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

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1. Introduction

- The aplyronine (A-H) comprise a family of structurally complex and extremely scarce marine macrolides isolated from the Japanese sea hare Aplysia kurodai by Yamada. The a polygons exhibit potent biological activity in vivo and picomolar cancer cell growth inhibition against the NCI 60 cell line panel. It forms an unprecedented heteronuclear 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.

- The aphonyrane side chain interacts into a hydrophobic crevice of actin with both amino acid residues protruding into the bulk solvent region. 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 aphonyronines incorporating a linker for conjugation to selected antibodies.

2. Retrosynthesis

3. First-Generation Total Synthesis

4. C₁₅–C₂₇ Aldehyde Synthesis

5. C₁–C₁₆ Phosphonate Synthesis

6. Completion of the Macrocycle and Conclusions

7. References

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