ORGANIC LETTERS

2008
Vol. 10, No. 17
3907−3909

Enantioselective Total Synthesis of (+)-Largazole, a Potent Inhibitor of Histone Deacetylase†

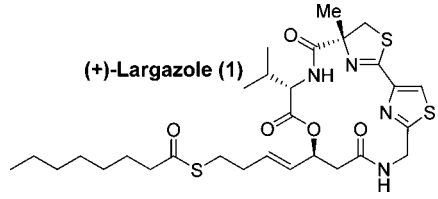
Arun K. Ghosh* and Sarang Kulkarni

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

akghosh@purdue.edu

Received June 27, 2008

ABSTRACT



An enantioselective total synthesis of the cytotoxic natural product (+)-largazole (1) is described. It is a potent histone deacetylase inhibitor. Our synthesis is convergent and involves the assembly of thiazole 3-derived carboxylic acid with amino ester 4 followed by cycloamidation of the corresponding amino acid. The synthesis features an efficient cross-metathesis, an enzymatic kinetic resolution of a β-hydroxy ester, a selective removal of a Boc-protecting group, a HATU/HOAt-promoted cycloamidation reaction, and synthetic manipulations to a sensitive thioester functional group.

In January 2008, Luesch and co-workers reported the isolation of largazole, a novel 16-membered depsipeptide from Floridian marine cyanobacterium *Symploca* sp.[1] Largazole's structure was elucidated by extensive NMR studies and through chemical degradation. It has shown impressive growth inhibitory activity of transformed mammary epithelial cells (MDA-MB-231) in a dose-dependent manner with a GI_{50} value of 7.7 nM. In addition, it has shown excellent selectivity over nontransformed murine mammary epithelial cells (NMuMG) with a GI_{50} of 122 nM. More recently, Luesch, Hong, and co-workers reported the first total synthesis of largazole. Their synthesis featured a macrocyclization at C6 and a late stage addition of the thioester using cross-metathesis. Subsequently, they determined that histone deacetylase (HDAC) is the molecular target for largazole.[2] This is very significant as HDAC inhibitors are emerging as a new and exciting class of antineoplastic agents for the treatment of solid and nematological malignancies.[3] Incidentally, a number of depsipeptides are undergoing clinical trials for treatment of various cancers.[4] Largazole's important biological activity, its selectivity for cancer cells, and its unique structural features led to considerable interest in its chemistry and biology. To establish structure-activity relationships and design novel structural variants, we sought a convergent route to largazole. Herein, we report an enantioselective synthesis of (+)-largazole.

As shown in Figure 1, our synthetic strategy involves a late-stage cycloamidation of a sterically less demanding carboxylic acid and an amine to form the 16-membered ring from the corresponding amino acid derived from **2**. Ester derivative **2** could be obtained by the formation of an amide bond between the acid arising from thiazole methyl ester **3** and the **4**-derived amine. Our plan is to carry out the

† Dedicated to Professor E. J. Corey with profound admiration and appreciation on the occasion of his 80th birthday.

(1) Taori, K.; Paul, V. J.; Luesch, H. *J. Am. Chem. Soc.* **2008**, *130*, 1806.

(2) Ying, Y.; Taori, K.; Kim, H.; Hong, J.; Luesch, H. *J. Am. Chem. Soc.* **2008**, *130*, 8455.

(3) (a) Vigushin, D. M.; Coombes, R. C. *Anti-Cancer Drugs* **2002**, *13*, 1. (b) Marchion, D.; Munster, P. *Expert Rev. Anticancer Ther.* **2007**, *7*, 583.

(4) Piekarz, R.; Bastes, S. *Curr. Pharm. Des.* **2004**, *10*, 2289.

10.1021/ol8014623 CCC: $40.75
Published on Web 07/29/2008

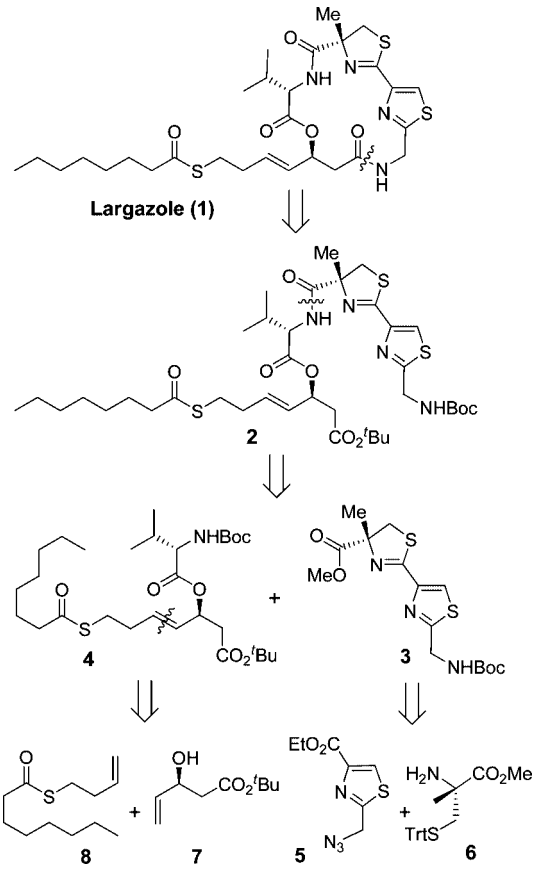
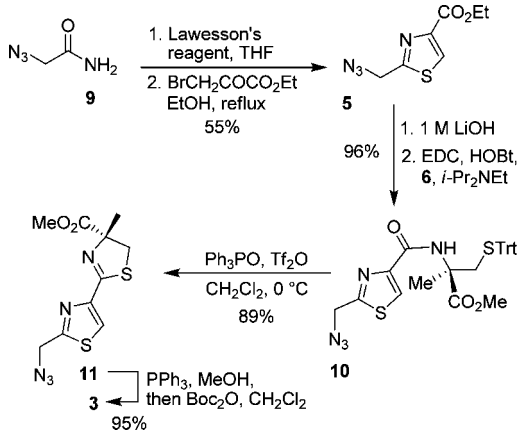


