ORGANIC LETTERS

2012
Vol. 14, No. 20
5192–5195

Asymmetric Total Synthesis of Apratoxin D

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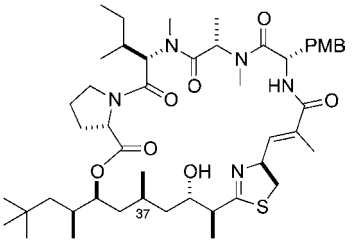
Received August 18, 2012

ABSTRACT



Apratoxin D

The first asymmetric total synthesis of the marine natural product apratoxin D, a highly potent inhibitor of H-460 human lung cancer cell growth (IC_{50} value of 2.6 nM), is described. Asymmetric *N*-amino cyclic carbamate (ACC) α,α-bisalkylation was utilized to establish the isolated C-37 methyl group with excellent selectivity. Other key asymmetric transformations employed were an Evans *syn*-aldol and a Paterson *anti*-aldol, both of which also proceeded with excellent stereoselectivity.

Apratoxin D (**5**) was recently isolated from two species of cyanobacteria, *L. majuscula* and *L. sordida*.[1] It exhibits highly potent in vitro cytotoxicity against H-460 human lung cancer cells with an IC_{50} value of 2.6 nM. Lung cancer is the deadliest form of cancer for both men and women and is responsible for 1.3 million deaths worldwide, annually. In fact, more people die of lung cancer than breast, colon, and prostate cancers combined.[2] Apratoxin D belongs to a family of cyclic depsipeptides that also includes compounds **1**–**4** (Figure 1).[3] All known apratoxins are potent inhibitors of cancer cell growth.[4] The potent biological activity exhibited by the apratoxins in general, combined with their intriguing molecular architecture, has drawn attention from the synthetic community. To date, only apratoxin A (**1**) has been prepared by total synthesis. Forsyth was the first to complete the asymmetric total synthesis of **1**,[5] and three other syntheses have since been described.[6,7] Herein, we report the first asymmetric total synthesis of apratoxin D.

Our plan for the synthesis of apratoxin D is shown in Scheme 1. Macrocyclization would be achieved by coupling between the proline and isoleucine residues, thereby avoiding late-stage esterification of the sterically congested C-39 hydroxyl.[5a] Coupling of tripeptide **6** and carboxylic acid **7** would set the stage for the macrocyclization event. Formation of the thiazoline moiety of **7** would be achieved by using Kelly's procedure,[8] which would require the preparation of D-cysteine-derived intermediate **8** and polyketide fragment **9**. Fragment **9** would be reached from intermediate **10** utilizing a *syn*-selective Evans aldol addition to set the C-39–C-40 stereochemistry, followed by a Paterson *anti*-aldol addition to establish the C-34 and C-35 stereogenic centers. The former transformation would also be leveraged as a means to install the C-41 *tert*-butyl group, giving rise to the neopentyl moiety. The neopentyl group of apratoxin D is unique in comparison to all other known apratoxins.

(1) Gutierrez, M.; Suyama, T. L.; Engene, N.; Wingerd, J. S.; Matainaho, T.; Gerwick, W. H. *J. Nat. Prod.* **2008**, *71*, 1099–1103.

(2) U.S. National Library of Medicine: PubMed Health. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0004529 (accessed Mar 1, 2012).

(3) (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. *Bioorgan. Med. Chem.* **2002**, *10*, 1973–1978. (c) Matthew, S.; Schupp, P. J.; Luesch, H. *J. Nat. Prod.* **2008**, *71*, 1113–1116.

(4) See also: Luesch, H.; Chanda, S. K.; Raya, R. M.; DeJesus, P. D.; Orth, A. P.; Walker, J. R.; Belmonte, J. C. I.; Shultz, P. G. *Nat. Chem. Biol.* **2006**, *2*, 159–167.

(5) (a) Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734–8735. (b) Chen, J.; Forsyth, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12067–12072.

