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Practical synthesis of fully-substituted peptide thiazoles

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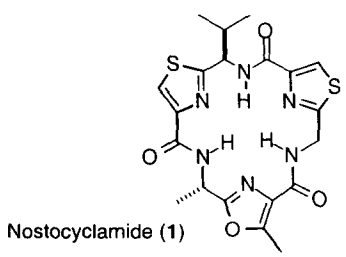
Abstract:

The synthesis of optically active 2,4,5-substituted 1,3-thiazoles (peptide thiazoles) is described. Both the chirality and the set of side chain functionality in this fully-substituted scaffold are derived from a combination of two amino acids and one organometallic reagent. Preliminary results, with two specific examples, highlight the potential of this strategy for the preparation of a diverse set of building blocks.

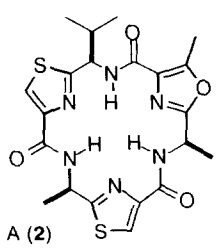
Keywords: Thiazoles; Amido-ketones; Amino acids and derivatives; Grignard reactions/reagents

Interest in the Lissoclinum peptide alkaloids has recently gained momentum and has prompted several reviews.[1,2,3] These 18 to 24-membered cyclopeptides are characterized by an alternating sequence of five-membered heterocycles (oxazole, oxazoline, thiazole, thiazoline) and hydrophobic amino acids, or peptide azole subunits. Several Lissoclinum peptide alkaloids have been the target of total synthesis efforts[1,2,4] and new or improved methodologies[5-13] have emerged for the asymmetric synthesis of the peptide azole subunit. The importance of the effect of the heterocycle saturation level on the secondary alkaloid conformation has also been the subject of recent studies[1,14,15] and is likely a major factor contributing to the variety of biological activities observed. For example, Nostacyclamide (**1**) (Figure 1) demonstrated anticyanobacterial and antialgal activity,[16] while the structurally similar Dendroamide A (**2**) exhibited P-glycoprotein-mediated multidrug-resistance reversing activity in MCF-7/ADR breast carcinoma cells.[17] Considering the continuing advances in combinatorial biosynthesis,[18] particularly those reported by Walsh[19-21] toward the biosynthesis of Microcin B17, and the ongoing discovery of thiazole-containing natural products, the need for improved methodologies for the synthesis of fully-substituted thiazoles is of current interest and is the subject of this communication.

Figure 1



Nostocyclamide (**1**)



Dendroamide A (**2**)

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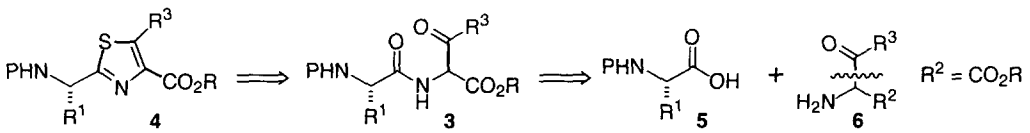
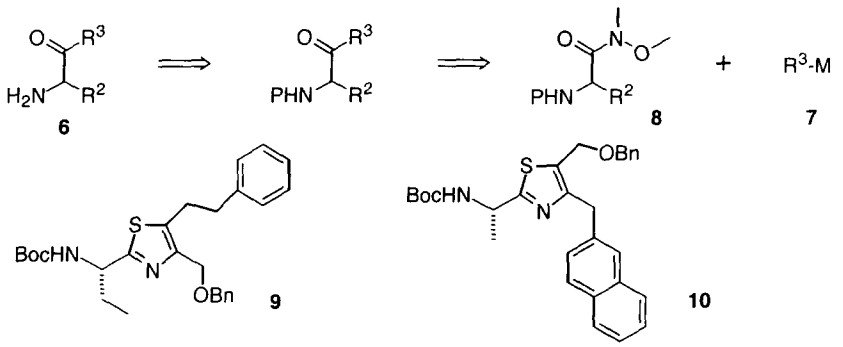
A series of papers from Sterling-Winthrop in 1993 revealed a general strategy (Scheme 1) for the synthesis of peptide azoles toward substance P antagonists.[11-13] This strategy was subsequently employed at Abbott for the preparation of endothelin antagonists.[22,23] Central to these efforts was the cyclization of an intermediate keto amide (**3**) to the corresponding oxazole, thiazole (**4**) or imidazole.[24] Keto amide **3** was derived from the coupling of an amino acid (**5**) with an α-amino-β-keto ester (**6**, $R^2 = CO_2R$), prepared by the acylation of a Schiff base anion of Gly-OMe. Our interest in peptide azoles arose out of our desire to prepare a diverse set of fully substituted thiazoles that could be used toward the syntheses of thiazole-containing natural and unnatural products, yet with greater flexibility in the allowed sets of substituents than provided in the aforementioned examples. Our modifications providing an efficient and general peptide thiazole synthesis are described below.

