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Mechanism-specified 5-*exo* termini differentiation of a C32-desmethyl C28–C34 aplyronine A analog segment

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ABSTRACT

A new mild, high yielding oxidative cleavage method allows access to a critical lactone aplyronine A analog precursor. Enhanced termini selectivity is achieved, granting access to a previously unavailable C28–C34 C-32-desmethyl actin binding tail fragment via vinyl sulfone polypropionate methodology.

Introduction

Aplyronine A (Fig. 1) is an *exceptionally scarce* (3×10^{-7} wt %) macrolide originally isolated from the sea hare *Aplysia kurodai*.[1] It has actin binding and depolymerizing properties,[2,3] as well as potent in vivo antitumor activity.[1] The initial inquiry into the mechanism of aplyronine A's antineoplastic properties strongly focused upon its interaction with actin. Actin is the most abundant protein in the eukaryotic cytoskeleton and is essential for the regulation of various cellular functions, such as muscle contraction, cell division, and the migration of tumor cells. Various additional small agents have been discovered that target actin show cytotoxicity[2] at concentrations above 100 nM. For example, ulapualides,[4] mycalolides,[5] kabiramides,[6] sphinxolides/reidispongiolides,[7] swinholides,[7] and bistramides[8] are all actin-depolymerizing agents. Complexes between these macrolides and actin are similar to the aplyronine A–actin complex.

While aplyronine A's ability to bind/depolymerize actin is similar to other macrolides, its exceptional cytotoxicity is starkly apparent. For example, jasplakinolide exhibits an IC_{50} of 100 nM against HL-60 cells,[9,7] Mycalolide B has an IC_{50} of 4.7 nM; but aplyronine A has an IC_{50} of 0.0029 nM after 72 h of incubation. Swinholide A depolymerizes actin at 4 nM–1 μM[7] while aplyronine A requires a concentration of 31 μM.[10–13] Aplyronine A *increases the lifespan* of mice between 201% and 566% in *5 different tumor models* (566%: Lewis lung; 545%: P388 leukemia; 398% Ehrlich carcinoma; 255%: Colon 26 carcinoma; and 201%: B16 melanoma).[9] These results provide convincing evidence that actin activity is not the sole determinant of antineoplastic activity.

Recent seminal work by Kigoshi[14] and co-workers has provided definitive mechanistic insight into the antineoplastic properties of aplyronine A (ApA). These results indicate that the potent cytotoxicity of ApA is not solely due to its F-actin severing properties. Photolabelling experiments revealed that the C7 trimethylserine ester group binds to β-tubulin, leading to the formation of a 1:1:1 tubulin/aplyronine A/actin complex (Fig. 1) that exhibits its antineoplastic activity at far lower concentrations than that of the aplyronine A–actin complex. Evidence suggests that the existence of this ternary complex in the interior of the cell inhibits tubulin polymerization and enhances microtubule depolymerization.

Results and discussion

A primary goal of the Fuchs vinyl sulfone program is to access biorelevant intermediates containing contiguous chiral carbon centers.[15] While the vinyl sulfone strategy has successfully enabled the construction of key intermediates of a number of natural products,[15] the aplyronine A approach has also revealed several limitations. The design for synthesis of the aplyronine A core features

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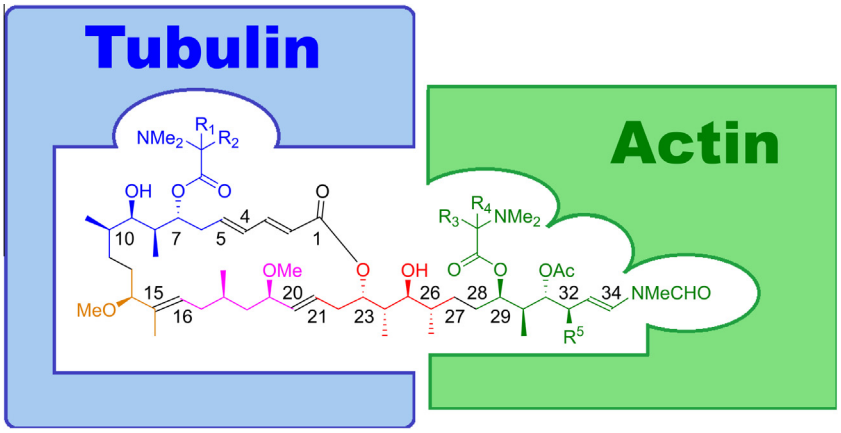


