Supplementary information for

Large scale conversion of trilobolide into the payload of Mipsagargin: 8-O-(12-aminododecanoyl)-8-O-debutanoylthapsigargin

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Product 1 (3-oxo-3-desangeloyl trilobolide)

Figure S1A – $^1$H NMR of product 1 (400 MHz, CDCl$_3$)
Figure S1B – $^{13}$C NMR of product 1 (100 MHz, CDCl$_3$)
Figure S1C - HMQC of product 1
Figure S1D - HRMS of product 1 - \([C_{22}H_{30}O_9+Na]^+ = 461.17824\)
Product 2 (2-octanoyl-3-oxo-3-desangeloyl trilobolide)

Figure S2A $^1$H NMR of product 2 (400 MHz, CDCl$_3$)
Figure S2B $^{13}$C NMR of product 2 (100 MHz, CDCl$_3$)
Figure S2C HMQC of product 2
Figure S2D LCMS of product 2 - $[\text{C}_{30}\text{H}_{44}\text{O}_{11}\text{+Na}]^+ = 603.27795$
Product 3 ((3S)-hydroxy-2-octanoyl-3-desangeloyl trilobolide)

Figure S3A $^1$H NMR of product 3 (400 MHz, CDCl$_3$)
Figure S3B $^{13}$C NMR of product 3 (100 MHz, CDCl$_3$)
Figure S3C HMQC of product 3
Figure S3D HRMS of product 3 - $[\text{C}_{30}\text{H}_{46}\text{O}_{11}+\text{Na}]^+ = 605.29364$
Product 4 (8-O-((2S)-Methylbutanoyl)-8-O-debutanoyl thapsigargin)

Figure S4A $^1$H NMR of product 4 (400 MHz, CDCl$_3$)
Figure S4B $^{13}$C NMR of product 4 (100 MHz, CDCl$_3$)
Figure S4C HMQC of product 4
Figure S4D HRMS of product 4 - $[\text{C}_{35}\text{H}_{52}\text{O}_{12}+\text{Na}]^+ = 687.33542$
Product 5 (8-O-debutanoyl thapsigargin)

Figure S5A $^1$H NMR of product 4 (400 MHz, CDCl$_3$)
Figure S5B $^{13}$C NMR of product 5 (100 MHz, CDCl$_3$)
Figure S5C HMQC of product 5
Figure S5D HRMS of product 5 - $[\text{C}_{30}\text{H}_{44}\text{O}_{11}\text{+Na}]^+ = 603.27805$
Product 6 (8-O-(Boc-12-aminododecanoyl)-8-O-debutanoyl thapsigargin)

Figure S6A ¹H NMR of product 6 (400 MHz, CDCl₃)
Figure S6B ¹³C NMR of product 6 (100 MHz, CDCl₃)
Figure S6C HMQC of product 6
Figure S6D HRMS of product 6 - \([\text{C}_{47}\text{H}_{75}\text{NO}_{14}+\text{Na}]^+ = 900.50827\]
Product 7 (8-O-(12-Aminododecanoyl)-8-O-debutanoyl thapsigargin)

Figure S7A $^1$H NMR of product 7 (400 MHz, CD$_3$OD)
Figure S7B $^{13}$C NMR of product 7 (100 MHz, CD$_3$OD)
Figure S7C HMQC of product 7
**Figure S7D** HRMS of product 7 - $[\text{C}_{42}\text{H}_{67}\text{NO}_{12}+\text{H}]^+ =$778.47428
2,4,6-trichlorobenzoic (Z)-2-methylbut-2-enoic anhydride (8)

Figure S8A $^1$H NMR of product 8 (400 MHz, CD$_3$Cl)
Figure S8B $^{13}$C NMR of product 8 (100 MHz, CD$_3$Cl)
Figure S8C HMQC of product 8
Figure S9A $^1$H NMR of product 9 (400 MHz, CD$_3$Cl)
Figure S9B  HRMS of product 9 - $[\text{C}_{17}\text{H}_{33}\text{NO}_4+\text{Na}]^+ = 338.23052$
Scheme S1. The reactions adopted from the literature published [s1*, s2**, s3***]. Reagents and conditions: a) CrO₃, HF, AcCN, MW-95 °C, 2 h; b) octanoic acid, Mn(OAc)₃·2H₂O, 120 °C, 6 h; c) Zn(BH₄)₂, Et₂O, -20 °C, 3.5 h, then H₂O; d) in situ preparation of 2,4,6-trichlorobenzoic (Z)-2-methylbut-2-enoic anhydride = acyl chloride, AngOH, TEA, in toluene; 90 °C, 18 h; e) TEA, MeOH, 0 °C→20 °C, 21 h; f) Boc-12-aminododecanoic acid, DCC, 4-DMAP, DCM, RT, 0 °C→RT, 6 h; g) TFA, DCM, H₂O, RT, 45 min. Under the arrows, the scale of the starting material is specified in green.
Scheme S2. Proposed mechanism of α-oxylation

References

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[s3] Jakobsen, C. M.; Denmeade, S. R.; Isaacs, J. T.; Gady, A.; Olsen, C. E.; Christensen, S. B. Design, synthesis, and pharmacological evaluation of thapsigargin analogues for targeting apoptosis to prostatic cancer cells. *J. Med. Chem.* 2001, 44, 4696-4703.