Scheme 1



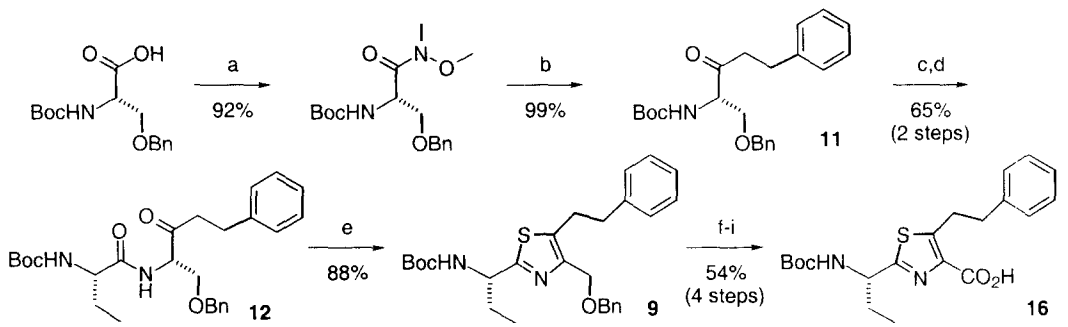
Key to our strategy, was the recognition that a more versatile variant of amino ketone **6** could be prepared by the addition of an organometallic reagent (**7**) to an amino acid-derived Weinreb amide (**8**) (Scheme 2). The functional groups at R^2 and R^3 can be chosen from the diverse set of readily available amino acid derivatives[29] and organometallic reagents.[30] The sense of chirality and functionality at R^1 (in **4**) continues to be derived from the appropriate amino acid. The preparation of thiazoles **9** and **10** demonstrates our general synthetic strategy as well as highlights its versatility toward the preparation of Lissoclinum analogs.

Scheme 2



Commercially available Boc-Ser(Bn)-OH was converted into the corresponding Weinreb amide in 92% yield using standard CDI conditions (Scheme 3). Addition of the phenethyl Grignard reagent provided ketone **11** in 99% yield.[30] Carbamate **11** was deprotected and the resulting amine salt then coupled with Boc-Abu-OH, giving rise to keto amide **12** in 65% yield (2 steps). Treatment of keto amide **12** with Lawesson's reagent effected cyclization, affording thiazole **9** in 88% yield.[31] The protected *amino acid-derived* hydroxymethyl can be readily converted to the corresponding carboxylic acid (**16**) inherent at the 4-position in the peptide alkaloids or manipulated into many other functional groups of varying chain lengths.[32]

