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A Novel Stereoselective Route to Some Uncommon Amino Acids

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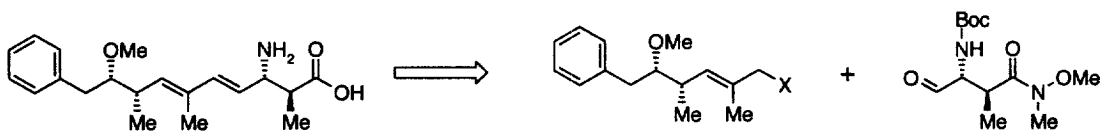
Abstract: An efficient synthesis of a D-*erythro*-β-methylaspartic acid analog was achieved in six steps from commercially available material. Evans' aldol reactions were utilized followed by Weinreb amide formation and Mitsunobu inversion to achieve the necessary stereochemistry of the amino acid target. The technique was applied to the synthesis of an aspartic acid analog as well as a diaminobutyric acid analog.

Nodularin, microcystin, and motuporin are non-selective inhibitors of protein phosphatases I and IIA [1,2]. Nodularin and microcystin were isolated from cyanobacteria (*Nodularia spumigena* and *Microcystis aeruginosa*, respectively), whereas motuporin was isolated from the marine sponge *Theonella swinhoei* [3,4]. These toxins contain the unusual amino acids Adda (**1**), an *iso*-(γ)-linked D-glutamic acid, an *iso*-(β)-linked D-*erythro*-β-methylaspartic acid, and either an α-(*N*-methylamino)-*Z*-dehydrobutyrate (in nodularin and motuporin) or an α-(*N*-methylamino)-dehydroalanine residue (in microcystin) [5]. Based upon isolated variants, the Adda unit appears to be necessary for the overall toxicity of the molecule [6,7]. Nevertheless, we plan to conduct a structure-activity relationship (SAR) study to further define the pharmacophore.



Adda (1) 2 3

X = PPh_3; Ts

Scheme 1

A structure-activity relationship study requires an efficient, gram-scale synthesis of the Adda

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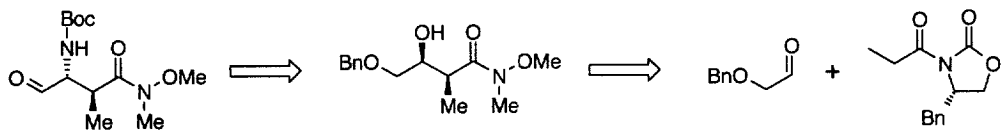
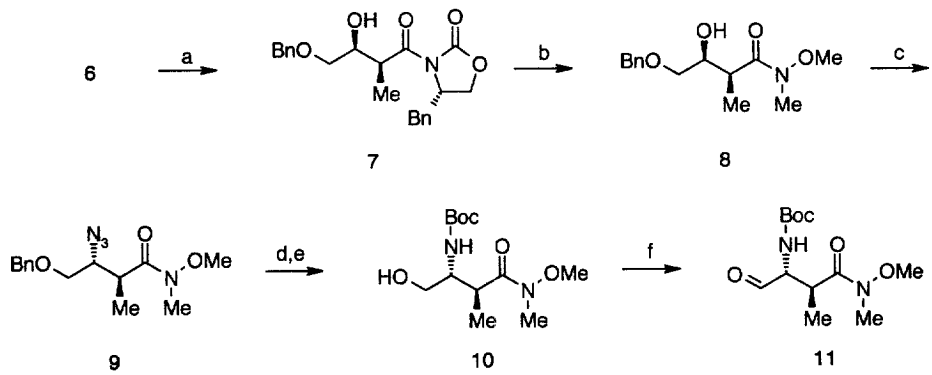
unit. Retrosynthetic analysis of Adda (**1**) defines an aromatic portion (**2**) and an amino portion (**3**) (Scheme 1). In the forward direction, these two subunits can be joined by a Wittig reaction or by a Julia coupling. Several syntheses of the Adda unit have been reported but most lack a short, efficient route to the amino portion (**3**) [7-15].



3 4 5 6

Scheme 2

Further retrosynthetic analysis indicates the amino portion **3** can be obtained by an S_N2 reaction involving alcohol **4** and a nitrogen nucleophile (Scheme 2). Retrosynthetic cleavage of alcohol **4** suggests an aldol condensation employing Evans' reagent, **6**, and benzyloxy-acetaldehyde, **5**. This approach provides easy access to all stereoisomers by modifying the stereochemistry of the chiral auxiliary in combination with a series of Mitsunobu inversions.