Aplyronine A: R_1 = H, R_2 = —CH_2OMe, R_3 = H, R_4 = Me, R_5 = Me
Aplyronine A Analog: R_1 = R_2 = —CH_2OMe; R_3 = R_4 = Me, R_5 = Me
Aplyronine A C32 des Methyl Analog: R_1 = R_2 = —CH_2OMe; R_3 = R_4 = Me, R_5 = H

Figure 1. Actin–aplyronine A analogs–tubulin ternary complex.

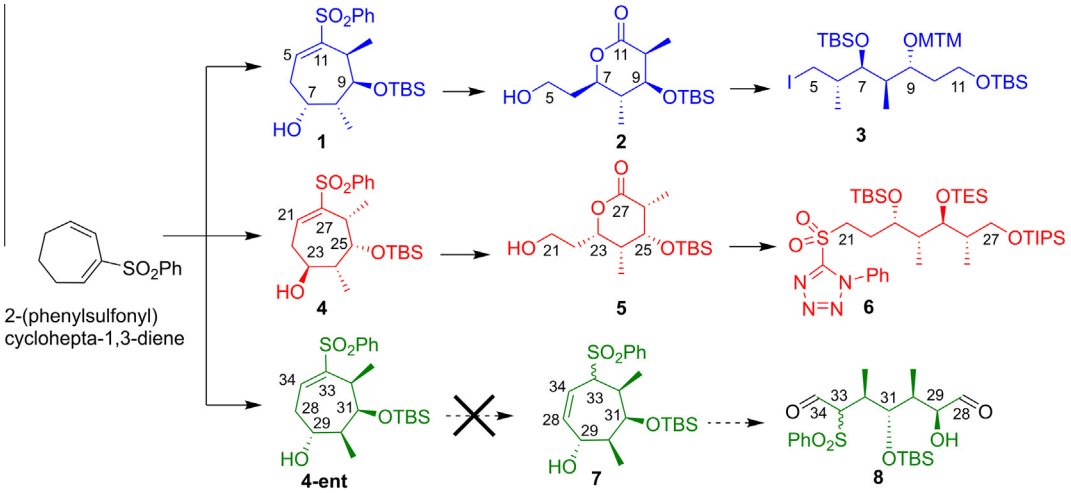
three key polypropionate arrays: C7–C10, C23–C26 and C29–C32. Successful assembly of the C7–C10 and C23–C26 and assembly of the C1–C23 macrolactone has been achieved by El-Awa, Noshi, and Hong (Fig. 1).[15]

Synthesis of enantiopure vinyl sulfones **1**, **4**, and **4-ent** featured catalytic Jacobsen epoxidation of achiral 2-phenylsulfonyl-1,3-cycloheptadiene, which is prepared from cycloheptanone in a single operation on the kilogram scale (Scheme 1).[16] Transformation of vinyl sulfones **1** and **4** to lactones **2** and **5** and further on to termini-differentiated segments **3** and **6** was previously reported.[17,18] Unfortunately, base-mediated vinyl sulfone chemistry, established in several isomeric substrates, was uniformly unsuccessful for the preparation of allylic sulfone **7** from **4-ent**.[19,20]

