

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

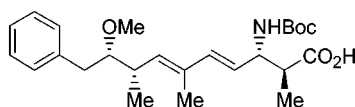
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ABSTRACT



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**. Nodularin¹ and the microcystins¹ have been isolated from cyanobacteria while motuporin² 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 deriva-

tives.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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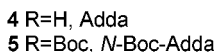
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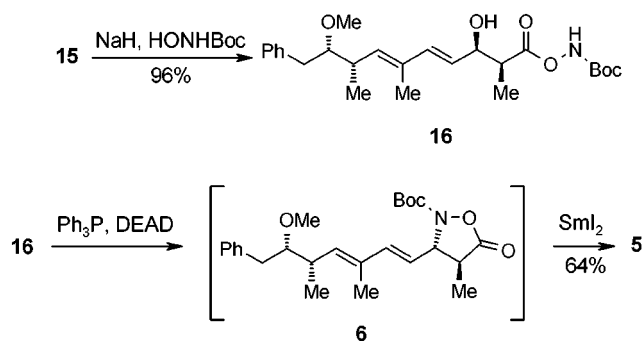
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Scheme 2



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

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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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