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Synthesis of the Apratoxin 2,4-Disubstituted Thiazoline via an Intramolecular Aza-Wittig Reaction

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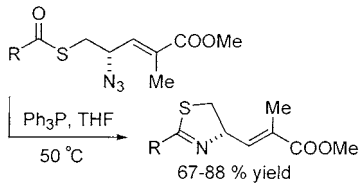
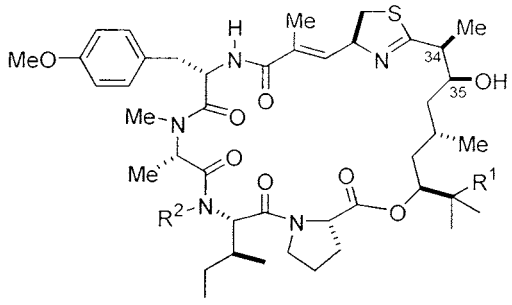
ABSTRACT



In developing a synthetic entry to the thiazoline-containing domain of the apratoxin natural products, we converted vicinal azido-thiolesters into 2,4-disubstituted thiazolines via sequential one-pot Staudinger reduction/aza–Wittig reaction. This method of de novo thiazoline formation provides a mild and versatile process that is particularly well suited to acid-sensitive substrates.

Thiazoline moieties occur in a variety of natural and nonnatural products.[1] Prominent recent examples include the apratoxins (**1**−**3**), which were isolated from the marine cyanobacterium *Lyngbya majuscula* Harvey ex Gomont and characterized by Moore, Paul, and co-workers (Figure 1).[2]



Apratoxin A (**1**), R^1 = Me, R^2 = Me
Apratoxin B (**2**), R^1 = Me, R^2 = H
Apratoxin C (**3**), R^1 = H, R^2 = Me

Figure 1. Structures of the Apratoxins.

The novel structures of the apratoxins, wherein ester and 2,4-disubstituted thiazoline moieties join ketide and peptide domains, are accompanied by potent levels of cytotoxicity. However, the molecular basis of their biological action is unknown.

In developing a synthetic entry to the apratoxin natural products,[3] we needed a method for the de novo synthesis of 2,4-disubstituted thiazoline moieties that contain acid-sensitive functionality. For this, the use of vicinal azido thiolesters for sequential one-pot Staudinger reduction/intramolecular aza-Wittig (S-AW) process was found to provide the target thiazolines under neutral conditions and without complications. The details and utility of this nondehydrative process for thiazoline synthesis are summarized herein.

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(2) (a) Luesch, H.; Yoshida, W. A.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418. (b) Luesch, H.; Yoshida, W. A.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *Bioorg. Med. Chem.* **2002**, *10*, 1973.

(3) (a) Chen, J.; Forsyth, C. J. *Abstracts of Papers*, 34th Great Lakes Regional Meeting of the American Chemical Society, Minneapolis, MN, June 2−5, 2002; American Chemical Society: Washington, DC, 2002; GEN ORG 274. (b) Chen, J.; Forsyth, C. J. *Abstracts of Papers*, 225th National Meeting of the American Chemical Society, New Orleans, LA, March 23−27, 2003; American Chemical Society: Washington, DC, 2003; ORG 208.

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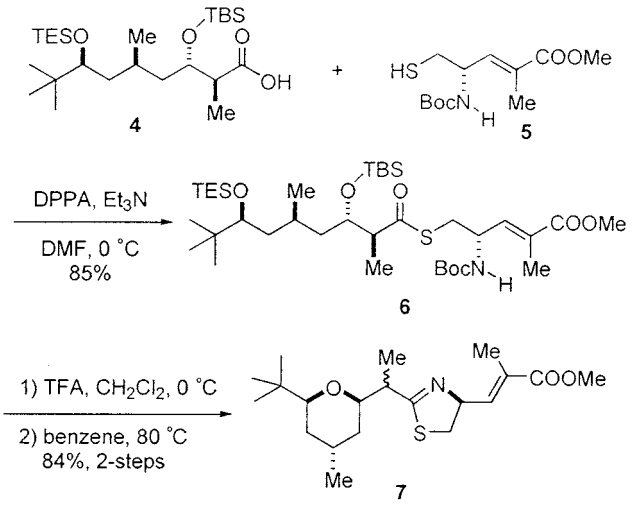
Central to the designed total synthesis of the apratoxins is the formation of the 2,4-disubstituted thiazoline moiety. Several methods have been developed for the construction of this type of structural motif.[4] These include the direct thermal intramolecular cyclization of thiolesters derived from vicinal amino thiols,[5] $TiCl_4$-induced dehydration of amides derived from vicinal amino thiols,[6] condensation of nitriles with 2-aminothiols,[7] addition of aminothiols to imidate esters,[8] combination of a thiolamide with ethyl bromopyruvate,[8] sulfurization of oxazolines,[9] cyclization of a serine-derived thiolamide with[10] or without[11] the use of Burgess' reagent, phosphine-induced annulation of thiolamides and 2-alkynoates,[12] and an intramolecular aza-Wittig reaction of a thiolester.[13] Due to its simplicity and directness, the application of Fukuyama's acid-induced cyclization of an α-amino thiolester[5] was explored first for the synthesis of apratoxins' thiazoline.

