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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. \bigcirc 1998 Elsevier Science Ltd. All rights reserved.

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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.



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

0040-4039/99/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)02383-1 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].



Further retrosynthetic analysis indicates the amino portion 3 can be obtained by an S_N^2 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.



Bu₂BOTf, Et₃N, 5, 98%. b. Me₂AlN(OMe)Me, 89%. c. PPh₃, DEAD, HN₃, 92%. d. H₂-Pd/C, Boc₂O, EtOAc, 99%. e. H₂-Pd/C, MeOH, 98%. f. TPAP, NMO, 87%.
Scheme 3

Our synthesis began with an enantiospecific aldol condensation between benzyloxyacetaldehyde, **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 Boc₂O (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].



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.



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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