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Enantiospecific Synthesis of *N*-Boc-Adda: A Linear Approach

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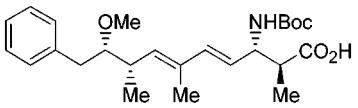
ABSTRACT



Synthesis of the unusual amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), a unit of numerous cyanobacterial toxins, is described. Construction of the target molecule was achieved in 13 steps with an overall yield of 40%. The work is highlighted by a novel one-pot transformation from isoxazolidin-5-one intermediate 6 to the final product, a step that can also be used to form *β*-amino acids.

Nodularin, **1**, motuporin, **2**, and microcystins, **3**, are marine-derived natural products (Figure 1) that contain the unusual amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda), **4**. Nodularin[1] and the microcystins[1] have been isolated from cyanobacteria while motuporin[2] was obtained from the marine sponge *Theonella swinhoei*. Nodularin and microcystins are hepatotoxins and tumor promoters whereas motuporin displays *in vitro* cytotoxicity against various cancer cell lines.[1,3] These compounds exhibit inhibitory activity against serine−threonine protein phosphatases associated with the intracellular signaling process.[3,4] Structure−activity relationship (SAR) studies on these compounds may shed new light on that process, but before comprehensive SAR studies can become a reality, a short and stereoselective route to Adda is required, one that is capable of producing **4** on a gram scale. Toward this goal we report here the first linear synthesis of Adda.

The unique structure of Adda has stimulated several groups to develop routes to the unusual amino acid or its derivatives.[5] Our procedure described in the present report provides *N*-Boc-Adda (**5**) in the fewest steps (13), from commercially available material, with a much higher overall yield (40%) than previously reported.[5] Our synthesis employs the Evans aldol reaction to lay the stereochemical framework for all stereogenic centers found in Adda.[6] The final step in the synthesis introduces a new "one-pot" procedure to stereoselectively synthesize allylic amines via an isoxazolidin-5-one intermediate (**6**).[7]

The stereochemistry at C-8 and C-9 of Adda was established using an Evans aldol reaction between acylated oxazolidinone **7** and phenylacetaldehyde (Scheme 1). Replacement of the chiral auxiliary with a Weinreb amide allowed for epimerization-free methylation of alcohol **8**.[5e] DIBAL-H reduction of Weinreb amide **9** followed by a

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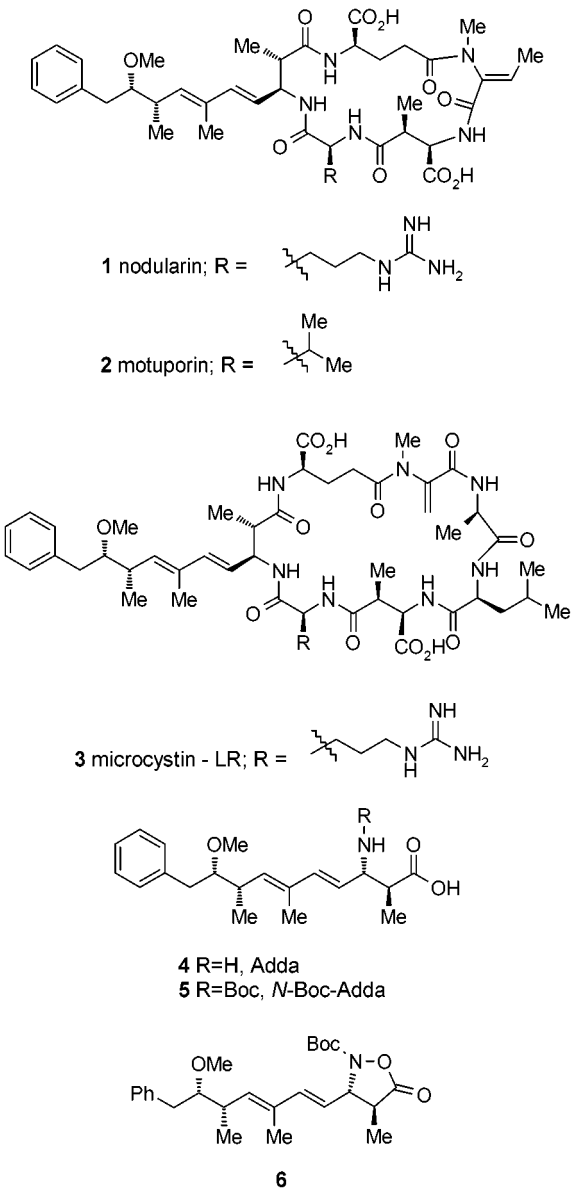
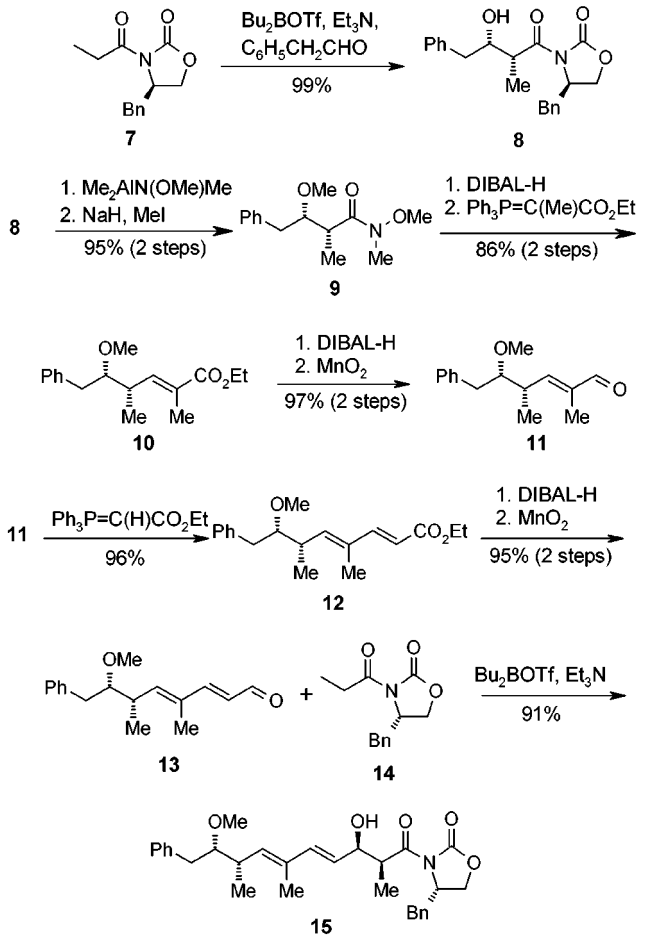


