Studies Towards a Scalable Second-Generation Total Synthesis of the Aplyronines as Novel Payloads for Antibody-Drug Conjugates

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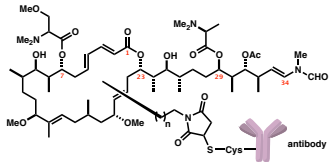
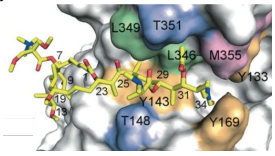
1. Introduction

Aplysia kurodai

- The aplyronines (A-H) comprise a family of structurally complex and extremely scarce marine macrolides isolated from the Japanese sea hare *Aplysia kurodai* by Yamada.[1]
- Aplyronine A exhibits potent biological activity *in vivo*[2] and picomolar cancer cell growth inhibition against the NCI 60 cell line panel.[3]
- It forms an unprecedented heterotrimeric complex with its cellular targets, cytoskeletal proteins actin and tubulin, disrupting cell division. This novel dual mode of action makes it an exciting payload candidate for a new class of antibody-drug conjugates for targeted cancer chemotherapy.[4]

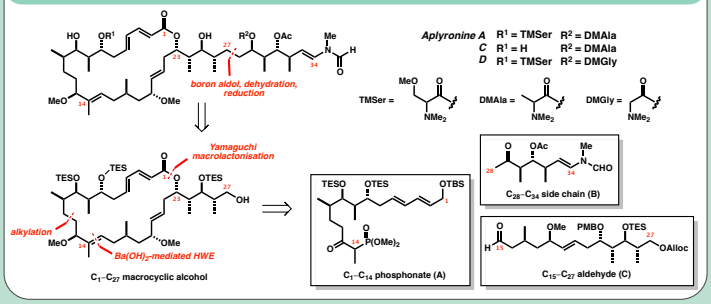




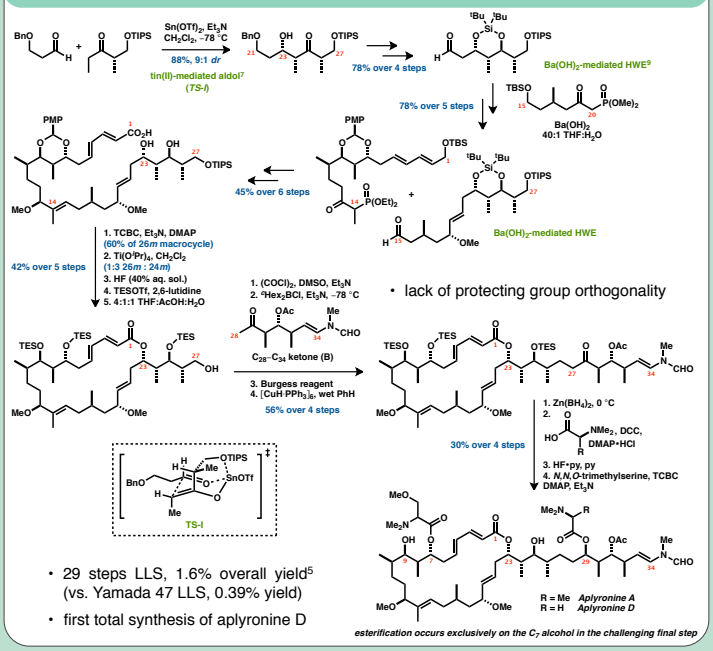
Aplyronine A-actin complex

- The aplyronine side chain intercalates into a hydrophobic cleft of actin with both amino acid residues protruding into the bulk solvent region.[4] This allows for attachment to antibodies through amino acid modification without foreseeable loss of actin binding ability.
- An efficient and scalable total synthesis is required to access viable quantities of suitably modified aplyronines incorporating a linker for conjugation to selected antibodies.

