 427 (1.00), 520 (0.10), 556 (0.08), 609 (0.07), 664 (0.41) nm. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.46 (s, 1H, 10-H), 9.24 (s, 1H, 5-
H), 8.61 (s, 1H, 20-H), 6.81 (s, 1H, 13^{2a}-H), 6.50 (s, 1H, 13^{2a}-H), 4.62 (d, J = 9.3 Hz, 1H, 17-H), 4.53 (q, J = 7.2 Hz, 1H, 18-H), 3.81 (q, J = 7.5 Hz, 2H, 3^{1}-CH_{2}), 3.66, 3.64, 3.30, 3.20 (each s, each 3H, OCH_{3} + CH_{3}), 3.64 – 3.56 (m, 2H, 8^{1}-CH_{2}), 2.72 – 2.60, 2.36 – 2.27, 2.07 – 1.96 (each m, total 4H, 17^{1} + 17^{2}-CH_{2}), 1.83 (d, J = 7.3 Hz, 3H, 18-CH_{3}), 1.71 (t, J = 7.6 Hz, 3H, 3^{2}-CH_{3}), 1.65 (t, J = 7.5 Hz, 3H, 8^{2}-CH_{3}), 0.08, -1.96 (each brs, each 1H, 2 × NH). \( ^{13}C \) NMR (101 MHz, CDCl_{3}) δ 187.13, 173.51, 171.43, 161.88, 154.78, 150.44, 149.65, 149.10, 145.00, 142.01, 141.90, 136.91, 136.51, 135.97, 131.15, 128.63, 128.46, 112.82, 106.64, 104.52, 97.04, 93.31, 51.69, 51.43, 49.79, 31.24, 29.31, 23.54, 19.47, 19.42, 17.50, 17.01, 12.20, 11.29, 10.99. MS (ESI): calcd for C_{35}H_{38}N_{4}O_{3} 562.3; found m/z 563.7 (MH^{+}). Anal. calcd for C_{35}H_{38}N_{4}O_{3} C 74.71, H 6.81, N 9.96. Found C 74.75, H 6.84, N 10.01. \( 6a \): UV-VIS (CH_{2}Cl_{2}) \( \lambda_{\text{max}} \) 408 (relative intensity, 1.0), 504 (0.09), 536 (0.09), 603 (0.08), 658 (0.35) nm. \( ^{1}H \) NMR (400 MHz, CDCl_{3}) δ 9.35 (s, 1H, 10-H), 9.06 (s, 1H, 5-H), 8.41 (s, 1H, 20-H), 5.06 (d, J = 11.5 Hz, 1H, 13^{2a}-CH_{2}), 4.84 (d, J = 11.5 Hz, 1H, 13^{2a}-CH_{2}), 4.73 (d, J = 11.4 Hz, 1H, 13^{2a}-CH_{2}), 4.55 (d, J = 11.3 Hz, 1H, 13^{2a}-CH_{2}), 4.42 – 4.32 (m, 2H, 17 + 18-H), 3.76 (q, J = 7.5 Hz, 2H, 3^{1}-CH_{2}), 3.64 – 3.53 (m, 2H, 8^{1}-CH_{2}), 3.58, 3.26, 3.18, 2.85 (each s, each 3H, OCH_{3} + CH_{3}), 2.51 – 2.35, 2.28 – 2.20, 2.13 – 2.01 (each m, total 4H, 17^{1} + 17^{2}-CH_{2}), 1.72 (t, J = 7.6 Hz, 3H, 3^{2}-CH_{3}), 1.67 – 1.61 (m, 6H, 8^{2} + 18-CH_{3}), 0.03, -1.19 (each brs, each 1H, 2 × NH). MS (ESI): calcd for C_{36}H_{42}N_{4}O_{5} 610.3; found m/z 611.7 (MH^{+}). Anal. calcd for C_{36}H_{42}N_{4}O_{5} C 70.80, H 6.93, N 9.17. Found C 70.83, H 6.91, N 9.20.