(6) (a) Doi, T.; Numajiri, Y.; Munakata, A.; Takahashi, T. *Org. Lett.* **2006**, *8*, 531–534. (b) Ma, D. W.; Zou, B.; Cai, G. R.; Hu, X. Y.; Liu, J. O. *Chem.—Eur. J.* **2006**, *12*, 7615–7626. (c) Numajiri, Y.; Takahashi, T.; Doi, T. *Chem.—Asian J.* **2009**, *4*, 111–125.

(7) Some analogues of apratoxin A have been synthesized; see: Chen, Q.-Y.; Liu, Y.; Luesch, H. *ACS Med. Chem. Lett.* **2011**, *2*, 861–865.

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

10.1021/ol302309c
Published on Web 10/11/2012

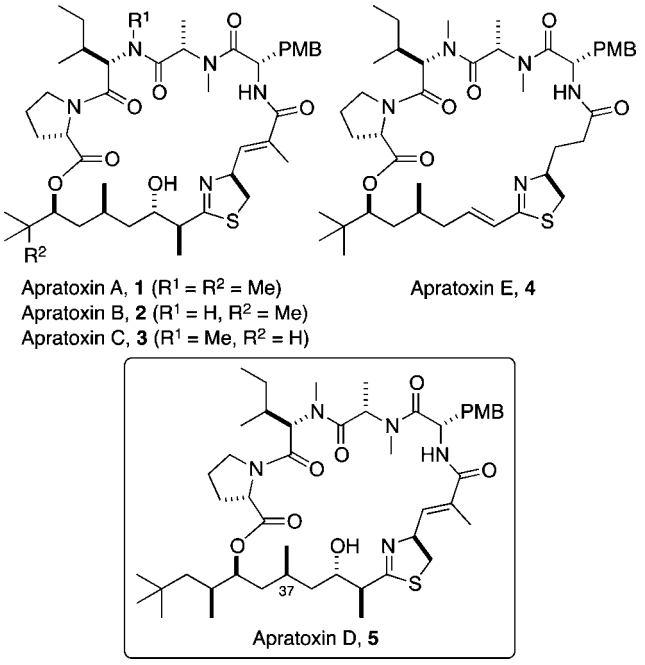
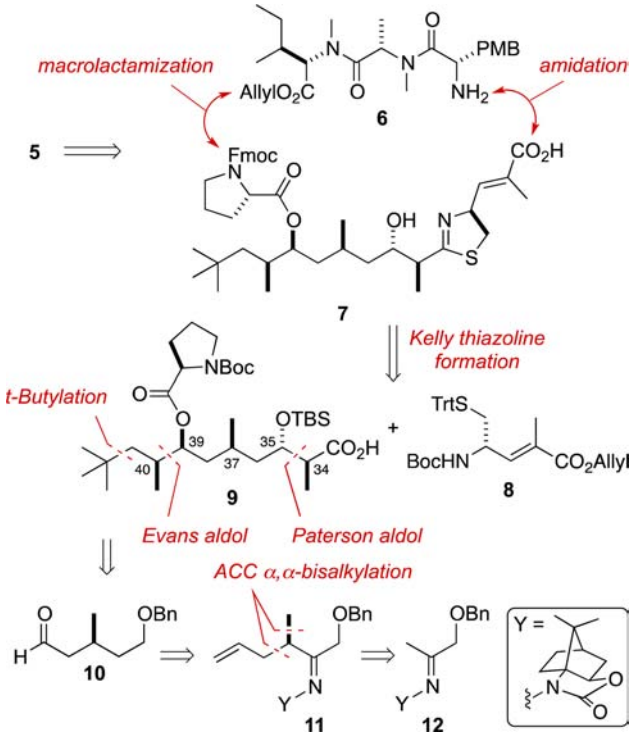


