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Total Synthesis of Apratoxin A

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Apratoxins A−C (**1**−**3**, respectively, Figure 1) are intriguing marine natural products of mixed biogenetic origin. Isolated from cyanobacterial *Lyngbya spp.* collected in Guam[1] and Palau[2] by Moore, Paul, and co-workers, **1**−**3** are cyclodepsipeptides that embody both polypeptide and polyketide domains. These include highly methylated amino acids joined via proline ester and thiazoline moieties to a novel 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid. The α,β-unsaturated thiazoline of **1**−**3** derives from a modified cysteine moiety and is sensitive toward acid-induced dehydration leading to (*E*)-34,35-dehydroapratoxin A (**4**).[2]

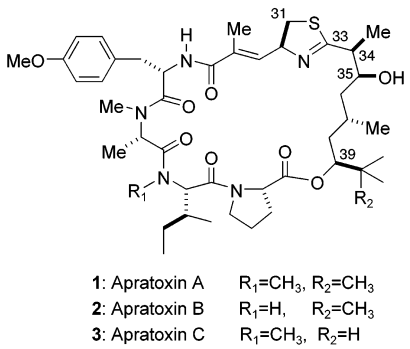


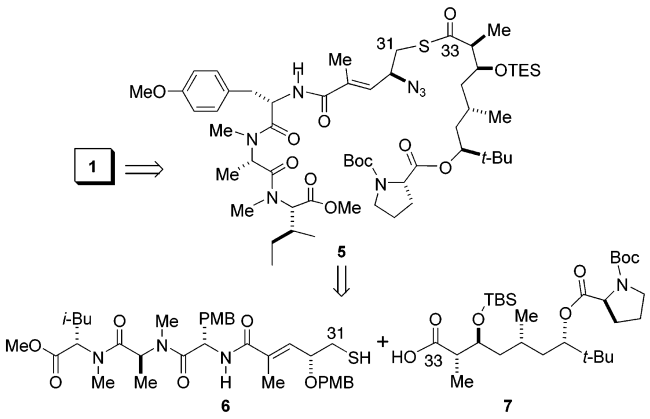
Figure 1. Structures of the apratoxins.

The unique structural features of **1** are accompanied by high levels of cytotoxicity against KB and LoVo cancer cells, with in vitro IC_{50} values of 0.52 and 0.36 nM, respectively.[1] However, **1** was poorly tolerated in vivo in mice. Although the mode of action of **1** remains unknown, it appears to effect neither microtubule polymerization dynamics nor topoisomerase I. Apratoxin C displayed an in vitro cytotoxicity profile similar to that of **1**, but **2** and **4** were from 1 to 2 orders of magnitude less potent. These results suggest that in vitro cytotoxicity of the apratoxins is closely related to subtle primary structural variations that are manifested in larger tertiary changes in molecular conformation. The small amounts of the apratoxins available via isolation from natural sources presently limit more in-depth biological studies.

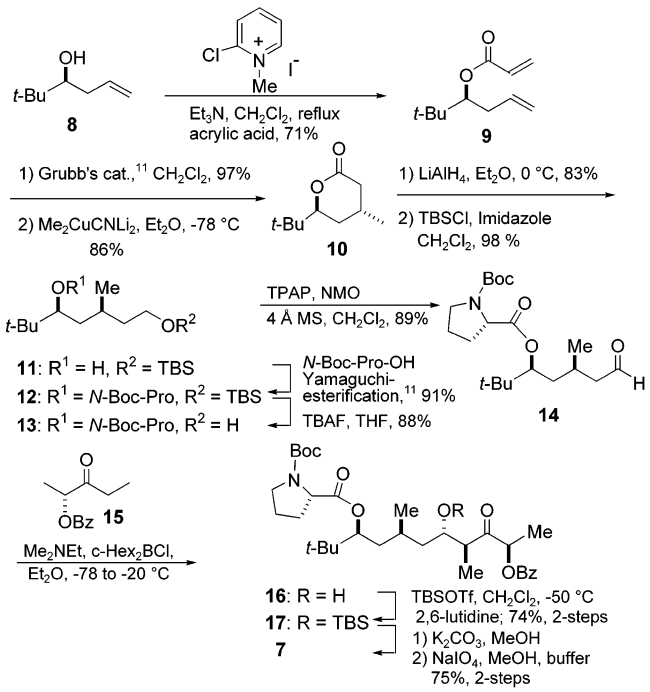
For the total synthesis of **1**, the robust proline ester was installed early, while assembly of the sensitive thiazoline moiety was deferred until a late stage. Methods to form the β-oxy thiazoline directly from carboxylate and vicinal amino thiol partners are limited. However, we found that the β-oxy thiazoline moiety could be constructed without complication under neutral conditions using a one-pot Staudinger reduction−intramolecular aza-Wittig (*S-aW*) process that utilizes an α-azido thiolester.[3] Hence, disconnection of **1** at the isoleucine-proline amide and thiazoline moiety was chosen to access the cyclic depsipeptide via α-azido thiolester **5** (Scheme 1). Thiolester **5** could be elaborated from triamide **6** and polyketide-prolyl ester **7**.