**Synthesis of methyl 20-hydroxymethyl mesopyropheophorbide a 7**

Methyl mesopyropheophorbide a 5 (200 mg, 0.363 mmol) and aqueous formalin (10 mL, 40%) was dissolved in a mixture of glacial acetic acid (10 mL), phosphoric acid (8 mL) and concentrated hydrochloric acid and allowed to stir at room temperature for 3 days. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was dissolved in 100 mL methanol containing 5% H_{2}SO_{4} and allowed to stir at room temperature under N_{2} atmosphere overnight to recover the 17^{3}-methyl ester structure. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-methanol, gradient 2-4% methanol) to give the unreacted
starting material 5 (52 mg, 0.094 mmol, 26%) as the fast-moving band and the title compound 7 as dark green solid (137 mg, 0.236 mmol, 65%). UV-VIS (CH₂Cl₂) λ_{max} 412 (relative intensity, 1.00), 511 (0.11), 544 (0.12), 609 (0.08), 666 (0.35) nm. ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H, 10-H), 9.32 (s, 1H, 5-H), 6.36 (d, J = 12.8 Hz, 1H, 20¹-H), 6.01 (d, J = 12.8 Hz, 1H, 20¹-H), 5.19 (d, J = 19.8 Hz, 1H, 13²-H), 5.13 (d, J = 19.8 Hz, 1H, 13²-H), 4.80 (q, J = 7.1 Hz, 1H, 18-H), 4.20 (dd, J = 8.2, 3.3 Hz, 1H, 17-H), 3.90 - 3.82 (m, 2H, 3¹-CH₂), 3.63, 3.54, 3.45, 3.27 (each s, each 3H, OCH₃ + CH₃), 3.66 (q, J = 7.6 Hz, 2H, 8¹-CH₂), 2.52 - 2.32, 2.23 - 2.11 (each m, total 4H, 17¹ + 17²-CH₂), 1.71 (t, J = 7.6 Hz, 3H, 3²-CH₃), 1.68 (t, J = 7.6 Hz, 3H, 8²-CH₃), 1.50 (d, J = 7.0 Hz, 3H, 18-CH₃), 0.70, -1.34 (each brs, each 1H, 2 × NH). MS (ESI): calcd for C₃₅H₄₀N₄O₄ 580.3; found m/z 581.3 (MH⁺). Anal. calcd for C₃₅H₄₀N₄O₄ C 72.39, H 6.94, N 9.65. Found C 72.28, H 6.84, N 9.69.

General procedure for the Michael reaction of compound 6 and the synthesis of compounds 8a-8c:

Methyl 13²-methylene mesopyropheophorbide a 6 (200 mg, 0.355 mmol) and corresponding reactive methylene compound (1 mL, acetylacetone for compound 8a; dimethyl malonate for compound 8b and ethyl acetoacetate for compound 8c) was dissolved in THF (20 mL), and a solution of sodium methoxide in methanol (1mol/L, 3.55 mL) was added under N₂ atmosphere, then the reaction mixture was stirring at room temperature under N₂ atmosphere for 3 h, monitoring the progress spectroscopically. pH value of the reaction mixture was adjusted to 4-6 by adding diluted hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-acetone, gradient 0.5-2.0% acetone) to give the desired compound 8a-8c as dark green solids (yield: 90-94%).

8a: Yield: 94%. UV-VIS (CH₂Cl₂) λ_{max} 410 (relative intensity, 1.00), 504 (0.10), 535 (0.09), 603 (0.08), 656 (0.35) nm. ¹H NMR (400 MHz, CDCl₃) δ 9.47(9.48) (s, 1H, 10-H), 9.15(9.17) (s, 1H, 5-H), 8.48 (s, 1H, 20-H), 5.25(5.38) (dd, J = 8.6, 3.4 Hz, 1H, 13²-H), 4.49 (d, J = 8.8 Hz, 1H, 17-H), 4.45 (t, J = 6.3 Hz, 1H, 13²b-H), 4.39 (q, J = 7.9 Hz, 1H, 18-H), 3.79 (q, J = 7.5 Hz, 2H, 3¹-CH₂), 3.66 (q, J = 7.6 Hz, 2H, 8¹-CH₂), 3.68, 3.54(3.58), 3.27, 3.21 (each s, each 3H, OCH₃ + CH₃), 3.37 – 3.31 (m, 1H, 13²a-H), 3.04 – 2.96 (m, 1H, 13²a-H), 2.65 – 2.51, 2.26 – 2.11 (each m, total 4H, 17¹ + 17²-CH₂), 2.37 (s, 3H, COCH₃), 1.98 (d, J = 7.3 Hz, 3H,
18-CH₃), 1.71 (t, J = 7.7 Hz, 3H, 3²-CH₃), 1.68 (t, J = 7.7 Hz, 3H, 8²-CH₃), 1.28 (s, 3H, COCH₃), 0.53, -1.60(-1.64) (each brs, each 1H, 2 × NH). ¹³C NMR (101 MHz, CDCl₃) δ 204.0, 203.6, 198.8, 180.0, 173.6, 172.4(172.3), 161.6, 155.9, 150.5, 149.0, 145.3, 142.6, 141.8, 137.5(137.3), 135.9, 131.6(131.5), 128.7, 127.7, 108.7, 104.3(104.2), 96.0, 92.7(92.5), 64.5, 55.6, 51.6(51.7), 50.6(50.7), 50.5(50.1), 31.0, 30.9, 30.1(30.0), 30.0(29.9), 29.6(29.7), 23.5(23.3), 19.5, 19.4, 17.5, 16.9, 12.1, 11.3, 11.0. MS (ESI): calced for C₄₀H₄₆N₄O₅ 662.4; found m/z 663.9 (MH⁺). Anal. calcd for C₄₀H₄₆N₄O₅ C 72.48, H 7.00, N 8.45. Found C 72.46, H 6.98, N 8.49.