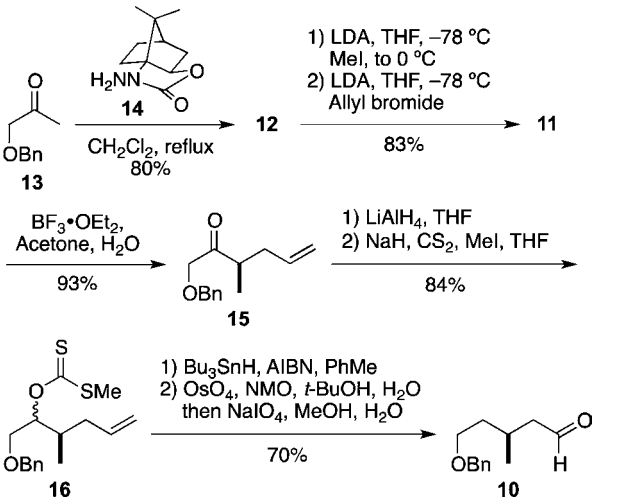
Figure 1. Apratoxins.

Scheme 1. Retrosynthetic Analysis of Apratoxin D (**5**)



At this stage, installation of the isolated C-37 methyl group had to be considered. We decided to approach this using our recently developed asymmetric *N*-amino cyclic carbamate (ACC) α,α-bisalkylation method (**12**→**11**).[9]

Scheme 2. Synthesis of Aldehyde **10**



The first phase of our synthesis of apratoxin D focused on the preparation of aldehyde **10**. This began with the acid catalyzed condensation of commercially available benzyloxyacetone (**13**) and ACC auxiliary **14** to give ACC hydrazone **12** (Scheme 2).[9,10] To set the required (*R*)-configuration at the α-carbon of **15**, compound **12** was subjected to methylation, and the product of that reaction was then allylated to give **11** as a single diastereomer. Auxiliary removal provided ketone **15**. Transformation of the ketone function of **15** to the required methylene began with $LiAlH_4$ reduction, which was followed by conversion of the resulting alcohols to xanthates **16**. Barton–McCombie reduction and Lemieux–Johnson oxidation then gave aldehyde **10** in very good overall yield.

With an effective route to aldehyde **10** secured, we undertook the preparation of advanced carboxylic acid **9** (Scheme 3). To do so, *N*-acyl oxazolidinone **17** and **10** were engaged in an Evans *syn*-aldol addition.[11] Silica gel chromatography of the product mixture gave the desired stereoisomer (**18**) in excellent yield, and this was then converted to silyl ether **19**. Reductive removal of the oxazolidinone auxiliary provided alcohol **20**. With **20** in hand, we attempted to convert it to the *tert*-butylated compound **22** in a variety of ways, none of which were suitably successful. We then tried a new method reported by Terao and Kambe for the cuprate-based alkylation of various electrophiles (chlorides, bromides, tosylates).[12] We were pleased to find that these conditions worked remarkably well in the case of tosylate **21**, providing compound **22** reliably and in very

