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Total Synthesis of Apratoxin A

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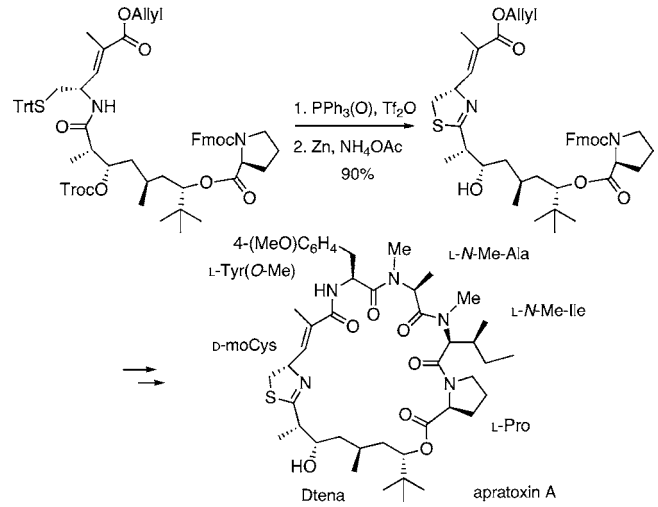
ABSTRACT



We have achieved a total synthesis of apratoxin A in which thiazoline formation was accomplished from the moCys containing amide 4 using $PPh_3(O)/Tf_2O$. Deprotection of the Troc and allyl ester in 17, coupling with tripeptide 3, and deprotection of the allyl ester and the Fmoc, followed by macrolactamization provided apratoxin A (1).

Apratoxin A (**1**), isolated from the marine cyanobacterium *Lyngbya majuscula*, exhibits potent cytotoxic activity.[1] Apratoxin A is a 25-membered cyclic depsipeptide consisting of a proline, three methylated amino acids (*N*-methylisoleucine, *N*-methylalanine, *O*-methyltyrosine), an α,β-unsaturated modified cysteine residue (moCys), and a dihydroxylated fatty acid moiety, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena). An elegant total synthesis of **1** has been achieved by Forsyth and Chen.[2] They prepared the thiazoline moiety via a unique intramolecular Staudinger reduction/aza-Wittig process on an α-azido thioester. The synthesis of an oxazoline analogue has recently been reported by Ma et al.[3,4] Having described a library synthesis of the cyclic depsipeptide aurilide and a number of analogues using a polymer support,[5] we became interested in the library synthesis of apratoxin A analogues. As a part of the effort, we now wish to report a total synthesis of apratoxin A.

Our synthetic strategy is illustrated in Scheme 1. In principle, apratoxin A (**1**) can be synthesized from the coupling of Fmoc−Pro−Dtena−moCys−OH **2** with the tripeptide, H−Tyr(*O*-Me)−*N*-Me−Ala−*N*-Me−Ile−OAll (**3**), if followed by macrolactamization[2] between the proline and *N*-methylisoleucine residues. The synthesis of **2** is potentially problematic because the thiazoline ring is labile toward acid hydrolysis, and there is a risk of epimerization at the chiral

(1) (a) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418−5423. (b) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem.* **2002**, *10*, 1973−1978.

(2) (a) Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734−8735. (b) Chen, J.; Forsyth, C. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 12067−12072.

(3) Zou, B.; Wei, J.; Cai, G.; Ma, D. *Org. Lett.* **2003**, *5*, 3503−3506.

(4) Total synthesis of apratoxin A has been presented in the 2nd Yamada Symposium on Key Natural Organic Molecules in Biological Systems, 2005, Hyogo, Japan.

(5) Takahashi, T.; Nagamiya, H.; Doi, T.; Griffiths, P. G.; Bray, A. M. *J. Comb. Chem.* **2003**, *5*, 414−428.