2. Retrosynthesis



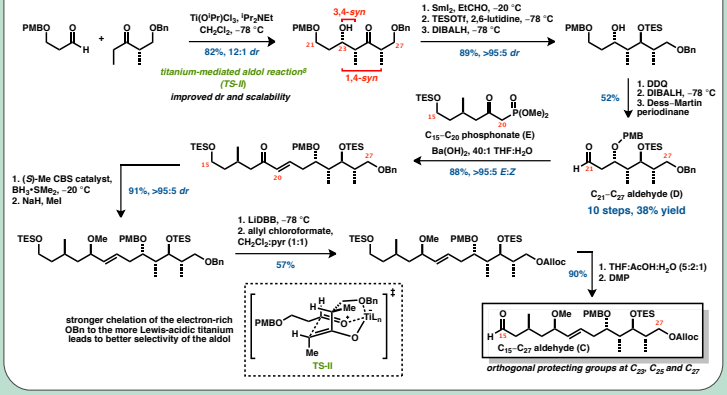
3. First-Generation Total Synthesis



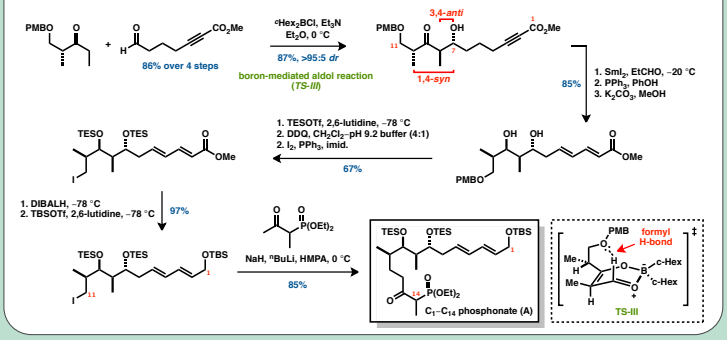
- lack of protecting group orthogonality
- 29 steps LLS, 1.6% overall yield[5] (vs. Yamada 47 LLS, 0.39% yield)
- first total synthesis of aplyronine D

esterification occurs exclusively on the C_7 alcohol in the challenging final step

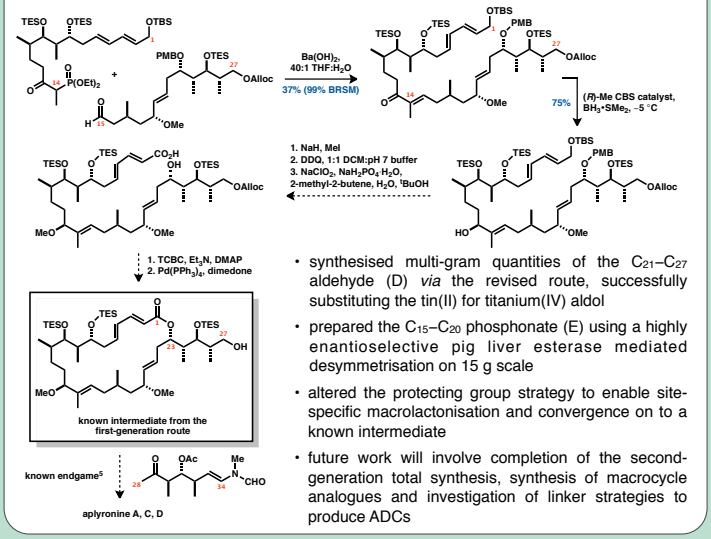
4. C_{15}–C_{27} Aldehyde Synthesis



5. C_1–C_{14} Phosphonate Synthesis



6. Completion of the Macrocycle and Conclusions



- synthesised multi-gram quantities of the C_{21}–C_{27} aldehyde (D) *via* the revised route, successfully substituting the tin(II) for titanium(IV) aldol
- prepared the C_{15}–C_{20} phosphonate (E) using a highly enantioselective pig liver esterase mediated desymmetrisation on 15 g scale
- altered the protecting group strategy to enable site-specific macrolactonisation and convergence on to a known intermediate
- future work will involve completion of the second-generation total synthesis, synthesis of macrocycle analogues and investigation of linker strategies to produce ADCs

7. References

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JAVNI SKLAD REPUBLIKE SLOVENIJE ZA RAZVOJ KADROV IN ŠTIPENDIJE

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