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Atom-Economical Synthesis of the N(10)–C(17) Fragment of Cyclotheonamides via a Novel Passerini Reaction–Deprotection–Acyl Migration Strategy[1]

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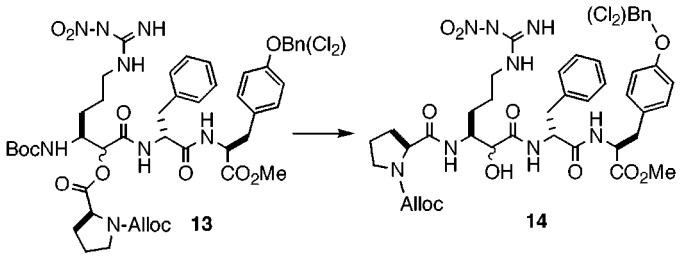
ABSTRACT



A novel variant of the atom-economical Passerini reaction between suitably protected argininal, dipeptide isonitrile, and proline components afforded adduct 13. Orthogonal *N*-deprotection of 13 led, via a smooth *O*- to *N*-acyl migration, to 14, which constitutes the N(10)–C(17) fragment of the cyclotheonamide family of serine protease inhibitors. Each reaction in this three-step protocol proceeds in good yield and under very mild conditions.

Peptidyl and peptidomimetic α-ketoamide scaffolds are useful in small molecule drug discovery programs as transition-state analogue (TSA) protease inhibitors.[2] Such covalent inhibitors generally exhibit potent in vitro enzyme inhibitory activity, with sub-nanomolar equilibrium inhibitor constants (K_i) being typical of representative members.[3] Accordingly, they are finding increasing applications as potential therapeutics for important disease indications.[4−7]

The cyclotheonamides CtA−CtE3 (**1a**−**g,** Figure 1) constitute a growing family of 19-membered macrocyclic pentapeptide derivatives isolated from the marine sponge *Theonella swinhoei*.[8] All contain the unusual vinylogous L-tyrosine, L-α-ketohomoarginine, and *β*-linked L-diaminopropanoic acid moieties in addition to more common L-proline and hydrophobic D-phenylalanine, D-leucine, or

(1) Dedicated to Ruth F. Nutt, respected and admired mentor, on the occasion of her 60th birthday.

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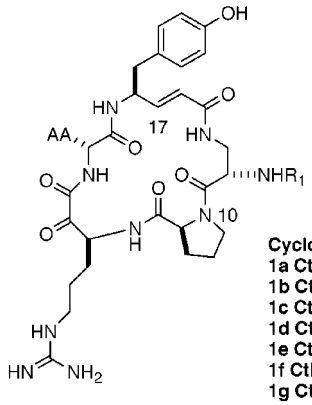

Cyclotheonamides (Ct):
1a CtA, AA = *d*-Phe, R_1 = CHO
1b CtB, AA = *d*-Phe, R_1 = Ac
1c CtC, = **1b** except dehydro-Tyr
1d CtD, AA = *d*-Leu, R_1 = Ac
1e CtE, AA = *d*-Ile, R_1 = PhAc-Alanyl
1f CtE2, AA = *d*-Ile, R_1 = Bz-Alanyl
1g CtE3, AA = *d*-Ile, R_1 = 3-Me-Butanoyl

Figure 1. Representative examples of biologically active α-ketoamides: members of the cyclotheonamide (Ct) class of marine natural products.

D-isoleucine subunits. They are potent, slow-binding inhibitors of several important trypsin-like serine proteases including thrombin (factor IIa), factor Xa, trypsin, plasmin, and tissue plasminogen activator.[9] From this group, CtA (**1a**) and CtE (**1e**) express the most potent thrombin inhibitory activity with K_i values of ≤1 and 2.9 nM, respectively. Such potent biological activity is derived from the key pharmacophore, an electrophilic α-ketoargininamide group, which docks into the S_1 pocket of serine proteases and engages the catalytic triad serine hydroxyl group to form a hemiketal (TSA) intermediate, which effectively but reversibly inhibits the enzyme.

Previous routes[10] to the cyclotheonamides proceeded via construction of individual protected amino acid subunits, peptide couplings, macrocyclization, and late stage oxidation to install the reactive ketoamide residue. In all cases, protected α-hydroxy-β-homoarginine derivatives served as the key L-α-ketohomoarginine precursors. They were prepared by multistep homologation−hydrolysis approaches from arginine or ornithine precursors via cyanohydrin[10c,d] (6−11 steps), orthothioformate,[10a,e] (7−8 steps) or furyllithium addition−oxidation[10b] (5 steps) protocols. Our interest in the design and synthesis of novel classes of α-ketoamides as small molecule inhibitors of serine proteases, including prolyl endopeptidase,[11] thrombin,[12] factor Xa,[3a,13] urokinase,[14] and NS3A hepatitis C protease,[4] led us to investigate multiple-component reaction-based (MCR) approaches to α-hydroxy-β-aminocarboxylic acid and amide derivatives. These versatile, stable intermediates readily undergo oxidation to ketoamide targets.