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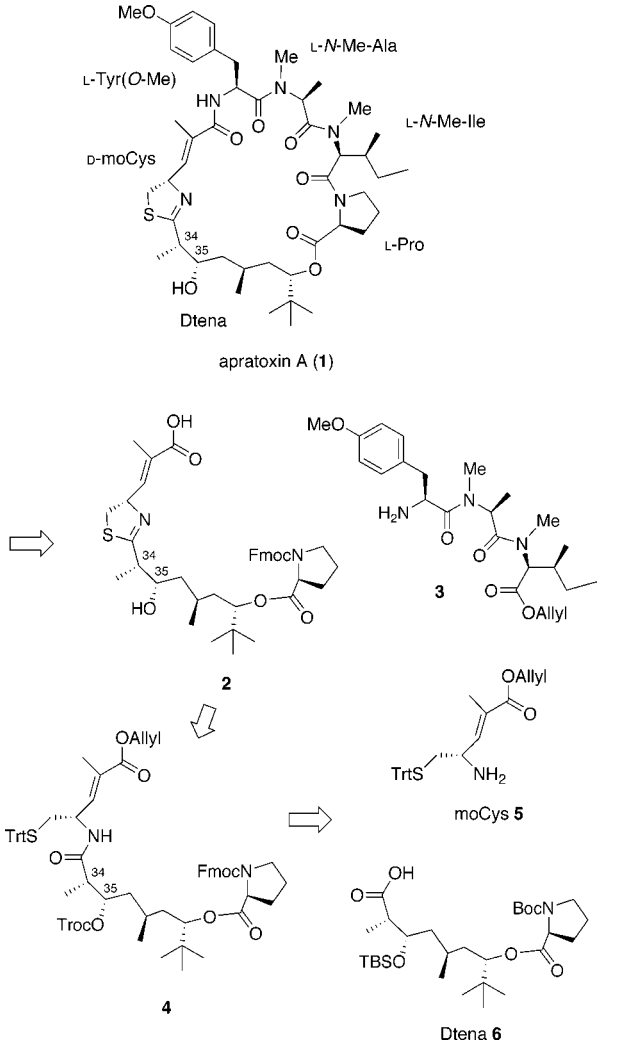
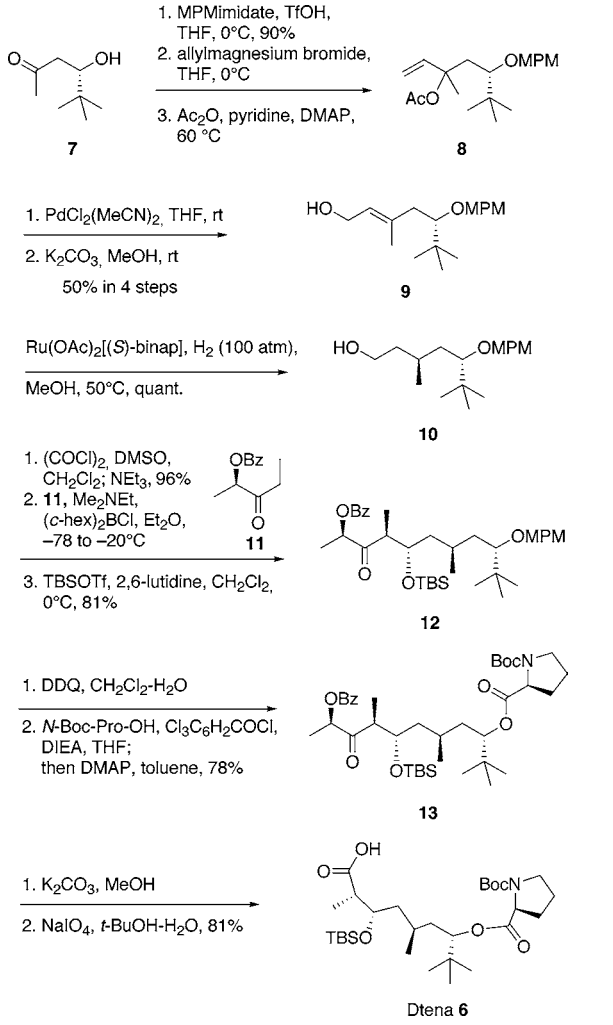
Scheme 1. Retrosynthesis of Apratoxin A (**1**)