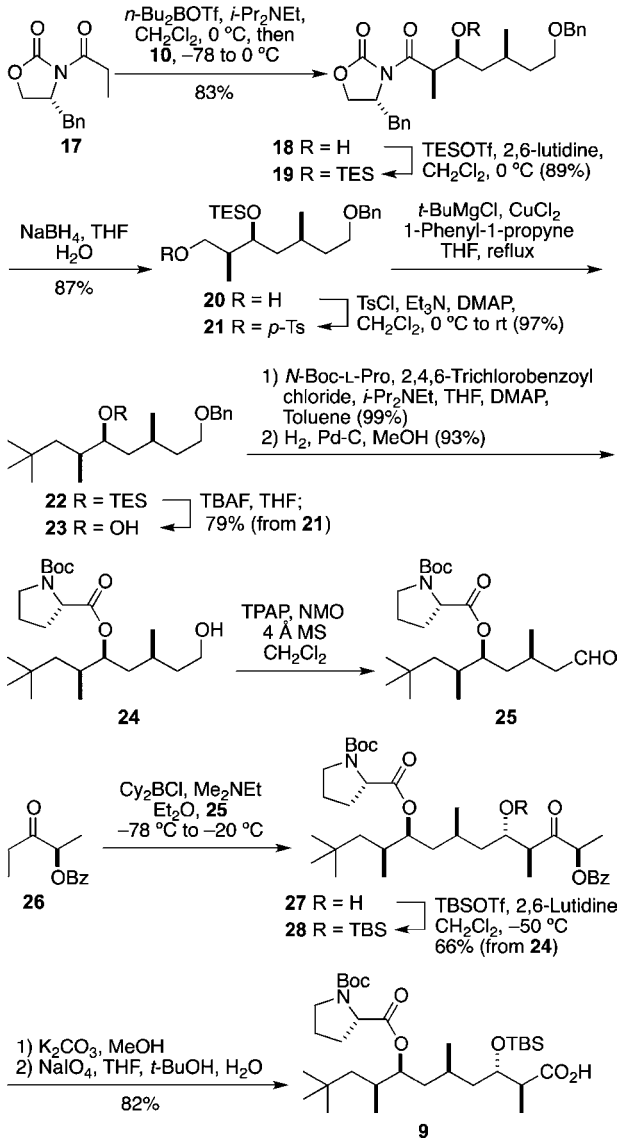
(9) Wengryniuk, S. E.; Lim, D.; Coltart, D. M. *J. Am. Chem. Soc.* **2011**, *133*, 8714–8720.

(10) (a) Lim, D.; Coltart, D. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5207–5210. (b) Krenske, E. H.; Houk, K. N.; Lim, D.; Wengryniuk, S. E.; Coltart, D. M. *J. Org. Chem.* **2010**, *75*, 8578–8584. (c) Garnsey, M. R.; Lim, D.; Yost, J. M.; Coltart, D. M. *Org. Lett.* **2010**, *12*, 5234–5237. (d) Garnsey, M. R.; Matous, J. A.; Kwiek, J. J.; Coltart, D. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2406–2409.

(11) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83–91.

(12) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086–2089.

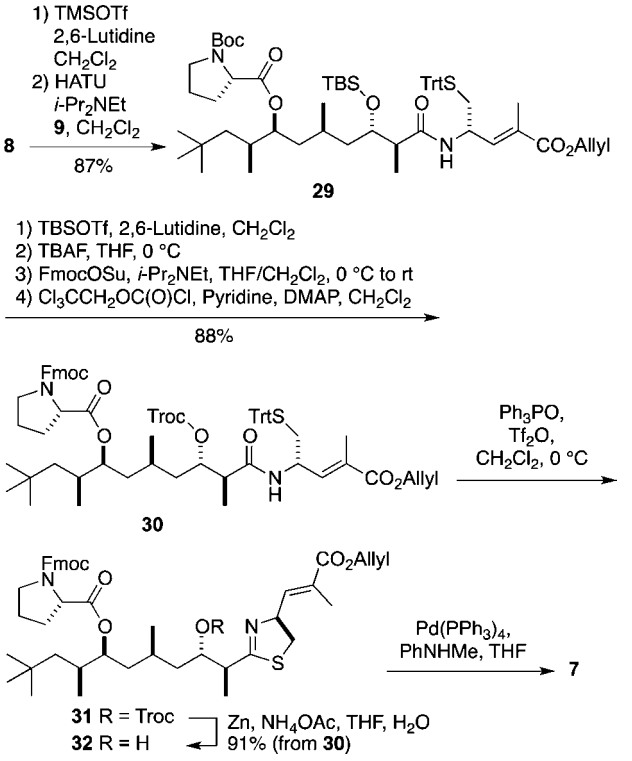
Scheme 3. Synthesis of Carboxylic Acid **9**