Utilizing the appropriate *N*-α-protected amino aldehyde precursors **2** (Figure 2), we recently disclosed novel variations of the atom-economical Passerini reaction[15] for the direct production of either α-acyloxy-β-amino amides **3**[2,16] or α-hydroxy-β-amino amide derivatives **4**.[2,16,17] In our hands,

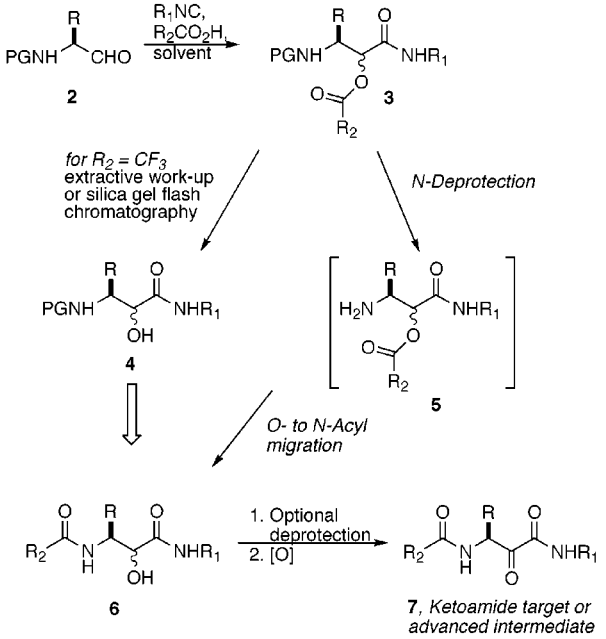

Figure 2. Passerini MCR strategy for the construction of α-hydroxy-β-amino amides **4** and **6** and their potential elaboration into the α-ketoamide subunit **7**. PG denotes *N*-protecting group.

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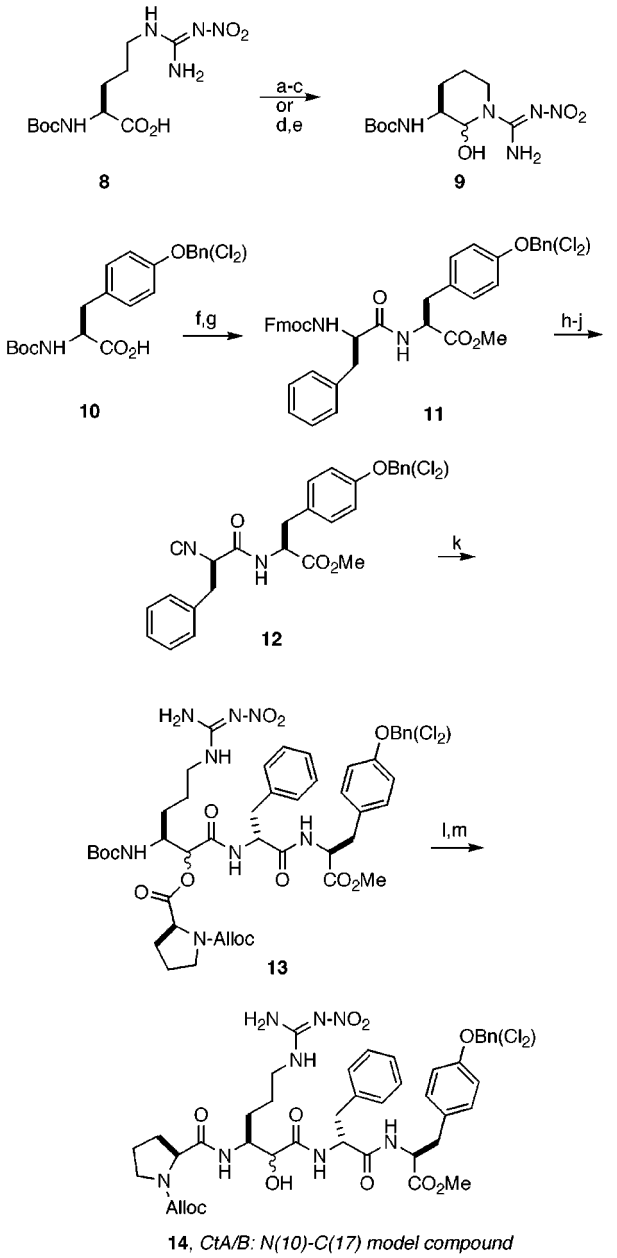
N-deprotection of **3** under mild conditions generated the α-acyloxy-*β*-amino intermediate **5**, which underwent a smooth *O*- to *N*-acyl shift and provided adduct **6** in high yield. Intermediates **4** and **6** routinely serve as useful advanced precursors to α-ketoamide derivatives **7** by oxidation, preferably at a very late synthetic stage. The recent report by Banfi et al.[18] on a related process prompts us to disclose our application of the Passerini reaction−deprotection−acyl migration strategy toward a concise synthesis of the N(10)−C(17) fragment of CtA (**1a**) and CtB (**1b**).