Scheme 2

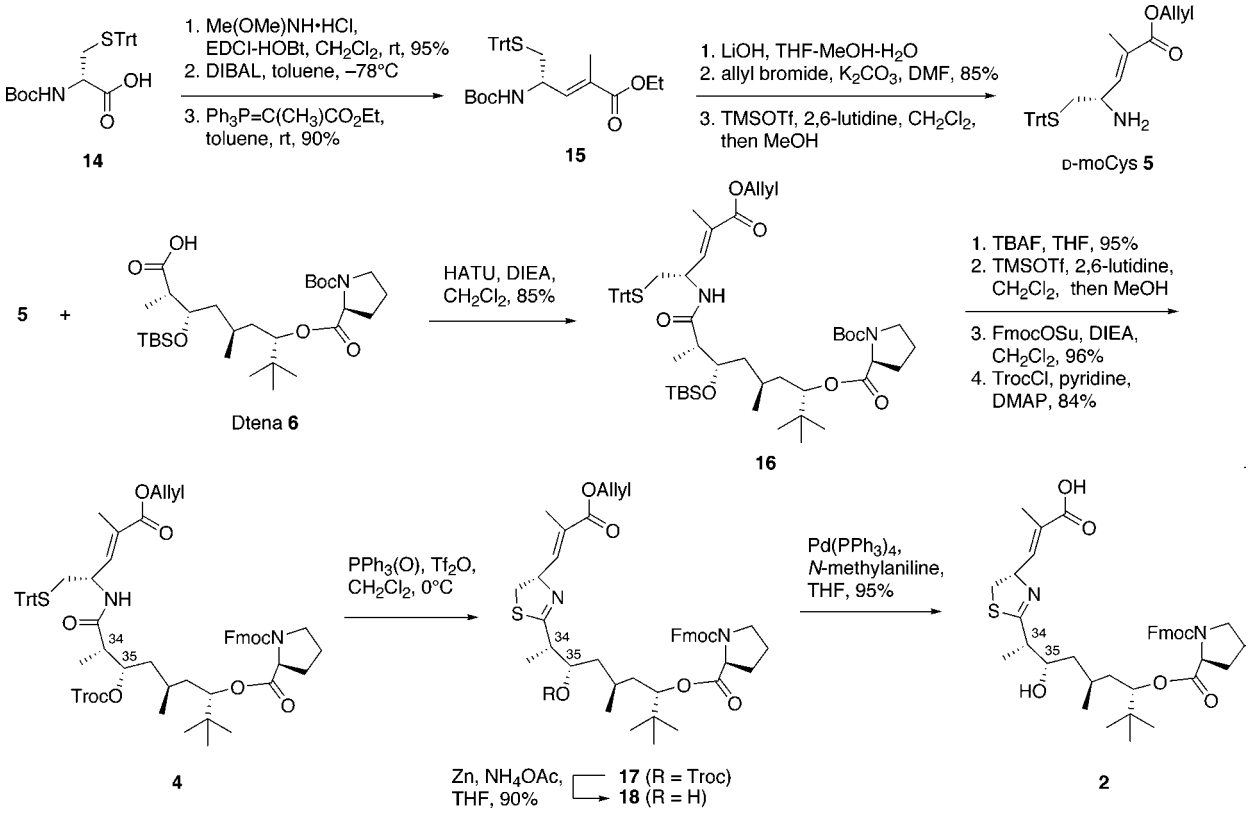


center attached to the 2-position of a thiazoline.[1b,2,6−8] As a consequence, we therefore planned to effect a dehydrative thiazoline formation on the moCys-containing amide **4**.[9,10] Amide **4** could potentially be prepared from the coupling of the moCys residue **5** with the Dtena moiety **6**.

