Available online at www.sciencedirect.com
ScienceDirect
Carbohydrate Research 343 (2008) 1743–1753
Carbohydrate RESEARCH

Synthesis of octahydropyrano[3,2-*b*]pyrrole-2-carboxylic acid derivatives from D-mannose

Jean-Rene Ella-Menye, Xiaoping Nie and Guijun Wang*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, United States

Received 25 November 2007; received in revised form 6 March 2008; accepted 10 March 2008
Available online 15 March 2008

Abstract—Bicyclic amino acids are useful building blocks in synthesizing biologically active molecules and peptidomimetics. 2-Carboxy-6-hydroxyloctahydroindole (Choi) is a novel bicyclic amino acid found in the marine natural products aeruginosins. Many compounds in the aeruginosin family exhibit inhibition activities toward serine proteases including thrombin and trypsin. The unique Choi structure is the common feature of this family of oligopeptides and this motif is important for their observed biological activities. To better understand the influence of the stereochemistry of the Choi core structure on the inhibition activities, we have previously synthesized ring-oxygenated variants from glucose. The preparation of octahydro-pyrano[3,2-*b*]pyrrole 2-carboxylic acids from D-mannose is reported here. These novel bicyclic amino acids can be used in the preparation of aeruginosin analogs, as well as conformationally constrained peptidomimetics or other biologically active molecules.

Keywords: Aerguginosin; Octahydroindole 2-carboxylic acid; Rigid conformation; Thrombin inhibitor

1. Introduction

Structurally constrained bicyclic amino acids are useful building blocks for the preparation of peptidomimetics and other biologically important molecules.[1–3] Several examples of these types of compounds (**1**–**5**) are shown in Chart 1. The conformationally constrained synthetic bicyclic amino acids **1**–**3** has been used in the preparation of thrombin inhibitors such as **6**–**8** (Chart 2).[4–6] 2-Carboxy-6-hydroxyloctahydroindole (Choi) **4** is another conformationally rigid amino acid, which is the core structure present in the marine natural products called aeruginosins.[7–11] The dihydroxylated compound **5** is the core structure of similar natural products, dysinosins (Chart 3).[12,13]

A majority of the naturally occurring aeruginosins share the same stereochemistry and substitution pattern although some exceptions have been reported. Several structures of aeruginosins and related compounds (**9**–**12**) are shown in Chart 3.[11,12] Many aeruginosins are found to be inhibitors of serine proteases including blood coagulation factors, such as thrombin and factor VIIa. The unusual octahydroindole core structure is important for their observed biological activities. Direct inhibition of thrombin has demonstrated utility in treating thrombosis-related disorders;[13] however, more

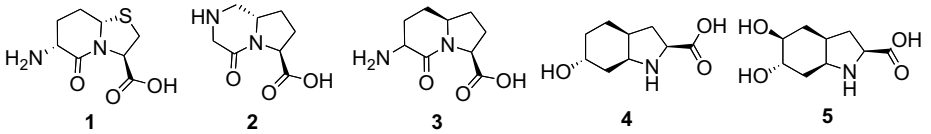

Chart 1. Structures of bicyclic amino acids that are useful building blocks.

* Corresponding author. Tel.: +1 504 280 1258; fax: +1 504 280 6860; e-mail addresses: gwang2@uno.edu; wangguij@yahoo.com

0008-6215/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2008.03.017

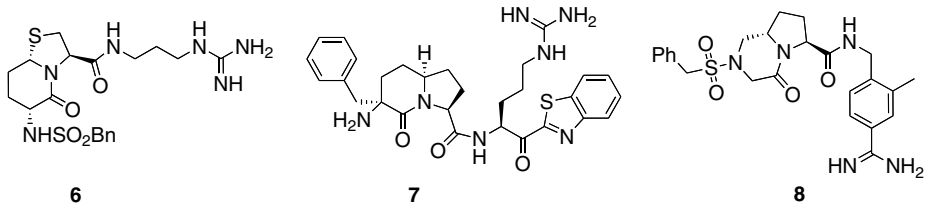

Chart 2. Structures of thrombin inhibitors containing fused amino acids.