The synthesis of **7** began with acylation[4] of **8**[5] with acrylic acid to provide diene **9** (Scheme 2). Ring-closing metathesis[6] of **9** gave

Scheme 1. Retrosynthetic Disconnections of Apratoxin A



Scheme 2. Synthesis of the Prolyl Ester-Polyketide Domain **7**



an α,β-unsaturated δ-valeryl lactone. Conjugate addition of a higher order methyl cuprate[7] installed the C37 methyl group in **10**. Reductive opening of the lactone and silylation of the resultant primary alcohol gave secondary alcohol **11**. The hydroxyl moiety of **11** could be esterified efficiently with *N*-Boc-L-proline under Yamaguchi conditions[8] to obtain **12**. The derived aldehyde **14** was subjected to an *anti*-selective aldol reaction with (*R*)-2-benzoyloxy-3-pentanone[9] (**15**) to yield β-hydroxyketone **16**. The *tert*-butyldimethylsilyl group was chosen for protection of the C35 hydroxyl group of **16** to provide **17**. Excision of the benzoyloxy-containing chiral directing functionality led to the target carboxylic acid **7**.

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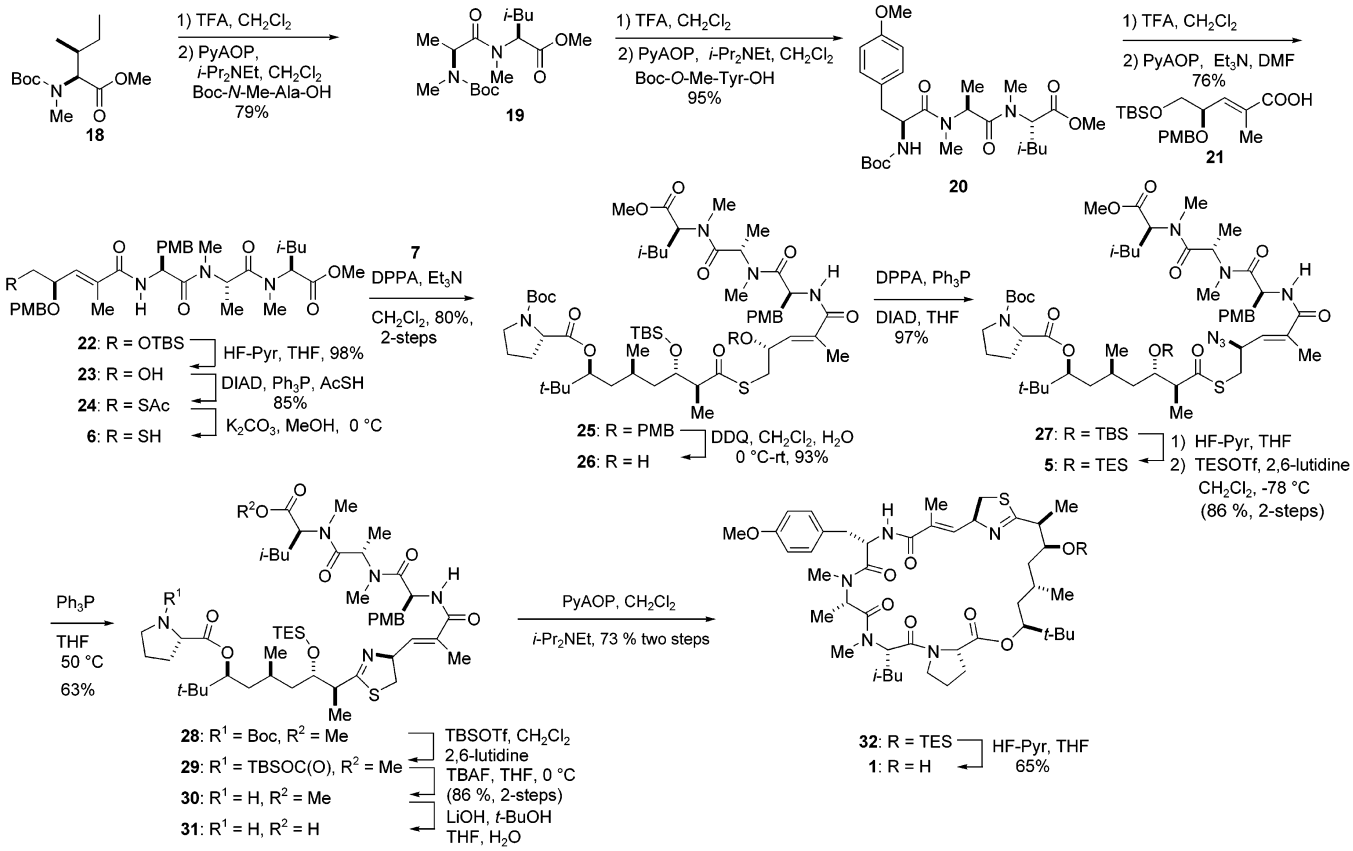
Scheme 3. Convergent Synthesis of Apratoxin A



Triamide **6** was assembled in a C → N fashion beginning with isoleucine derivative **18** (Scheme 3). Coupling of N-deblocked **18** with *N*-Boc,*N*-methyl-L-alanine yielded **19**. Carbamate cleavage followed by a second PyAOP-mediated condensation[10] with *N*-Boc,*O*-methyl-tyrosine gave diamide **20**. To implement the key *S-aW* strategy, an α-azido thiolester would be incorporated from the latent vincinal diol in modified cysteine surrogate **21**.[11] Hence, **21** was joined with **20** to yield triamide **22**. Thiol **6** was derived from **22** in a stepwise fashion.