The MPM protection of (*S*)-5,5-dimethyl-4-hydroxy-2-hexanone (**7**), prepared by a proline-catalyzed aldol reaction of acetone with pivaldehyde,[11] was followed by allylation and acetylation to afford **8** (Scheme 2). Palladium(II)-catalyzed isomerization of allylic acetate (*E*/*Z* = 9:1), followed by removal of the acetyl group, provided primary allylic alcohol **9** in 78% yield after separation by silica gel column chromatography. Ru(OAc)$_2$[(*S*)-binap]-catalyzed asymmetric hydrogenation of **9** under 100 atm of hydrogen[12] afforded **10** in quantitative yield (>95% ds).[13] Swern oxidation of **10**, followed by a Paterson anti-aldol reaction with **11**,[14] and protection of the resultant adduct with TBS provided **12** in 67% overall yield.[15] Removal of the MPM group from **12** was next accomplished with DDQ, and a subsequent coupling with *N*-Boc−Pro−OH by the Yamaguchi method[16] afforded **13**, which was in good accordance with Forsyth's intermediate.[2] Removal of the benzoate from **13** and oxidative cleavage of the resultant α-hydroxyketone provided acid **6**, as reported previously.[2]

(6) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358−12367.
(7) McKeever, B.; Pattenden, G. *Tetrahedron* **2003**, *50*, 2713−2727.
(8) Yu, S.; Pan, X.; Lin, X.; Ma, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 135−138.
(9) Forsyth reported that thiazoline formation from the thioester of the modified cysteine derivative could not avoid elimination of the adjacent hydroxy group corresponding to the C35 position.
(10) We attempted thioamide formation from *N*-Boc−Pro−Dtena(*O*-TBS)−moSer(*O*-TBS)−OAll using a Lawesson reagent. However, it failed because of Michael addition of the formed thioamide to the α,β-unsaturated ester. The similar result was also recently reported. Xu, Z.; Ye, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1905−1912.
(11) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) List, B. *Synlett* **2001**, 1675−1685. (c) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575.
(12) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596−1597.
(13) The stereochemistry was determined by nOe observation after formation of lactone with the secondary alcohol.
(14) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639−652.
(15) Forsyth did the aldol reaction after attachment with proline carboxylic acid. See ref 2.
(16) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

