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SCIENCE DIRECT
Tetrahedron 61 (2005) 8821–8829
Tetrahedron

Concept and synthetic approach for a kilogram scale synthesis of octa-D-arginine amide nonahydrochloride salt

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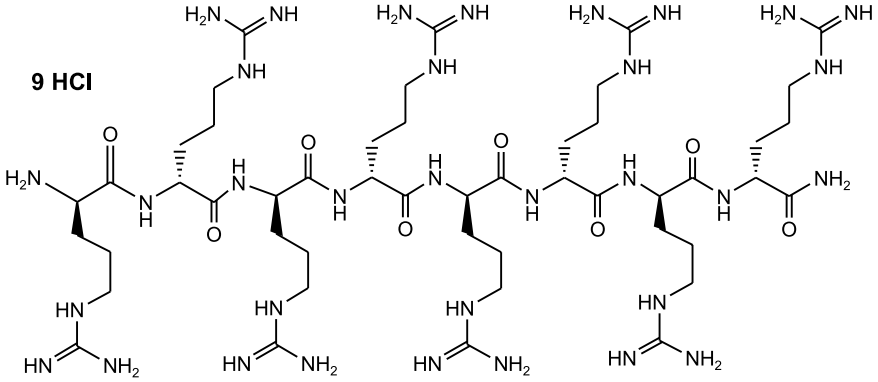
Received 4 April 2005; revised 1 July 2005; accepted 8 July 2005

Available online 28 July 2005

Abstract—Oligomers of arginine, such as octa-D-arginine amide, are excellent transporters for active drugs through cell membranes and tissue. The synthesis of octa-D-arginine amide, as the nonahydrochloride salt, was approached via a solution phase synthetic route involving the preparation of an octa-D-ornithine intermediate, which was then converted into the desired octa-D-arginine compound through a guanidinylation step. The multi-step synthesis was carried out at pilot scale, resulting in the preparation of 700 g of the target molecule. No chromatographic purification was needed at any step of the process.

1. Introduction

Timing and development of scalable processes are critical to the successful production of a peptide-based drug.[1] Although solid phase synthesis is a common approach used to prepare oligopeptides, this method can have limitations, such as the high cost of excess reagents and protected amino acids, the high volume of solvents used, potential limited scalability, and the usual requirement for a chromatographic purification once the peptide is cleaved from the resin. A solution phase synthesis appeared to be a more attractive approach for the preparation of our target molecule, octa-D-arginine amide nonahydrochloride salt[2–11] (**6**) (Scheme 1) in terms of robustness, scalability, and the potential to minimize labor-intensive purification. The limited availability and cost of protected D-arginine derivatives led us to explore the development of a synthesis in which D-ornithine is substituted for the D-arginine residues. A per-guanidinylation step would then



Scheme 1. Octa-D-arginine amide hydrochloride.

Keywords: Amino acids and derivatives; Arginine; Guanidinylation; Peptide transport; Peptide process development; Minimal isolation peptide synthesis.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.07.037