[12] Thiolester formation[13] between **6** and **7** followed by cleavage of the C30 PMB ether and treatment with diphenylphosphoryl azide under Mitsunobu conditions provided α-azido thiolester **27**.[14] Attempts to cleave the C35 TBS ether at the ultimate step of our initial total synthesis effort were unsuccessful,[15] so the TBS group was exchanged for TES at the stage of **27** to give **5**. Thiazoline formation was then accomplished by treating the α-azido thiolester **5** with Ph_3P in THF under anhydrous conditions to generate **28**.[3,16] No elimination across C34,35 occurred, as had been observed with **4**.[2] The one-pot, intramolecular *S-aW* conditions were uniquely successful among alternatives explored for thiazoline formation.

The *N*-Boc group of **28** was converted into silyl carbamate **29** using TBSOTf.[17] Selective desilylation with TBAF then generated amine **30**. The isoleucine methyl ester was saponified, and the resultant amino acid **31** was subjected to macrolactam formation to afford the cyclic depsipeptide **32**. Finally, the TES group of **32** was removed uneventfully to deliver **1**, which matched an authentic sample.[11]

The total synthesis of **1** features stereocontrolled access to the novel polyketide domain and the late-stage installation of the sensitive 2,4-disubstituted thiazoline moiety using an intramolecular *S-aW* process. In addition to corroborating the structure of **1**, this work will enable further studies of the apratoxins and their analogues.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1**, **5**−**13**, **17**, and **19**−**32** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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