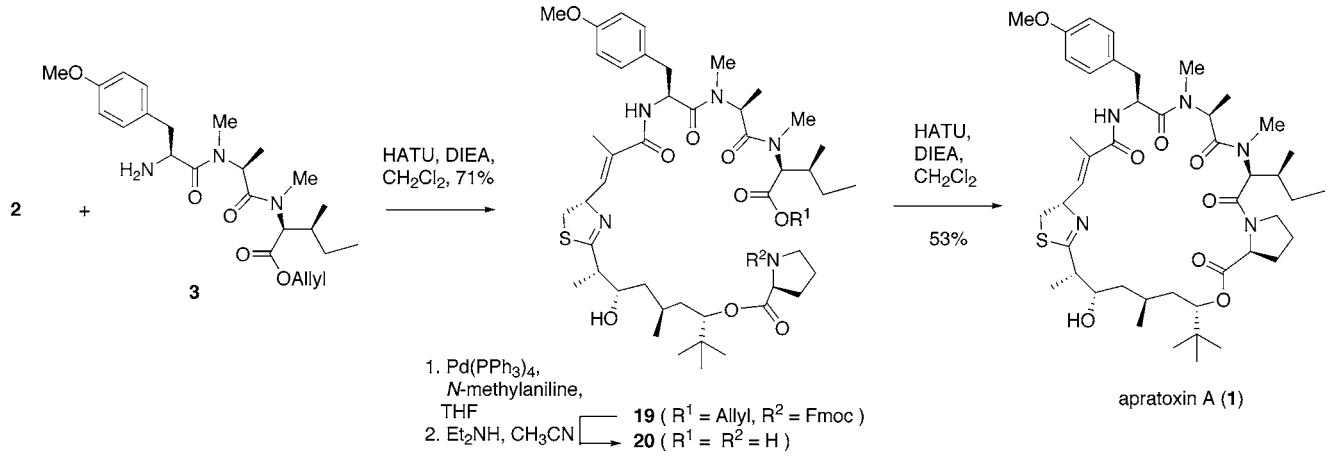
Scheme 3



The key intermediate **4** was prepared from *N*-Boc−D-Cys-(*S*-Trt)−OH (**14**) as follows (Scheme 3): DIBAL reduction of its Weinreb amide, followed by Wittig olefination, afforded (*E*)-**15**, selectively. Hydrolysis of the ethyl ester, allyl ester formation, and selective deprotection of the *N*-Boc group in the presence of *S*-Trt (TMSOTf/2,6-lutidine; MeOH) provided **5**.[17] Condensation of **5** and **6** (HATU[18]/DIEA/CH_2Cl_2) gave **16** in 85% yield. Following multistep conversion of TBS ether **16** into the 2,2,2-trichloroethoxycarbonyl (Troc) ester **4**, the latter was treated with $PPh_3(O)/Tf_2O$ in CH_2Cl_2 at 0 °C to induce thiazoline formation.[19,20] The reaction proceeded cleanly to give the desired thiazoline **17**.[21] Compound **17** was then immediately treated with Zn−NH_4-OAc[22] to remove its Troc group; this did not adversely affect the thiazoline ring or the adjacent stereogenic center and gave **18** in 90% yield. Treatment of **18** with $Pd(PPh_3)_4$/*N*-methylaniline[3,23] provided **2** in 95% yield.[24]

Tripeptide **3** was prepared by sequential coupling of *N*-methylisoleucine allyl ester with *N*-Boc−*N*-methylalanine and *N*-Fmoc−*O*-methyltyrosine by repeated treatment with HATU-DIEA and then finally Et_2NH in CH_3CN. Coupling of **2** and **3** (HATU/DIEA/CH_2Cl_2) provided **19** in 71% yield

Scheme 4



(Scheme 4). Cleavage of the *O*-allyl ester from **19** with Pd(PPh_3)$_4$/*N*-methylaniline, followed by removal of the Fmoc group with Et_2NH/CH_3CN, afforded the cyclization precursor **20**. Finally, the macrolactamization of **20** was performed with HATU/DIEA. After purification by silica gel chromatography, apratoxin A (**1**) was isolated in 53% yield. The spectral data of the synthetic **1** were identical to those of the natural product reported previously.[1,2]

In summary, a total synthesis of apratoxin A has been achieved via a convergent strategy involving HATU macrolactamization. Thiazoline formation in **2** was also successfully accomplished from the moCys amide **4** using $PPh_3(O)/Tf_2O$. Further refinement of the synthetic scheme for the synthesis of a combinatorial library of its analogues is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of **1**−**6**, **9**, **10**, **12**, **13**, **15**, **16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate: Carpino, L. A. *J. Am. Chem. Soc*. **1993**, *115*, 4397−4398.

(19) You, S.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed*. **2003**, *42*, 83−85.

(20) Although other methods were evaluated for effecting this transformation, these proved problematic. (a) Walker, M. A.; Hearthcock, C. H. *J. Org. Chem*. **1992**, *57*, 5566−5568. (b) Parsons, R. L. J.; Heathcock, C. H. *Synlett* **1996**, 1168−1170. (c) Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron* **1997**, *53*, 8323−8334. (d) Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett*. **2000**, *2*, 3289−3292 and references therein.

(21) The β-elimination of the *O*-Troc group was observed during silica gel column purification.

(22) The use of acetic acid instead of NH_4OAc resulted in hydrolysis of the thiazoline ring.

(23) Ciommer, M.; Kunz, H. *Synlett* **1991**, 593−595.

(24) The use of morpholine instead of *N*-methylaniline cleaved the Fmoc group on the proline ring in **2**.