8b: Yield: 90%. UV-VIS (CH₂Cl₂) λₘₐₓ 410 (relative intensity, 1.00), 504 (0.10), 535 (0.08), 603 (0.07), 657 (0.36) nm. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H, 10-H), 9.17 (s, 1H, 5-H), 8.49 (s, 1H, 20-H), 5.38 (dd, J = 8.1, 3.2 Hz, 1H, 13₂-H), 4.52 (d, J = 8.5 Hz, 1H, 17-H), 4.40 (q, J = 7.4 Hz, 1H, 18-H), 4.06 (t, J = 7.1 Hz, 1H, 13₂b-H), 3.79 (q, J = 7.4 Hz, 2H, 3¹-CH₂), 3.77, 3.67, 3.55, 3.28, 3.22, 2.36 (each s, each 3H, OCH₃ + CH₃), 3.67 (q, J = 7.3 Hz, 2H, 8¹-CH₂), 3.47 – 3.41 (m, 1H, 13₂²-H), 3.19 – 3.08 (m, 1H, 13₂²-H), 2.66 – 2.52, 2.26 – 2.13 (each m, total 4H, 17₁ + 17₂-CH₂), 1.98 (d, J = 7.3 Hz, 3H, 18-CH₃), 1.72 (t, J = 7.7 Hz, 3H, 3₂-CH₃), 1.69 (t, J = 7.7 Hz, 3H, 8₂-CH₃), 0.46, -1.64 (each brs, each 1H, 2 × NH). ¹³C NMR (101 MHz, CDCl₃) δ 198.36, 173.60, 172.13, 170.02, 169.99, 161.46, 155.60, 150.45, 149.10, 145.22, 142.41, 141.77, 137.48, 137.26, 135.77, 131.48, 128.91, 127.86, 108.24, 104.34, 96.01, 92.51, 55.34, 52.67, 51.64, 51.63, 50.64, 50.39, 48.64, 31.25, 30.97, 30.06, 23.28, 19.49, 19.37, 17.47, 16.91, 12.11, 11.28, 10.96. MS (ESI): calced for C₄₀H₄₆N₄O₅ 694.3; found m/z 695.9 (MH⁺). Anal. calcd for C₄₀H₄₆N₄O₅ C 69.15, H 6.67, N 8.06. Found C 69.21, H 6.65, N 8.09.