Figure 1. Structures of nodularin, motuporin, microcystin LR, Adda, and *N*-Box-Adda.

Wittig reaction with (carbethoxyethylidene)triphenylphosphorane provided olefin **10** in 81% yield from **7**.[5e] DIBAL-H reduction of **10** followed by allylic alcohol oxidation (MnO_2) provided aldehyde **11** in 97% yield. A second Wittig reaction, between **11** and (carbethoxymethylene)triphenylphosphorane, provided ester **12** in 96% yield, completing the diene system of Adda. A second DIBAL-H reduction and MnO_2 oxidation gave aldehyde **13**. An Evans aldol reaction between **13** and acylated oxazolidinone **14** (the enantiomer of **7**) yielded alcohol **15** in 91% yield, completing the stereochemical framework of Adda.

The next step involved replacing the alcohol at C-3 of **15** with an amine, resulting in inversion of configuration.[8] To avoid conjugate addition and potential [3,3] sigmatropic rearrangements, we proposed replacing the chiral auxiliary

Scheme 1



with a two unit "linker" (-X-N-R) that could undergo an intramolecular Mitsunobu reaction to give a five-membered ring product (conjugate addition would result in a seven-membered ring) followed by cleavage of the linker between the N−X bond to give the amine target.

To accomplish this goal, alcohol **15** was added to a mixture of NaH and *tert*-butyl-*N*-hydroxycarbamate to give **16** (Scheme 2). Intramolecular Mitsunobu reaction of **16** provided isoxazolidin-5-one, **6**, which was isolated in low yield due to decomposition on silica gel. Various reagents were investigated that are capable of cleaving N−O bonds under Mitsunobu conditions, thereby eliminating the need to isolate the labile isoxazolidin-5-one. SmI_2 has been reported to effect N−O bond cleavage and served as a valuable reagent for our purposes.[9] *N*-Boc-Adda (**5**) was synthesized in 64% yield from **16** by a Mitsunobu cyclization followed by SmI_2 reduction in a "one pot" process. SmI_2 cleaves N−O bonds in high yield; however, the reagent is expensive and the

(8) A Mitsunobu reaction between **15** and HN_3 gave good yields of the azide but with complete loss of stereocontrol (possibly due to [3,3] sigmatropic rearrangement). Mitsunobu reactions were also tested with phthalimide and *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide, but the yields were low and stereocontrol was poor.

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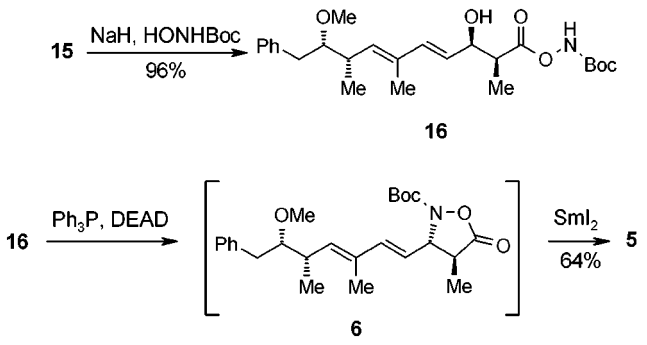
Scheme 2



reaction is sluggish at low temperatures. Sodium naphthalide is an inexpensive alternative that effects N−O bond cleavage at −78 °C. "One-pot" sodium naphthalide reduction of **16** provided *N*-Boc-Adda (**5**) in equivalent yields but with greater diastereomeric purity at a much lower cost than SmI_2. The "one-pot" Mitsunobu reaction and sodium naphthalide (or SmI_2) reduction provide an efficient route to allylic amines that can be carried out at low temperatures with excellent levels of stereocontrol (less than 1% of a diastereomer detected at −78 °C).

This approach provided *N*-Boc-Adda (**5**) in 40% yield from 13 steps using commercially available starting material. Our earlier synthesis of *N*-Boc-Adda was accomplished by a convergent procedure that required 16 steps with an overall yield of 29%.[10] Other representative sequences gave 12% in 23 steps,[5d] 5% in 21 steps,[5e] or 5% in 19 steps.[5h] We have also used the present methodology to synthesize D-*erythro*-*β*-methylaspartic acid, a component of nodularin, the microcystins, and motuporin, from *trans*-cinnamaldehyde. This approach has the advantages of brevity and stereocontrol and the possibility of utilizing the olefin portion as a synthon for other functional groups, including the enantiospecific synthesis of allylic and nonallylic amines.

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Supporting Information Available: Complete experimental procedures and characterization for compounds **5**−**16**. This material is available free of charge via the Internet at http:/pubs.acs.org.

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