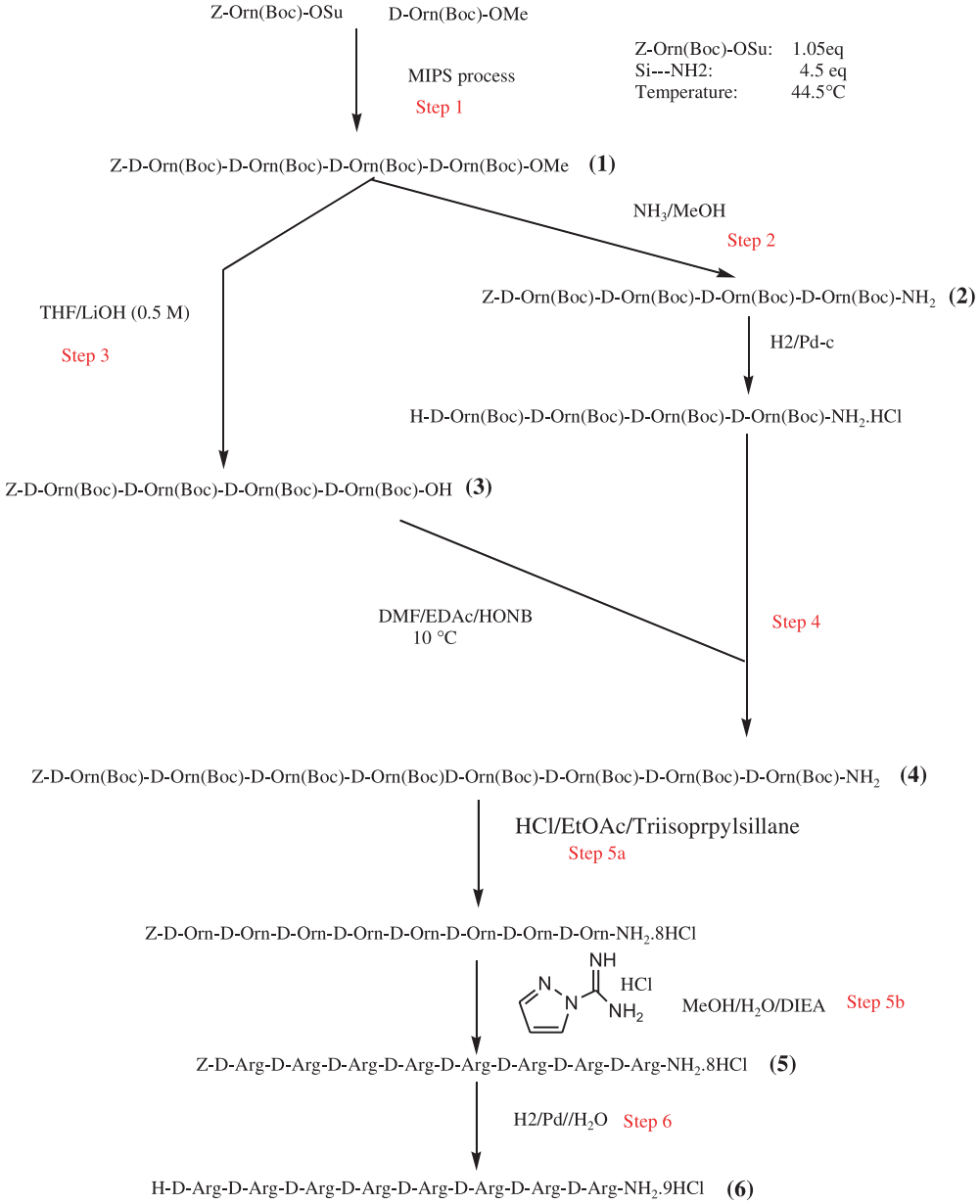
be used for conversion of the 8 ornithine residues to the corresponding arginine residues.[12–18]

The synthetic process, as described in Scheme 2, resulted in the preparation of 0.7 kg of the desired compound, isolated as a hydrochloride salt (**6**). The main features of the process were the synthesis of a key crystalline tetrapeptide ester intermediate (**1**) with only one isolation, followed by the preparation of two crystalline tetrapeptide intermediates (**2**) and (**3**) from the common tetrapeptide ester (**1**). Coupling of the N-terminal deprotected (**2**) with C-terminal deprotected (**3**) gave the fully protected octa-D-ornithine intermediate (**4**), which upon global removal of 8 amine-protecting groups followed by global guanidinylation of the free amines in one step gave the desired D-arginine residues. No chromatographic purification was used at any step of the process. At the final step a simple activated carbon treatment of the desired octa-D-arginine amide hydrochloride salt (**6**) in water was sufficient for purification.

2. Results and discussion

In step 1, *Z*-[D-Orn(Boc)]$_4$-OMe (**1**) (Scheme 3), was prepared following a continuous process (MIPS, minimal isolation peptide synthesis) to minimize the isolation steps of the intermediate dipeptide and tripeptide.

The general procedure for conducting the MIPS process is described in Scheme 4 below. Excess *N*-benzyloxycarbonyl-protected amino acid *N*-hydroxysuccinimide ester[19] (*Z*-AA-OSu) is used to drive the acylation to completion. Residual *Z*-AA-OSu is captured/scavenged by the addition of amine-derivatized insoluble resin or silicagel,[20,21] which



Scheme 2. Octa-D-arginine amide—overall process.