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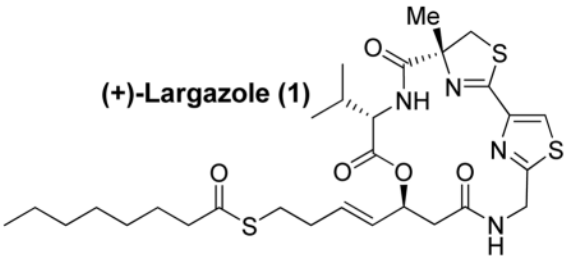
Enantioselective Total Synthesis of (+)-Largazole, a Potent Inhibitor of Histone Deacetylase

Arun K. Ghosh* and **Sarang Kulkarni**
Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, IN 47907

Abstract



An enantioselective total synthesis of 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.

akghosh@purdue.edu.

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

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 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.

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 2 steps. The conversion to thiazole-thiazoline fragment **11** was achieved following a procedure reported by Kelly and co-workers.[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 2 steps.

Optically active synthesis of β-hydroxy ester and its conversion to ester **15** is shown in Scheme 2. Racemic aldol product **12** was prepared by LDA deprotonation of *t*-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 enantio enriched alcohol **13** and acetate derivative **14** in 45% and 42% yields respectively. Selective removal of the acetate 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-butene thiol[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% Grubbs' 2nd 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. 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 *t*-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 *t*-butyl groups; (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 (2 steps). The spectral data (^{1}H- and ^{13}C-NMR) of synthetic (+)-largazole (**1**, $[\square]^{23}_D$ +24, *c* 0.13, MeOH; lit.[1] $[\square]^{20}_D$ +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]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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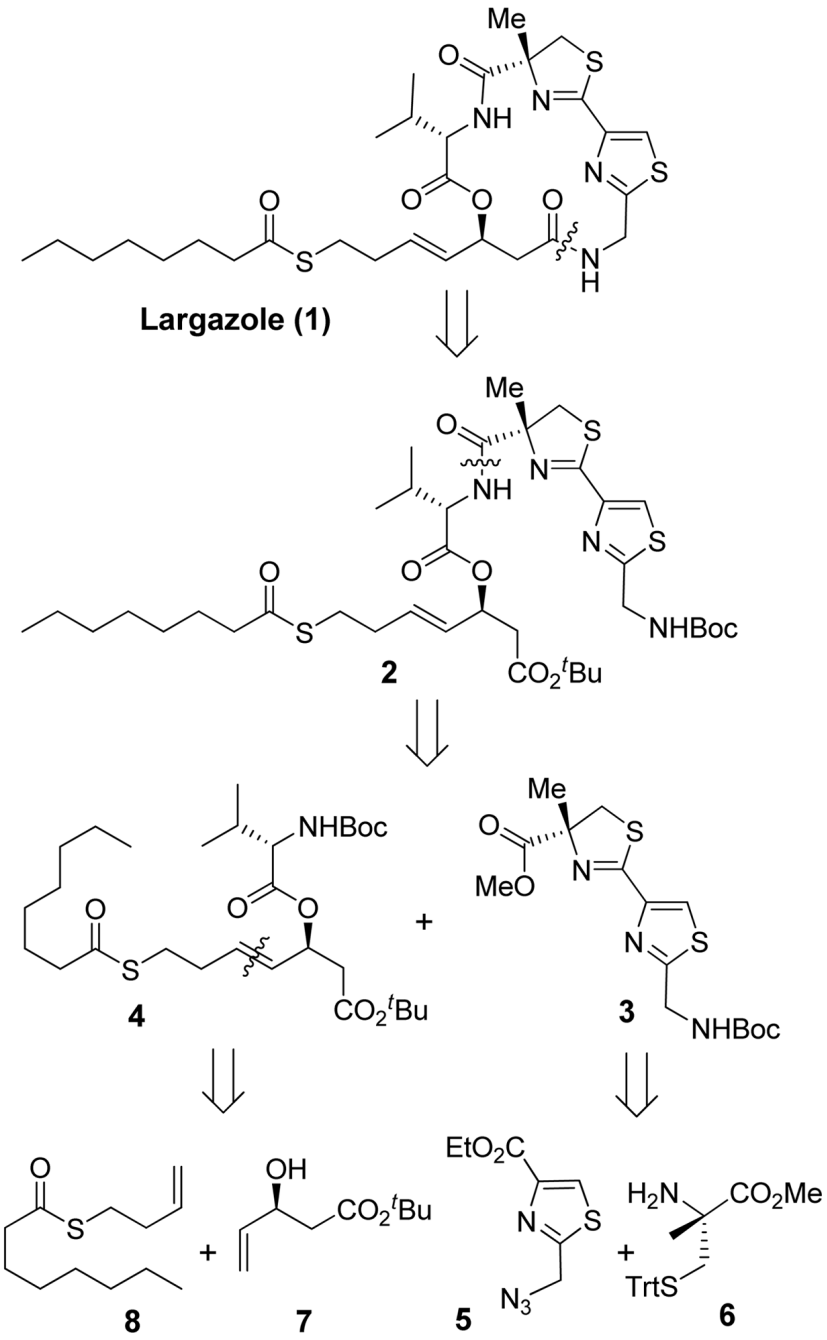
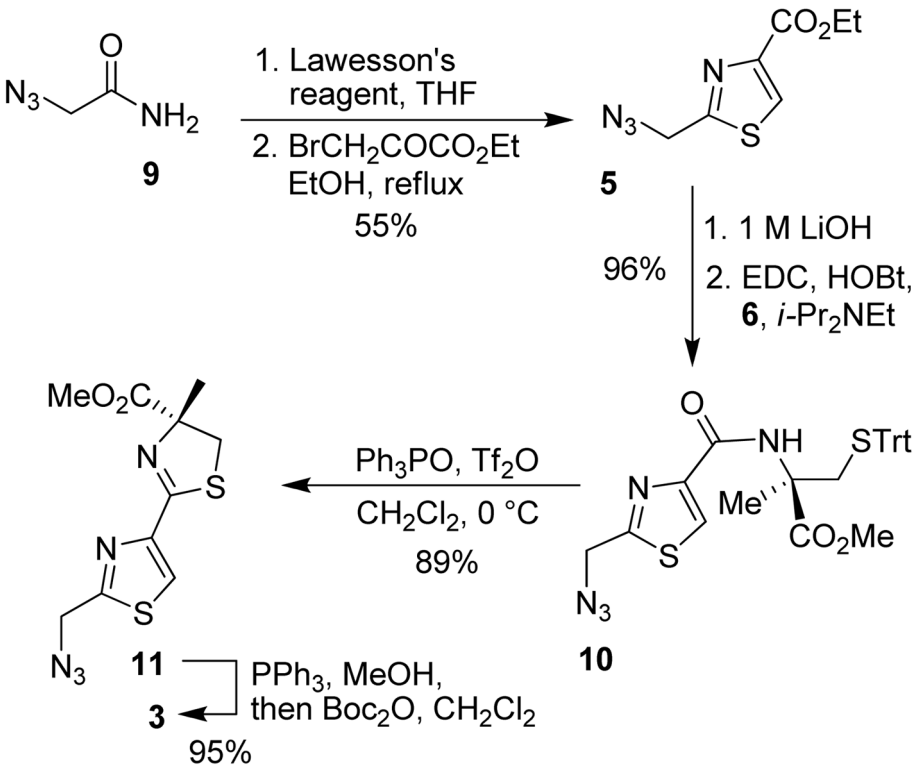
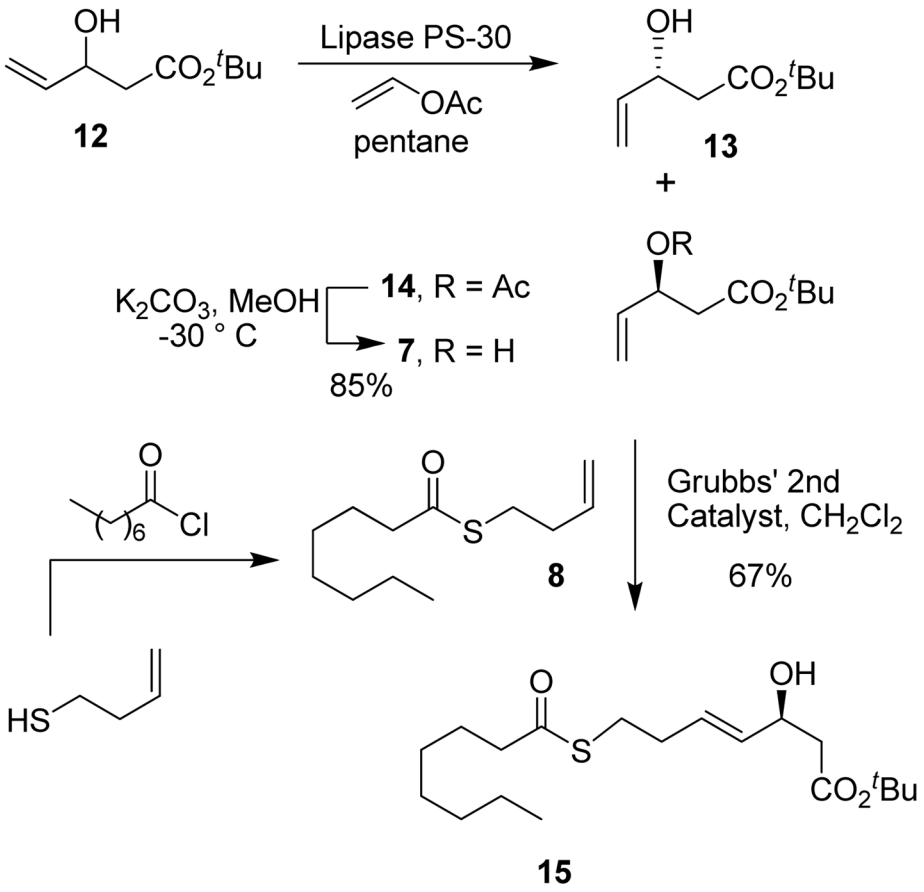