Thiol ester **6**, in which the amine was engaged in a *tert*-butyl carbamate, was prepared from carboxylic acid **4** and the thiol **5** (Scheme 1).[14] Compound **4** represents the

Scheme 1. Dehydrative Thiazoline/Tetrahydropyran Formation



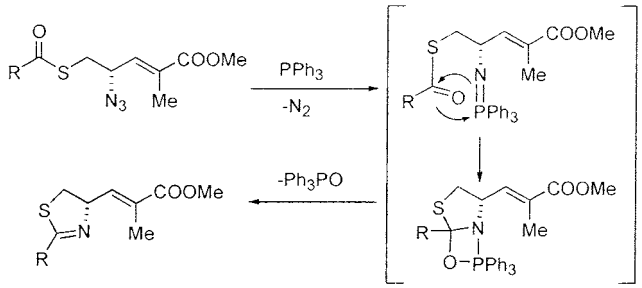
polyketide domain of apratoxins A and B, and **5** is an N- and C-blocked version of the modified cysteine moiety of the apratoxins. Following the Fukuyama protocol,[5] exposure of **6** to TFA in CH_2Cl_2 to cleave the carbamate moiety followed by removal of solvent and excess TFA gave a residue that was heated at reflux in benzene.

This provided two major diastereomeric products **7**, both of which contained the anticipated thiazoline unit. However, both diastereomers unexpectedly also had incorporated a tetrahydropyran.

This likely results from acid-induced β-elimination to form a trisubstituted alkene and hetero-Michael addition of the residual hydroxyl moiety resulting from TES ether cleavage. The β-elimination process is clearly related to the reported acid-catalyzed dehydration of apratoxin A to form (*E*)-34,35-dehydroapratoxin A in $CDCl_3$.[2] To prevent unwanted dehydration, several thiol esters with different amino and hydroxyl protecting groups were investigated under the Fukuyama acid-induced cyclization conditions. But none of those examined were fruitful. Hence, a key synthetic challenge en route to the total synthesis of the apratoxins was underscored: installation and maintenance of the 2-(β-hydroxy)-thiazoline.

Thus, an alternative process for mild thiazoline formation that would avoid the observed propensity of dehydration/elimination to give a 2-alkenyl-substituted thiazoline was sought. This requirement, in conjunction with the basic synthetic strategy toward the apratoxins, led to the identification of a uniquely mild process for de novo thiazoline formation. The neutral reaction conditions involved in phosphinimine generation from an azide via Staudinger reduction and the opportunity for subsequent intramolecular aza-Wittig reaction under the same anhydrous reaction conditions[15] prompted the exploration of vicinal azido thiolesters for mild thiazoline formation in the apratoxin system (Scheme 2). This concept was found to have

Scheme 2. Staudinger Reduction/Intramolecular Aza-Wittig Process for Nondehydrative Thiazoline Formation



precedence in the generation of pyranoside-fused thiazolines as protected forms of vicinal amino-thiols.[13]

The S-AW process has also been applied to the synthesis of cyclic imines and an oxazoline.[16] However, the acid sensitivity of the apratoxins' 2-(β-hydroxy)-thiazoline moiety presented an unprecedented challenge for convergent thiazoline synthesis under mild, nondehydrative conditions.