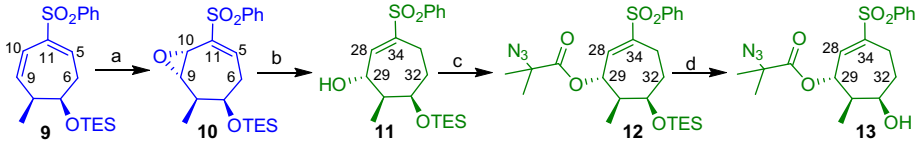
Faced with a looming program deadline and encouraged by in silico modeling by Hirst,[21] which had previously calculated F-actin depolymerization ability, predicted pIC_{50} values of 4.40, 4.08, and 4.05 for aplyronine A, aplyronine A C32 epi-methyl, and aplyronine A C32 desmethyl respectively. Authentic aplyronine A has a pIC_{50} value of 4.51 which correlates well with the calculated value of 4.40.[22] Based on these calculations, it was decided that synthesis of C32 desmethyl analog would provide a more expeditious approach to the desired target.

The new scheme (Scheme 2) returned to **9** the enantiopure stereodiad precursor of blue fragment **1**, thus avoiding preparation of **4-ent** altogether. Epoxidation of diene **9**,[19] with dimethyldioxirane (DMDO) formed in situ from Oxone® and acetone provides enantiopure epoxide diastereomer **10**.[18,19] Nucleophilic addition of sodium borohydride effects reduction of **10** to provide alcohol **11** in 82% yield. 2-Azido-2-methylpropanoic acid was prepared from 2-bromo-2-propionic acid and sodium azide using a simplification of the existing literature protocol.[23] 2-Azido-2-methylpropanoic acid forms the acid chloride in situ with oxalyl chloride, dimethylformamide (DMF), dimethylaminopyridine (DMAP), and triethylamine (TEA), which suffers reaction with alcohol **11** to smoothly afford azapivalate ester **12**. Cleavage of the silylether of **12** with camphorsulfonic acid or cerium chloride yields C31 alcohol **13**, thus setting the stage for oxidative cleavage of the vinylsulfone moiety of C32 desmethyl C28–C34 triad **13**.

Ozonolysis of **13** generates the Criegee intermediate, thus testing the competitive reactivity of the C34 acyl sulfone and the C28 oxonium carbon with the C31 hydroxyl oxygen. In the event, the free hydroxyl, which is equidistant from both functions, suffers regiospecific addition to the C28 carbonyl oxide (pathway a) rather than the C34 acylsulfone (pathway b) yielding lactol **14** (Fig. 2). The



Scheme 1. Initial aplyronine A vinyl sulfone polyketide segment strategy.



Scheme 2. Generation of vinylsulfone **13**. Reagents and conditions: (a) Oxone®, $NaHCO_3$, acetone–H_2O, 0 °C, 87%; (b) $NaBH_4$, MeOH, 82%; (c) 2-azido-2-methylpropanoic acid, $(COCl)_2$, DMF, DMAP, TEA, 75%; (d) (1*S*)-(+)-10-CSA, MeOH 78% or $CeCl_3$, MeOH 100%.