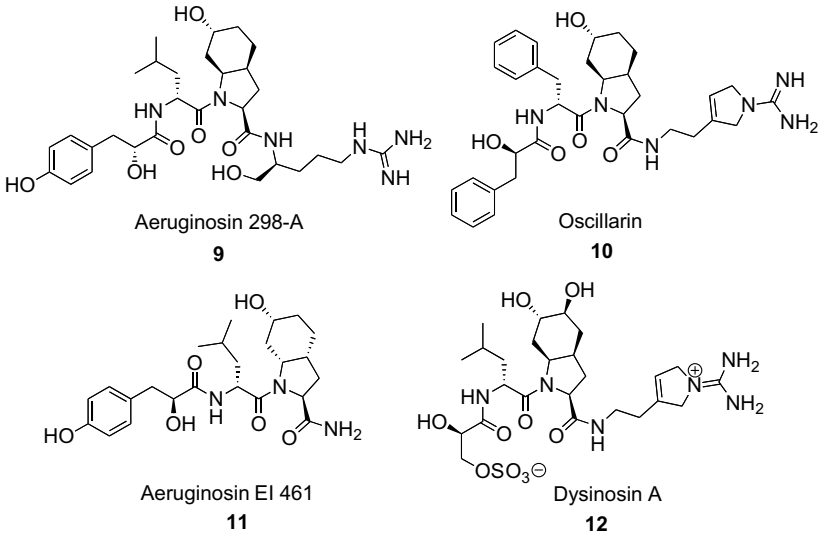

Chart 3. Structures of aeruginosins and related compounds.

efficient oral anticoagulants remain elusive. In this regard, aeruginosins are promising natural products that can be explored and optimized to obtain potent and selective thrombin inhibitors.

Because of the biological importance of this class of molecules, the total synthesis of Aeruginosin 298-A (Chart 3),[14–17] Aeruginosin EI461,[18] Oscillarin,[11] and Dysinosins[19,20] have been accomplished by a few research groups. Several syntheses of the Choi fragment and analogs have also been reported.[21–25] In addition, aeruginosin analogs have also been designed and synthesized in the search for improved thrombin inhibitors.[26–28] We were intrigued by this unusual amino acid and developed an efficient method to synthesize protected ring-oxygenated variants (**14**, **15**) from D-glucose **13** as shown in Figure 1.[25,29] Sugars are readily available renewable resources, and they contain abundant chiral centers that can be used as chiral pool starting materials for the synthesis of more complex molecules. We have also synthesized the bicyclic amino acid **16** using L-glucose as the starting material and tetrapeptides containing the Choi variant **16**.[29] We envisioned that by using a different monosaccharide such as D-mannose as the starting material, bicyclic amino acids **17** and **18** can be prepared using a similar method for the preparation of **14** and **15**. Similarly, if D-galactose is used as the starting material, the *trans O*-Choi analogs **19** can be synthesized. These ring-oxygenated variants of 2-carboxy-6-hydroxyoctahydroindole can be used as surrogates of Choi in the design and synthesis of

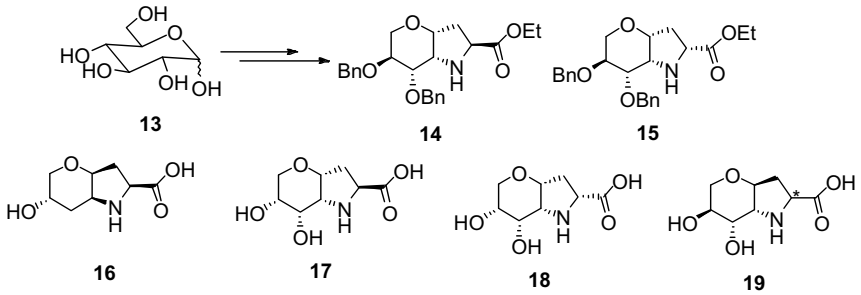

Figure 1. *O*-Choi analogs that can be synthesized from monosaccharides.