Towards the total synthesis of enacyloxin IIa

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Polyketide natural products are an invaluable resource for the development of new antibiotics. Enacyloxin IIa is a linear polyketide produced by Burkholderia ambifaria AMMD, isolated by Watanabe in 1982[1-2] and later again by Challis group at Warwick,[3] which shows potent activity against multidrug-resistant Gram-negative bacteria, such as Acinetobacter baumannii. We establish synthetic strategies to access, and vary, each portion of the enacyloxin framework to enable SAR studies.

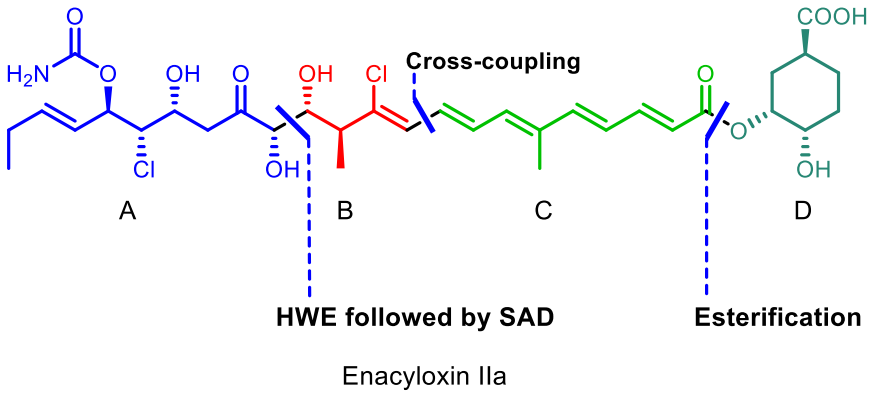

Figure 1. Disconnection strategy for enacyloxin IIa

The synthetic strategy is built around four subregions the polyhydroxylated tale (A), the central linker containing chlorine (B), polyene motif (C), and the ester head (D). With key disconnections being cross coupling cross coupling-based assembly of the pentaene, HWE to link the western polyhydroxylated fragment, and esterification to incorporate the ester head group.

(1) T. Watanabe, et al., J. Antibiot., 1982, 35, 1141-1147.
(2) T. Watanabe, et al., Agric. Biol. Chem., 1990, 54, 259-261
(3) E. Mahenthiralingam et al., Chem. Biol. 2011, 18, 665.