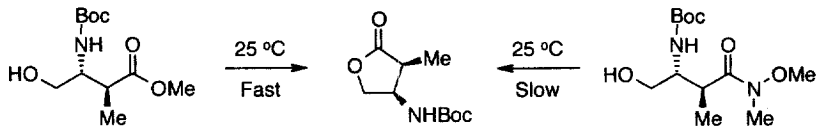
7 8 9 10 11

a. Bu_2BOTf, Et_3N, **5**, 98%. b. $Me_2AlN(OMe)Me$, 89%. c. PPh_3, DEAD, HN_3, 92%. d. H_2-Pd/C, Boc_2O, EtOAc, 99%. e. H_2-Pd/C,MeOH, 98%. f. TPAP, NMO, 87%.

Scheme 3

Our synthesis began with an enantiospecific aldol condensation between benzyloxy-acetaldehyde, **5**, and **6** to give aldol **7** in good yields (Scheme 3) [16]. Displacement of the alcohol with various amine nucleophiles under Mitsunobu conditions as well as substitution for triflate, mesylate, or tosylate resulted in elimination to give a dehydrated product. Replacement of the chiral auxiliary with a Weinreb amide (**8**) allowed for Mitsunobu inversion (92% yield) with no elimination [11, 17]. Azide **9** was reduced and the resulting amine was protected in a one-pot process by hydrogenation in the presence of Boc_2O (99%) [18]. Benzyl ether

deprotection was accomplished by hydrogenation in methanol to give alcohol **10** in 97% yield. Attempts were made to reduce the azide, protect the resulting amine, and effect benzyl ether cleavage in one pot by high pressure hydrogenation but these led to incomplete reactions. Oxidation of alcohol **10** with catalytic tetrapropylammonium perruthenate and stoichiometric amounts of 4-methylmorpholine-*N*-oxide gave aldehyde **11** in good yield [19].

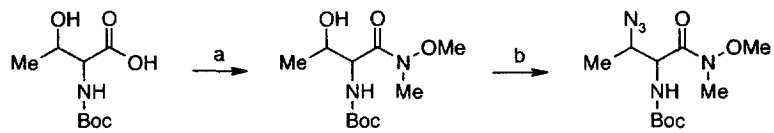


12 13 10

Scheme 4

Other syntheses of the amino portion have been reported; most utilize an ester to protect the acid functionality [7,9,10,11,14]. In our hands, these procedures gave poor yields due to the rapid cyclization of alcohol **12** to give the γ-lactone **13** (Scheme 4). Upon oxidation of **12**, the resulting aldehyde rapidly epimerizes. Our approach not only has the advantage of brevity but essentially no lactonization of **10** occurs upon standing at room temperature for prolonged periods of time. Aldehyde **11** can be stored for months at -20 °C with no decomposition or loss of stereochemistry.

The Weinreb amide is easily removed by literature procedures and serves as an excellent protection group with the ability to "stabilize" sensitive molecules [20]. We propose the Weinreb amide serves to inhibit elimination and epimerization by reducing the α-methine proton's (H-2) acidity. Lactonization is suppressed due to the strength of amide bonds relative to esters.



14 15 16

a. DMAP, HOBt, MeONHMe-HCl, EDCI, 69%. b. PPh_3, HN_3, DEAD, 88%.

Scheme 5

To our knowledge, this is the first report of the synthesis of unusual amino acid analogs involving Evans' aldol condensation followed by Weinreb amide formation and Mitsunobu inversion. We have also employed Weinreb amides to stabilize Mitsunobu inversion of Boc-D,L-threonine to give a differentially protected 2,3-diaminobutanoic acid analog, **16**, a constituent of various peptide antibiotics, in excellent yields, (Scheme 5) [21]. *N*-Protected

threonine methyl esters, on the other hand, have been reported to undergo dehydration under Mitsunobu conditions [17].

Gram quantities of the amino portion **11** of Adda have been enantiospecifically synthesized in 6 steps (from commercially available materials) in 68% overall yield. Two new syntheses of Adda and a total synthesis of nodularin will be reported in the near future.

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[5] Adda is an abbreviation for (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid. Other abbreviations used in this manuscript: Bu_2BOTf, dibutylboron triflate; TPAP, tetrapropylammonium perruthenate; NMO, 4-methylmorpholine *N*-oxide; HOBT, 1-hydroxybenzotriazole; EDCI, 1-ethyl-3-[(3-dimethylamino)-propyl]carbodiimide hydrochloride.
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