8c: Yield: 93%. UV-VIS (CH₂Cl₂) λₘₐₓ 410 (relative intensity, 1.00), 504 (0.09), 534 (0.09), 601 (0.08), 657 (0.40) nm. ¹H NMR (400 MHz, CDCl₃) δ 9.50(9.49) (s, 1H, 10-H), 9.18 (s, 1H, 5-H), 8.50(8.49) (s, 1H, 20-H), 5.30 (d, J = 7.8 Hz, 1H, 13₂-H), 4.57(4.49) (d, J = 8.3 Hz, 1H, 17-H), 4.40 (q, J = 7.2 Hz, 1H, 18-H), 4.33 – 4.19 (m, 3H, 13₂b-H+ 13₂b-CO₂CH₂CH₃), 3.81 (q, J = 7.6 Hz, 2H, 3¹-CH₂), 3.68 (q, J = 7.3 Hz, 2H, 8¹-CH₂), 3.69, 3.56(3.54), 3.29, 3.24, 2.38(1.47) (each s, each 3H, OCH₃ + CH₃), 3.48 – 3.34 (m, 1H, 13₂²-H), 3.06 – 2.92 (m, 1H, 13₂²-H), 2.78 – 2.51, 2.25 – 2.16 (each m, total 4H, 17₁ + 17₂-CH₂), 1.97(1.96) (d, J = 7.0 Hz, 3H, 18-CH₃), 1.77 – 1.67 (m, 6H, 3² + 8²-CH₃), 1.29 (t, J = 7.1 Hz, 3H, 13₂b-CO₂CH₂CH₃), 0.49,
1.61(-1.63) (each brs, each 1H, 2 × NH). 13C NMR (101 MHz, CDCl3) δ 203.3(203.1), 198.9, 173.6, 172.2, 169.8, 169.5, 161.5(161.4), 155.7(155.6), 150.5, 149.0(148.9), 145.2(145.1), 142.4, 141.8(141.7), 137.4, 137.3, 135.8(135.7), 131.6(131.5), 128.8(128.7), 127.7, 104.24, 95.95, 92.66(92.54), 61.59, 60.64, 56.29(56.04), 55.39(55.32), 51.62(51.58), 50.65(50.44), 31.03(30.99), 30.39(30.15), 30.04(29.54), 23.44(23.27), 19.48, 19.36, 17.47, 16.91, 14.11, 12.89, 12.11, 11.28, 10.96. MS (ESI): calcd for C₄₁H₴₈N₄O₆ 692.4; found m/z 693.6 (MH⁺). Anal. calcd for C₄₁H₴₈N₄O₆ C 71.08, H 6.98, N 8.09. Found C 71.12, H 7.00, N 8.05.

**Synthesis of 20-formyl meso pyropheophorbide a 9**

Compound 7 (100 mg, 0.172 mmol) was dissolved in 10 mL dry dichloromethane containing NMO (26 mg, 0.258 mmol). After stirring the mixture for 10 min, TPAP (10 mg, 0.028 mmol) was added and allowed to stir at room temperature for 1 h. The reaction mixture was diluted with dichloromethane and then washed with sodium sulphite solution and brine. The organic layer was dried over sodium sulfate, and evaporated in vacuum. The residue was separated on silica gel (eluent: dichloromethane-acetone, gradient 0.5-2.0% acetone) to give the title compound 9 as dark green solid (68 mg, 0.117 mmol, 68%). UV-VIS (CH₂Cl₂) λ max 412 (relative intensity, 1.00), 513 (0.07), 549 (0.13), 631 (0.08), 689 (0.29) nm. 1H NMR (400 MHz, CDCl₃) δ 11.80 (s, 1H, 20-CHO), 9.27 (s, 1H, 10-H), 9.21 (s, 1H, 5-H), 5.18 (q, J = 7.0 Hz, 1H, 18-H), 5.05 (d, J = 20.0 Hz, 1H, 13²-H), 4.98 (d, J = 20.0 Hz, 1H, 13²-H), 4.03 (dd, J = 9.1, 3.1 Hz, 1H, 17-H), 3.74 (q, J = 7.6 Hz, 2H, 3¹-C₂H₂), 3.55 (q, J = 7.6 Hz, 2H, 8¹-C₂H₂), 3.61, 3.52, 3.24, 3.14 (each s, each 3H, OCH₃ + CH₃), 2.65 – 2.57, 2.50 – 2.42, 2.34 – 2.27, 2.17 – 2.06 (each m, total 4H, 17¹ + 17²-C₂H₂), 1.66 (t, J = 7.6 Hz, 3H, 3²-C₂H₃), 1.63 (t, J = 7.6 Hz, 3H, 8²-C₂H₃), 1.42 (d, J = 7.0 Hz, 3H, 18-CH₃), 0.88, 0.04 (each brs, each 1H, 2 × NH). MS (ESI): calcd for C₃₅H₃₈N₄O₄ 578.3; found m/z 579.3 (MH⁺). Anal. calcd for C₃₅H₃₈N₄O₄ C 72.64, H 6.62, N 9.68. Found C 72.68, H 6.67, N 9.70.

4. NMR (1D, 2D, 1H, 13C) and MS (ESI) spectrum of products
6a
8a

+Q1: 238 MCA scans from Sample 4 (TuneSampleID1414) of Ijaz acquitted Turbo Spray
Max. 5.0e7 cps.

8a
5. References