Several thiolester-azides related to the modified cysteine moiety of the apratoxins were prepared (Scheme 3). Selective

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(5) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449.
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(7) Ehrler, J.; Farooq, S. *Synlett* **1994**, 702.
(8) (a) Inamli, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *115*, 8449. (b) Pattenden, G.; Thom, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629.
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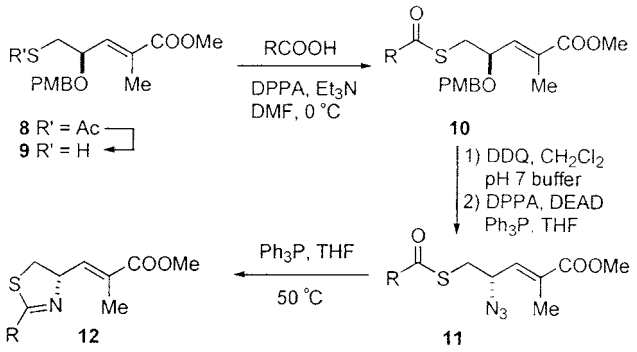
(11) Zarantonello, P.; Leslie, C. P.; Ferritto, R.; Kazmierski, W. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 561.
(12) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595 and references therein.
(13) Brossmer, R.; Mack, H. *Tetrahedron Lett.* **1981**, *22*, 933.
(14) Details of the preparation of **4**−**12d** will be reported in due course.
(15) For reviews on the Staudinger/aza-Wittig process, see: (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (b) Eguchi, E.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced.* **1992**, *24*, 209.
(16) Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *Synthesis* **1996**, 123.

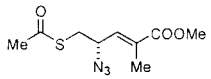
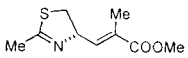
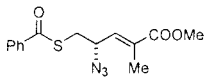
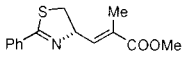
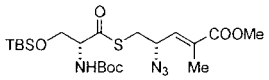
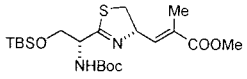
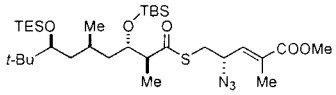
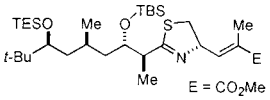
Scheme 3. Staudinger/Aza-Wittig Formation of 2,4-Disubstiuted Thiazolines



saponification of thiolacetate **8** gave thiol **9**, which was esterified with several different carboxylic acids to provide thiolesters **10**. PMB ether cleavage with DDQ[17] followed by azide formation using diphenylphosphoryl azide (DPPA) under Mitsunobu conditions[18] provided vicinal azido thiolesters **11a**−**d** (Table 1) from **10**.

Thiazoline formation was accomplished by treatment of simple thiolacetate **11a** with Ph_3P in anhydrous THF at 50 °C, which produced **12a** in excellent yield. More complicated thiolesters **11b**−**d** were also converted smoothly into the corresponding thiazolines (Table 1). Thiazolines **12c** and **12d** (entries 3 and 4) were obtained in good yield without any detectable epimerization of the 2-substiutents' α-stereogenic centers or at the 4-position of the thiazolines. Entries 3 and 4 also demonstrate the utility of this method for the formation of thiazolines that contain acid-sensitive functionality. Silyl ethers and a *tert*-butylcarbamate were successfully maintained throughout the S-AW process. The ability to affect thiazoline formation from an azido-thiolester in the presence of an *N*-Boc-containing substrate (**11c**) via orthogonal activation of a nitrogen-containing functionality may be particularly useful. Entry 4 demonstrates thiazoline formation in an acid-sensitive substrate related to the apratoxins without dehydration to a 2-alkenyl-substituted thiazoline or cleavage of a TES ether. This latter result supports the application of the S-AW process to thiazoline formation in the context of a total synthesis of the apratoxins. Progress toward this goal will be reported in due course.

Table 1. Thiazoline Formation from Azido-Thiolesters[a]

entry	azido-thiolester	thiazoline
1	 **11a**	 **12a** (88% yield)
2	 **11b**	 **12b** (87% yield)
3	 **11c**	 **12c** (82% yield)
4	 **11d**	 **12d** (67% yield)

[a] Under standard conditions: Ph_3P, THF, 50 °C, reaction time. Yields are of isolated, chromatographed, and homogeneous products.

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Supporting Information Available: Experimental procedures and characterization data for the synthesis of **11d** and **12d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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