Figure 1. Retrosynthetic analysis of largazole.

remainder of the synthesis with the sensitive thioester functional group attached. The synthesis of thiazole **3** can be achieved from a **5**-derived thiazole acid and protected (*R*)-2-methyl cysteine **6**.[5] Amino ester **4** could be accessed by a cross-metathesis reaction between thioester **8** and optically active allylic alcohol **7** followed by a Yamaguchi esterification with the appropriately protected L-valine. Alcohol **7** could be prepared by a lipase-mediated kinetic resolution of racemic β-hydroxy ester.

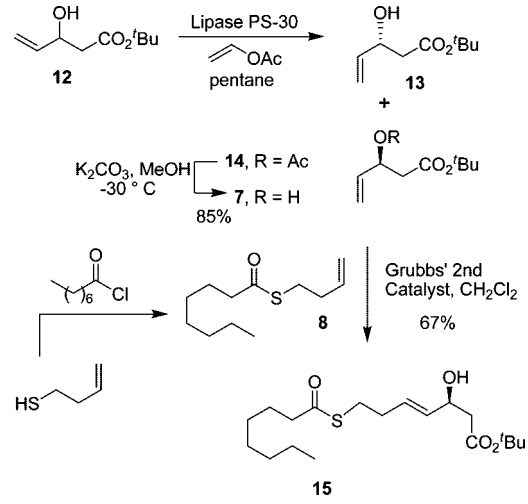
Scheme 1. Synthesis of Segment **3**



As shown in Scheme 1, our synthesis starts with the known azido amide **9**[6] which was treated with Lawesson's reagent in THF for 12 h to provide the corresponding thioamide in 67% yield.[7] The resulting thioamide was then reacted with ethyl bromopyruvate in refluxing ethanol for 1 h which provided thiazole **5** in 82% yield.[8] Saponification of ester **5** with 1 M aqueous LiOH gave the acid. The resulting acid was then coupled with trityl-protected α-methyl cysteine[9] under EDC/HOBt conditions in the presence of diisopropylethylamine to furnish amide **10** in 96% yield over two steps. The conversion to thiazole−thiazoline fragment **11** was achieved following a procedure reported by Kelly and coworkers.[10] Accordingly, amide **10** was reacted with 3 equiv of triphenylphosphine oxide and 1.5 equiv of Tf_2O in CH_2Cl_2 at 0 °C for 10 min to provide ester **11** in 89% yield. The azide group in **11** was reduced using PPh_3 in refluxing methanol[11] to give the amine which was then exposed to Boc_2O to furnish fragment **3** in 95% yield over two steps.

Optically active synthesis of β-hydroxy ester and its conversion to ester **15** are shown in Scheme 2. Racemic aldol

Scheme 2. Synthesis of Thio Ester **15**



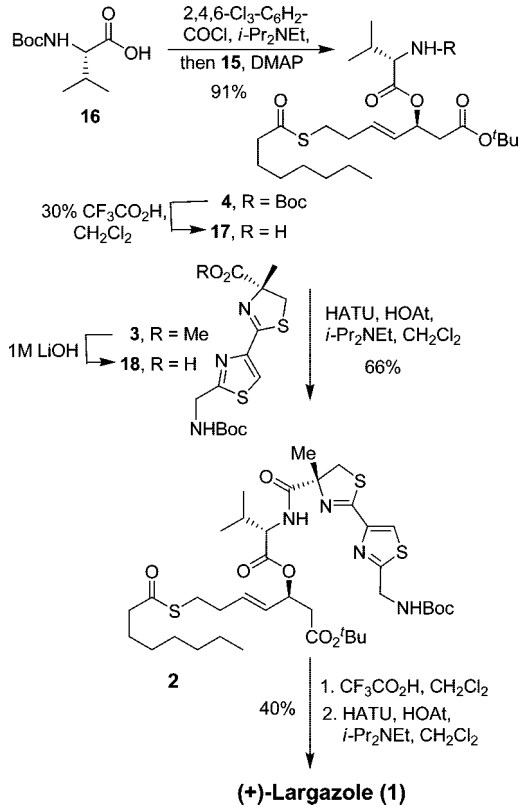
product **12** was prepared by LDA deprotonation of *tert*-butyl acetate followed by reaction of the resulting enolate with acrolein at −78 °C to provide **12** in 81% yield. The racemic alcohol was then exposed to lipase PS-30 in pentane in the presence of excess vinyl acetate at 23 °C for 12 h to provide enantioenriched alcohol **13** and acetate derivative **14** in 45% and 42% yields, respectively. Selective removal of the acetate