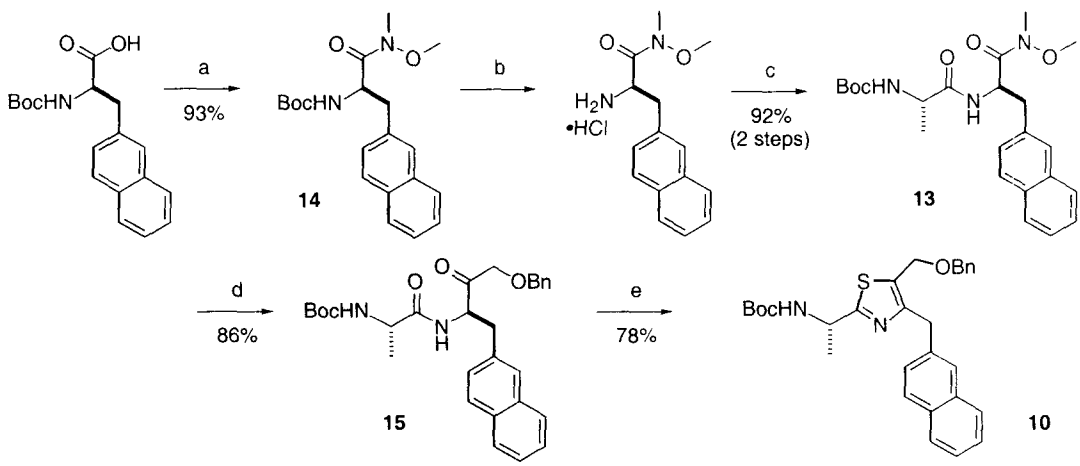
Scheme 3



Reagents and Conditions: (a) CDI, CH_2Cl_2, 0 °C, 10 min, then DIEA, NH(Me)OMe•HCl, rt, 17 h; (b) $PhCH_2CH_2MgCl$, THF, 0 °C, 10 min, then rt, 3.1 h; (c) 3 N HCl, 1:1 dioxane-EtOAc, rt, 2.5 d; (d) DIEA, CH_2Cl_2, Boc-Abu-OH, EDC•HCl, HOBT, rt, 9 h; (e) Lawesson's reagent, THF, 67 °C, 4 h; (f) BCl_3, CH_2Cl_2, -78 °C to 0 °C, 5 h; (g) BOC-ON, Et_3N, dioxane, H_2O, rt, 19 h; (h) MnO_2, CH_2Cl_2, rt, 2h; (i) $NaClO_2$, 50% H_2O_2, CH_3CN, H_2O, 0 °C to rt, 7 h.

The synthesis of thiazole **10**, demonstrating a slightly modified sequence, is shown in Scheme 4. In this case, the addition of the organometallic reagent takes place with a slightly more complex intermediate (**13**). Again, standard Weinreb amide formation was employed, providing amide **14** in 93% yield from commercially available Boc-D-2-Nal-OH. Carbamate **14** was deprotected and the resulting amine salt then coupled with Boc-Ala-OSu, giving rise to amido amide **13** in 92% yield (2 steps). Addition of (benzyloxymethyl)lithium[33,34] to Weinreb amide **13** proceeded smoothly, giving keto amide **15** in 86% yield. Treatment of **15** with Lawesson's reagent provided thiazole **10** in 78% yield.[31] The protected *organolithium reagent-derived* hydroxymethyl can be converted to the corresponding carboxylic acid (as shown for **16**), thus providing a peptide thiazole building block whereby the thiazole heteroatoms have been transposed (or 2,4- vs. 2,5- amino acid orientation).

Scheme 4



Reagents and Conditions: (a) CDI, CH_2Cl_2, 0 °C, 10 min, then DIEA, NH(Me)OMe•HCl, rt, 21 h; (b) 3 N HCl, 1:1 dioxane-EtOAc, rt, 17 h; (c) Et_3N, DME, Boc-Ala-OSu, rt, 19 h; (d) Bu_3SnCH_2OBn, *n*-BuLi, DME, -78 °C then amide **13**, THF, -78 °C, 2.5 h; (e) Lawesson's reagent, THF, 67 °C, 1.5 h.

The syntheses[35] of thiazoles **9**[36] and **10**[37] provide examples of an efficient and general synthesis of optically active 2,4,5-substituted 1,3-thiazoles, or peptide thiazoles. The ready availability of protected natural and unnatural amino acids[29] as well as Grignard and other organometallic reagents provides a rich source for the functionality and chirality of these peptide thiazole building blocks.

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35. All compounds were purified to homogeneity and exhibited satisfactory analytical and spectroscopic properties.
36. Data for **9**: Colorless oil; R_f = 0.60 (1/1 hexanes-EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.00 (m, 10H), 5.25 (m, 1H), 4.84 (m, 1H), 4.53 (s, 2H), 4.43 (s, 2H), 3.06 (t, J = 7.8 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.04 (m, 1H), 1.82 (m, 1H), 1.45 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H); HRMS calcd for $C_{27}H_{35}N_2O_3S$ $(M+H)^+$, 467.2368; found, 467.2347.
37. Data for **10**: Pale oil; R_f = 0.54 (2/1 hexanes-EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.80-7.70 (m, 3H), 7.55 (s, 1H), 7.44-7.38 (m, 2H), 7.36-7.24 (m, 6H), 5.20 (m, 1H), 5.03 (m, 1H), 4.61 (s, 2H), 4.49 (s, 2H), 4.20 (s, 2H), 1.56 (d, J = 6.8 Hz, 3H), 1.44 (s, 9H); HRMS calcd for $C_{29}H_{33}N_2O_3S$ $(M+H)^+$, 489.2212; found, 489.2198.