Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 2457–2460
Bioorganic & Medicinal Chemistry Letters

# Synthesis of dehydroalanine fragments as thiostrepton side chain mimetics

Benjamin K. Ayida,[a] Klaus B. Simonsen,[a,†] Dionisios Vourloumis[a] and Thomas Hermann[b,*]

[a]*Department of Medicinal Chemistry, Anadys Pharmaceuticals, Inc., 3115 Merryfield Row, San Diego, CA 92121, USA*
[b]*Department of Structural Chemistry, Anadys Pharmaceuticals, Inc., 3115 Merryfield Row, San Diego, CA 92121, USA*

Received 14 February 2005; revised 18 March 2005; accepted 21 March 2005
Available online 12 April 2005

**Abstract**—Syntheses of dehydroalanine derivatives via a solid-support route, starting from selenocystein, and via conventional solution phase chemistry are described along with initial biological testing. The target compounds were designed as mimetics of the dehydroalanine side chain of the macrocyclic antibiotic thiostrepton that acts on the bacterial ribosome.


Thiostrepton is a cyclic peptide antibiotic that inhibits bacterial translation by blocking the function of the ribosomal GTPase center (Fig. 1A).[1] The macrocycle interacts with 23S rRNA at the GTPase-associated domain of the 50S ribosomal subunit and shuts down GTP-dependent reactions during translation. The insoluble nature of thiostrepton has prevented its broad use as an antibiotic and complicated structural studies to elucidate its interaction with the ribosomal target. Despite the fact that a total synthesis of thiostrepton has been published,[2] its complex chemical structure hampers selective derivatization. Previous synthetic efforts were focused on fragments of the macrocycle as potential lead structures for antibacterial discovery targeting the ribosome.[3] While emerging structural data suggest that the thiostrepton macrocycle might be interacting with both ribosomal S23 RNA and the L11 protein,[4] the role of the bis(dehydroalanine) side chain remains elusive. To provide model compounds for the study of the biological activity of the thiostrepton side chain, we synthesized dehydroalanine fragments **1** and **2** as mimetics of the bis(dehydroalanine) moiety (Fig. 1).

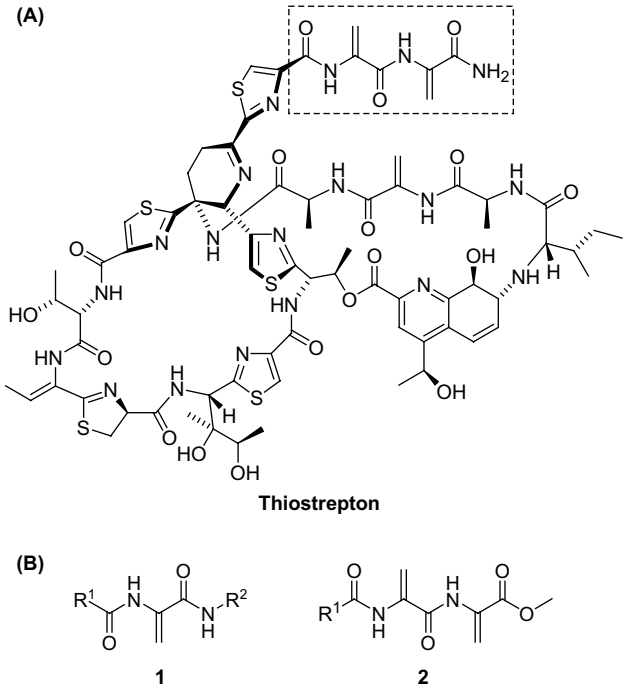
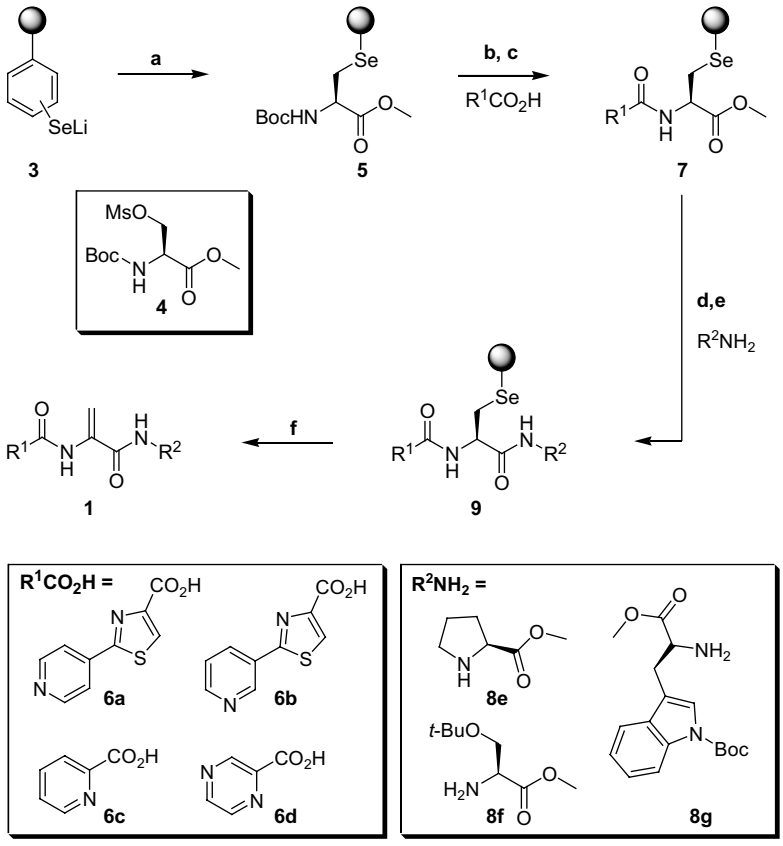



**Figure 1.** (A) Thiostrepton, a ribosome-binding cyclic peptide antibiotic first isolated from *Streptomyces azureus*. (B) Mimetics **1** and **2** of the thiostrepton bis(dehydroalanine) side chain (boxed in **A**), whose synthesis and preliminary biological testing is described in this communication.