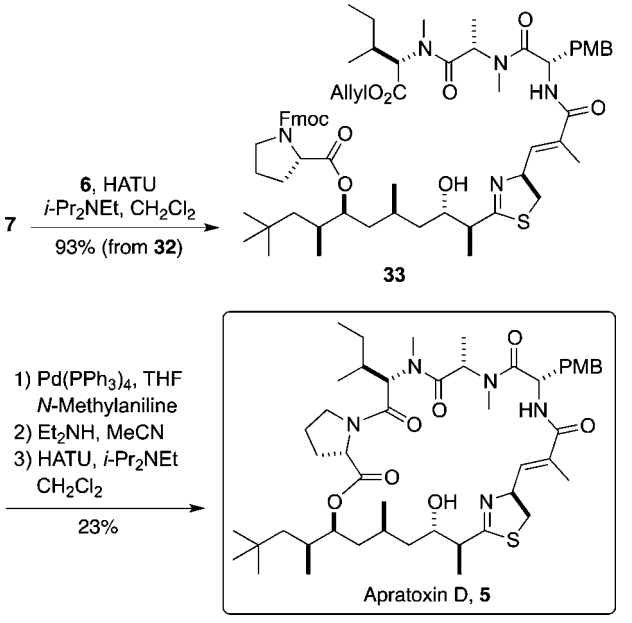
good yield. We next removed the TES protecting group from **22** to enable incorporation of the C-39 proline residue via the Yamaguchi procedure.[13] This was followed by hydrogenolysis of the benzyl ether to give alcohol **24**. Oxidation of **24** provided aldehyde **25**, as required for the planned *anti*-selective Paterson aldol using α-benzoyloxy ketone **26**.[14] In the event, the aldol addition produced compound **27** in both excellent yield and diastereoselectivity. A sequence of TBS protection, benzoate hydrolysis, and oxidation produced carboxylic acid **9**.

As indicated above, we planned to generate the required thiazoline moiety via the Kelly procedure, which, in this instance, would be conducted on compound **30** (Scheme 4). Preparation of **30** began with the coupling of carboxylic

Scheme 4. Synthesis of Carboxylic Acid **7**



Scheme 5. Completion of the Synthesis of Apratoxin D (**5**)



acid **9** and compound **8**. At this stage the Boc protecting group on the proline residue was exchanged for an Fmoc group to simplify the pending macrocyclization event in a practical sense. In addition, the TBS group on the C-37 hydroxyl was exchanged for a Troc group,[5,6] giving

(13) Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(14) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652.

compound **30**. Compound **30** smoothly underwent cyclization to produce the desired thiazoline (**31**) in excellent yield. Removal of the Troc group from **31** was followed by deprotection of the C-terminal carboxylic acid, providing advanced intermediate **7**.

With compound **7** in hand, we embarked on the final steps of the synthesis of apratoxin D (Scheme 5). Thus, **7** was coupled to the tripeptide **6**[6a] using HATU and Hünig's base, giving **33** in very good yield. At this stage, conversion of the allyl ester to the corresponding carboxylic acid was achieved by treatment with $Pd(PPh_3)_4$ and *N*-methylaniline. Removal of the Fmoc moiety from the proline residue was followed by HATU-mediated macrolactamization, which successfully provided apratoxin D. The spectrometric data obtained for our synthetic material matched in all respects with the data reported for its isolation.[15]

In conclusion, we have achieved the first asymmetric total synthesis of apratoxin D, a compound that exhibits highly potent cytotoxicity against H-460 human lung cancer cells. Evaluation of the cytotoxicity of our synthetic material against a range of cancer cell lines, as well as related SAR studies, are currently underway and will be described in due course.

Acknowledgment. We are grateful to Professor Jeffrey L. C. Wright and Allison K. Stewart (UNC Wilmington) for their assistance with the purification of our synthetic apratoxin D. We thank Dr. Mark C. Kohler (Duke University) for his assistance in preparing compound **6** and Dr. Emily M. Tarsis, Dr. Guoqiang Zhou, and Insun Chong (Duke University) for their assistance in conducting certain experiments. B.D.R. holds a C. R. Hauser Fellowship, and S.E.W., a Kathleen Zielek Fellowship from Duke University. We also thank the NSF for a Graduate Fellowship for S.E.W. and for additional support (NSF 1012287).

Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) See the Supporting Information for details.

The authors declare no competing financial interest.