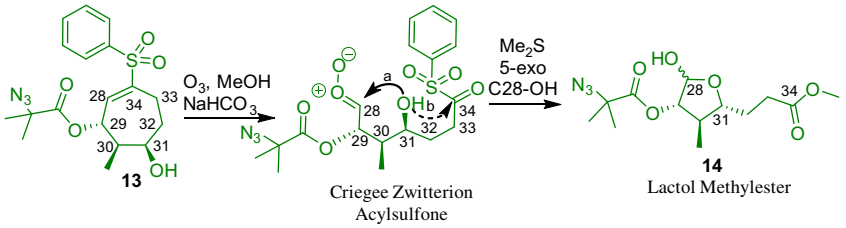
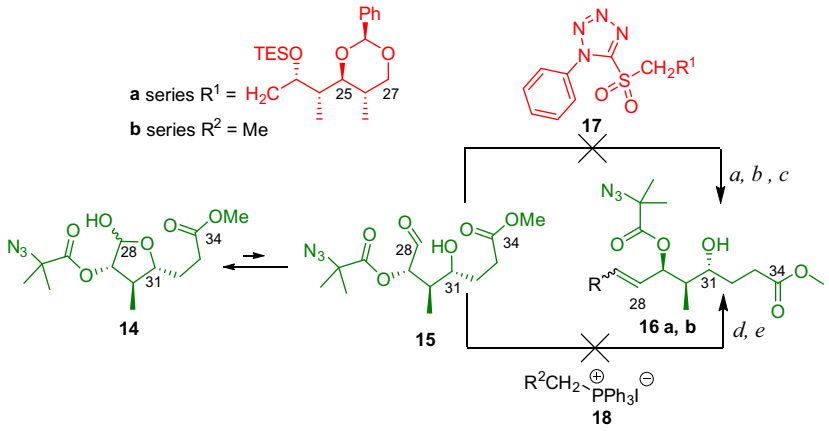
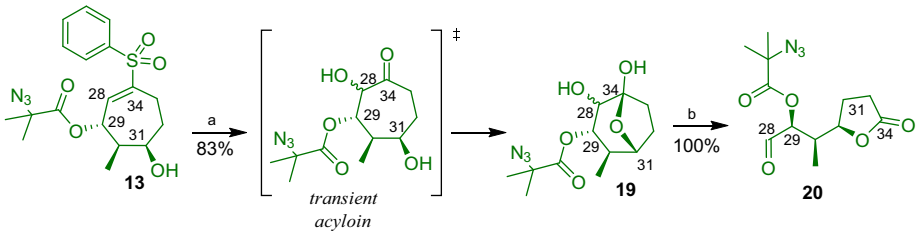


Figure 2. Ozonolysis of C32 desmethyl cyclic vinylsulfone **13**.



Scheme 3. Attempted in situ olefination of lactol **14**. Reagents and conditions: [a]LiHMDS (1.2 equiv), THF/HMPA (5:1), −78→0 °C, 30 min; [b]LiHMDS (1.2 equiv), THF/DMF/HMPA (3:9:1), −78→0 °C, 30 min; [c]NaH (50 equiv), THF, −78→0 °C, 30 min; [d]*n*-BuLi, THF, −42 °C→25 °C, 20 h; [e]DBU, THF, −40 °C→25 °C, 30 min.



Scheme 4. Osmylation and oxidative cleavage of stereotetrad **14**. Reagents and conditions: (a) *N*-methylmorpholine-*N*-oxide (NMO) (2.5 equiv), citric acid (3.0 equiv), K_2OsO_4 (0.10 equiv), MeCN/H_2O (v/v 4:1), rt, 24 h; (b) $Pb(OAc)_4$ (2.5 equiv), MeOH, rt, 5 min.

complete recovery of *trans–anti-trans* lactol **14** suggests this substrate is incapable of providing significant equilibrium populations of aldehyde **15** to furnish adduct **16** from nucleophiles **17**,[24,25] and **18** under the olefination conditions of Scheme 3.

Since the ozonolysis method was incapable of generating a reactive termini-differentiated lactol, an alternative oxidative cleavage was developed. The vinyl sulfone polypropionate strategy has recently been augmented by a new mild, citric acid assisted catalytic dihydroxylation reaction.[26] In Scheme 4 the transient acyloin formed from the dihydroxylation of vinyl sulfone **13** forms bridged bicyclic α-hydroxy lactol **19** via addition of the C31 alcohol to the C34 ketone. Finally, Criegee oxidation of lactol **19** smoothly affords target containing C34 lactone terminus C28 lactone-aldehyde **20**, thereby achieving regiospecific termini-differentiation unattainable by ozonolysis (Scheme 4).

Conclusion

This investigation solves an initial limitation of the vinyl sulfone polyketide strategy. The scope of the polypropionate is also increased. A previously unattainable positioning of the polyketide

on the carbon backbone furnishes a novel isomer. A mechanism-specified 5-*exo* termini-differentiation oxidative cleavage of the cyclic vinyl sulfone intermediate **13** has been achieved. The complementarity of ozonolysis and osmylation has been elucidated. Access to the C32 desmethyl, actin-binding tail, lactone precursor (**20**) of the of the aplyronine A analog has been established.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.098.

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