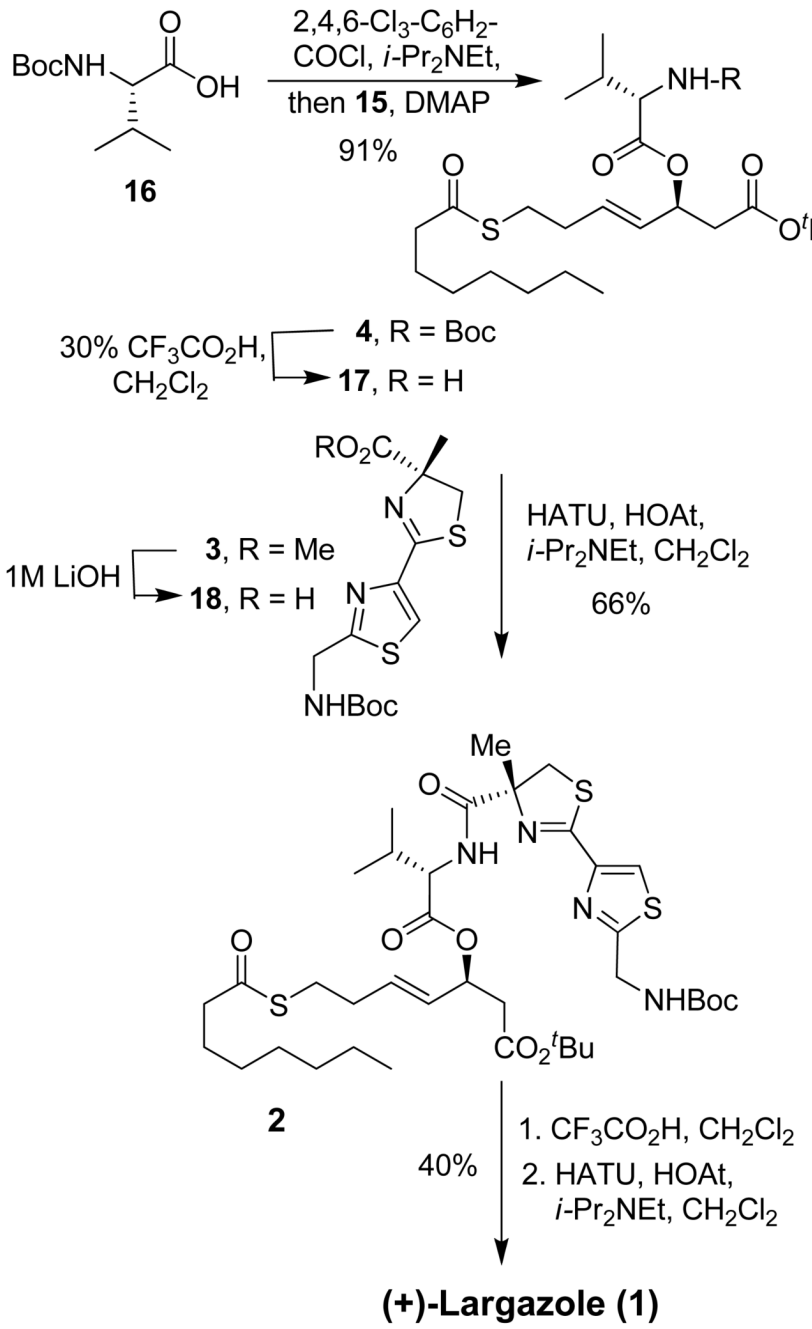
Figure 1.
Retrosynthetic analysis of largazole



Scheme 1.
Synthesis of segment **3**



Scheme 2.
Synthesis of thio ester **15**



Scheme 3.
Synthesis of Largazole