Established routes for the synthesis of dehydroalanine and derivatives thereof include (a) conversion of masked

*Keywords*: Antibiotics; Dehydroalanine; Ribosome; Thiostrepton; Translation.
* Corresponding author. Tel.: +1 858 530 3659; fax: +1 858 527 1540; e-mail: thermann@anadyspharma.com
† Present address: H. Lundbeck A/S, Ottiliavey 9, 2500 Copenhagen Valby, Denmark.

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.03.084

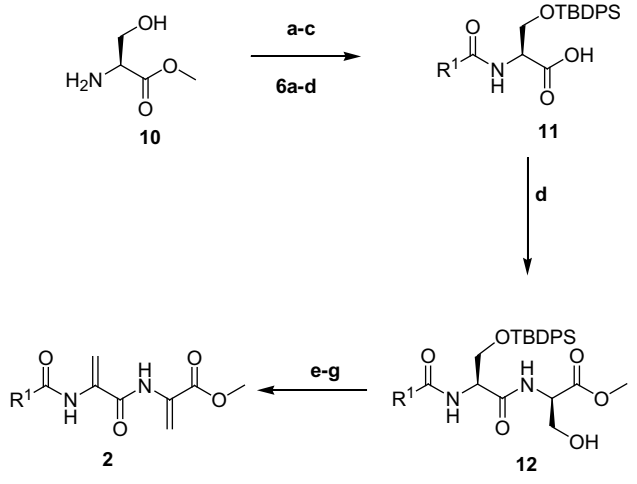



**Scheme 1.** Reagents and conditions: (a) **4** (2.0 equiv), THF (0.22 M), 2 h, 23 → 50 °C; (b) 55% TFA in $CH_2Cl_2$, 2 h, 23 °C; (c) DIC (6.0 equiv), HOBt (7.0 equiv), $R^1CO_2H$ (**6a**–**d**, 4.0 equiv), DMF (0.07 M), 20 h, 23 °C; (d) LiOH (10.0 equiv), THF/$H_2O$ (5:1, 0.47 M); (e) DIC (5.0 equiv), HOBt (5.0 equiv), $R^2NH_2$ (**8e**–**g**, 3.0 equiv), DMF (0.07 M), 20 h, 23 °C; (f) $H_2O_2$ (30% aq, 6.0 equiv), $Me_2S$ (10.0 equiv), 1 h, 23 °C. THF = tetrahydrofuran; TFA = trifluoroacetic acid; HOBt = 1-hydroxybenzotriazole; DMF = *N*,*N*-dimethyl-formamide; DIC = 1,3-diisoproylcarbodiimide.

serine and threonine residues, either as mesyloxy intermediates or halides,[5] (b) direct elimination of β-hydroxy groups,[6] via asparagine residues, and (c) Hoffmann elimination of 2,3-diaminopropionic acids.[7] Few examples have been reported using phenyl selenocysteine to promote site specific and chemoselective introduction of dehydroalanine residues.[8] In this communication, we report the use of selenocysteine as a solid phase selenium linker for peptide synthesis that, upon oxidative cleavage from the solid support, yields the dehydroalanine functionality by elimination.

Selenium-functionalized resin **3**, obtained following a protocol reported by Nicolaou and co-workers,[9] was alkylated with 2-amino-3-methanesulfonyloxy-propionic acid methyl ester **4** to yield solid-supported selenocysteine precursor **5** (Scheme 1).

Methyl ester **4** was synthesized from L-serine methyl ester **10** (Scheme 2) by treatment with di-*tert*-butyl dicarbonate followed by mesylation of the serine hydroxy group.[10] The efficiency of resin loading was determined by oxidative cleavage ($H_2O_2$/$Me_2S$) of an aliquot of the alkylated intermediate **5**, followed by NMR quantitation using 2,5-dimethylfuran as internal reference.[11] Acidic removal of the Boc protecting group, followed by coupling with various acids (**6a**–**d**) proceeded under standard conditions (DIC, HOBt) to produce amides




**Scheme 2.** Reagents and conditions: (a) $R^1CO_2H$ (1.0 equiv), BOP (1.1 equiv), *i*-$Pr_2NEt$ (2.2 equiv), $CH_2Cl_2$ (0.12 M), 3 h, 23 °C; (b) TBDPSCl (1.2 equiv), imidazol (2.2 equiv), THF (0.07 M), 3 h, 0 → 23 °C; (c) LiOH (2.0 equiv), MeOH (0.11 M), 1.5 h, 23 °C; (d) **10** (1.2 equiv), BOP (1.2 equiv), *i*-$Pr_2NEt$ (2.2 equiv), $CH_2Cl_2$ (0.12 M), 3 h, 23 °C; (e) MsCl (6.0 equiv), $Et_3N$ (10.0 equiv), $CH_2Cl_2$ (0.04 M), 3 h, 23 °C; (f) TBAF (1.2 equiv), THF (0.05 M), 3 h, 23 °C; (g) MsCl (6.0 equiv), $Et_3N$ (10.0 equiv), $CH_2Cl_2$ (0.04 M), 3 h, 23 °C. BOP = benzotriazol-l-yl-oxy-tris-(dimethylamino)phosphonium hexafluorophosphate; TBDPSCl = 1,1-dimethylethyl-diphenylsilyl chloride; TBAF = tetrabutylammonium fluoride; for reagent abbreviations see also legend to Scheme 1.