(5) Pattenden, G.; Thom, S. M.; Jones, M. F. *Tetrahedron* **1993**, *49*, 2131.
(6) Dyke, J. M.; Levita, G.; Morris, A.; Ogden, J. S.; Dias, A. A.; Algarra, M.; Santos, J. P.; Costa, M. L.; Rodrigues, P.; Barros, M. T *J. Phys. Chem. A* **2004**, *108*, 5299.
(7) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210.
(8) Boyce, R. J.; Pattenden, G. *Tetrahedron* **1995**, *51*, 7313.
(9) For synthesis of the enantiomer, see: Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 1081.
(10) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83.
(11) Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317.

was carried out by exposure of **14** to potassium carbonate in methanol at −30 °C to afford optically active β-hydroxy ester **7** in high enantiomeric purity (93% ee). The enantiomeric excess was determined by formation of the corresponding Mosher ester of alcohol **15** followed by analysis of ^{19}F NMR.[12] The kinetic resolution of β-hydroxy ester has provided a convenient access to optically active esters.[13] For preparation of alcohol **15** we planned a cross-metathesis of alcohol **7** and thioester **8**. The requisite thioester was prepared by reaction of 3-butenethiol[14] and octanoyl chloride in the presence of DMAP. A cross-metathesis reaction of alcohol **7** and thioester **8** in the presence of 3 mol % of Grubbs' second-generation catalyst afforded *E*-olefin **15** exclusively in 67% yield.[15]

The final assembly of the largazole fragment is shown in Scheme 3. *N*-Boc-valine **16** was subjected to esterification with alcohol **15** using Yamaguchi's protocol.[16] Accordingly, reaction of **16** with 2,4,6-trichlorobenzoyl chloride in the presence of diisopropylethylamine gave the anhydride.

Scheme 3. Synthesis of Largazole



Reaction of the resulting anhydride with alcohol **15** and DMAP furnished thioester **4** in 91% yield. Selective deprotection of the Boc group in the presence of a *tert*-butyl ester was carried out by exposure of **4** to 30% trifluoroacetic acid in CH_2Cl_2 at 0 °C for 20 min to provide amine **17**. For assembly of the largazole subunits, saponification of methyl ester **3** was carried out with 1 M aqueous LiOH to give acid **18**. Coupling of acid **18** with amine **17** was accomplished by using HATU and HOAt in the presence of diisopropylethylamine to furnish the requisite protected amino ester **2** in 66% yield. Formation of the 16-membered cycloamide was carried out in a two-step sequence involving (1) exposure of **2** to trifluoroacetic acid at 23 °C for 3 h to remove both the Boc and the *tert*-butyl groups and (2) treatment of the resulting amino acid with 2 equiv of HATU and 2 equiv of HOAt in the presence of diisopropylethylamine under dilute conditions to provide synthetic (+)-largazole (**1**) in 40% isolated yield (two steps). The spectral data (^1H and ^{13}C NMR) of synthetic (+)-largazole (**1**, $[\alpha]^{23}_D$ +24, *c* 0.13, MeOH (lit.[1] $[\alpha]^{20}_D$ +22, *c* 0.1, MeOH)) is identical with that reported for the natural (+)-largazole.[1]

In summary, we have accomplished an enantioselective synthesis of (+)-largazole (**1**). The synthesis will provide a convenient access to a variety of largazole derivatives. Structural modifications are currently in progress.[17]

Acknowledgment. Partial financial support by the National Institute of Health is gratefully acknowledged. We thank Mr. David D. Anderson of Purdue University for his help with the HPLC analysis.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for compounds **1**−**5**, **7**−**11**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8014623

(12) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(13) (a) Vrielynck, S.; Vandewalle, M.; García, A. M.; Mascareñas, J. L.; Mouriño, A. *Tetrahedron Lett.* **1995**, *36*, 9023. (b) Pollini, G. P.; Risi, C. D.; Lumento, F.; Marchetti, P.; Zanirato, V. *Synlett* **2005**, 164.
(14) Minozzi, M.; Nanni, D.; Walton, J. C. *Org. Lett.* **2003**, *5*, 901.
(15) (a) Scholl, M.; Ding, S.; Lee, C.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(16) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(17) During the review of this manuscript, two other syntheses have appeared in the literature; see: (a) Nasveschuk, C. G.; Ungermannova, D.; Liu, X.; Phillips, A. J. *Org. Lett.* **2008**, *10*, 3595–3598. (b) Seiser, T.; Kamena, F.; Cramer, N. *Angew. Chem.* DOI:, 10.1002/anie.200802043.