As outlined in Scheme 1,[19] commercially available *N*-α-Boc-*N*^{g}-nitroarginine **8** was converted in two steps to the corresponding Weinreb amide, which was reduced with lithium aluminum hydride to afford *N*-α-Boc-*N*^{g}-nitroargininal **9** in 65% overall yield (100 g scale).[20] An alternate route to **9** proceeded via borane reduction of **8** to the corresponding argininol (MeOH quench, 300 g scale) followed by efficient oxidation in DMSO employing the Parikh−von Doering protocol[21] to deliver **9** in 71−76% overall yield (10−20 g scale).

Concurrent acid-catalyzed esterification and *N*-deprotection of the commercially available tyrosine derivative **10** followed by EDC/HOBt-mediated peptide coupling with Fmoc-D-phenylalanine afforded the corresponding dipeptide **11** in nearly quantitative overall yield. Sequential *N*-deprotection, *N*-formylation, and mild diphosgene-mediated formamide dehydration according to the Ugi protocol[22] afforded the configurationally stable[23] dipeptide isonitrile **12** in satisfactory overall yield.

The key Passerini reaction between argininal **9**, isonitrile **12**, and *N*-Alloc-proline fragments proceeded under very mild, essentially neutral conditions over 2 days and delivered

Scheme 1[a]



[a] Reagents and conditions: (a) *i*-BuOCOCl, NMP, THF, −5 °C; (b) Me(OMe)NH, −5 °C to rt, 88%; (c) $LiAlH_4$, THF, −78 °C; $KHSO_4$, H_2O, −70 to −30 °C, 74%; (d) BH_3, THF, −78 to −20 °C, 12 h; MeOH, −78 °C to rt, 95%; (e) SO_3·Pyr, DMSO, Et_3N, 5 °C to rt, 1 h, 75−80%; (f) MeOH, HCl, 0 °C to rt, 98%; (g) Fmoc-D-Phe-OH, EDC, HOBt, NMM, CH_3CN, rt, quant; (h) Et_2NH, CH_2Cl_2, 0 °C to rt, 99%; (i) HCO_2H, Ac_2O, CH_2Cl_2, rt to reflux, 79%; (j) CCl_3OCOCl, NMM, −40 to 0 °C, CH_2Cl_2, 75%; (k) Alloc-Pro-OH, Boc-Arg(NO_2)-H (**9**), CH_2Cl_2, 0 °C to rt, 2 days, 59%; (l) HCl, MeOH, 0 °C to rt, quant.; (m) Et_3N, pH 9, MeOH, 0 °C to rt, 15 h, 98%.

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(24) **Experimental Details for 13.** A solution of **9** (382.2 mg, 1.26 mmol), *N*-Alloc-proline (298.0 mg, 1.50 mmol), and isonitrile **12** (590.0 mg, 1.15 mmol) in anhydrous dichloromethane (4.6 mL) was stirred at ambient temperature for 16 h. Solvent was slowly removed in vacuo, and the resultant thick residue was stirred for 1 day. Standard extractive workup in ethyl acetate gave a crude product, which was purified by silica gel flash chromatography using dichloromethane/isopropanol 98:2 as eluent to afford 690 mg (59.3% yield) of product **13** as an amorphous, colorless solid. RP-HPLC analysis (Vydac 5 m C18, 5−75% CH_3CN, H_2O with 0.1% TFA): t_R = 21.1 and 21.3 min, 1.6:1 mixture at diastereomeric α-acyloxy center. TLC: (silica gel; dichloromethane/isopropanol 9:1) R_f = 0.6; (ethyl acetate) R_f = 0.4, 0.3; UV, PMA visualization. MS: $[MH]^+$ 1013.9, $[MNa]^+$ 1035.9. ^{1}H NMR (400 MHz, CD_3OD): δ 1.40 + 1.45 (2s, 9H), 1.32−1.47 (obscured m, 2H), 1.49−1.70 (m, 2H), 1.90−2.12 (m, 3H), 2.30 (m, 1H), 2.70−2.89 (complex br m, 1H), 2.95 (m, 1H), 3.02−3.25 (complex m, 4H), 3.39−3.59 (m, 2H), 3.68 + 3.72 (major + minor s, 3H, ratio ∼1.4−1.6:1), 3.88 + 4.01 (2m, 1H), 4.40 (m, 1H), 4.50 (m, 2H), 4.57−4.76 (complex m, 2H), 5.03 + 5.11 (minor + major m, 1H α-C*H*O-acyl methine, ratio 1:2), 5.16−5.37 (m, 2H), 5.25 + 5.27 (2s, 2H), 5.85 + 5.97 (minor + major m, 1H), 6.95 (m, 2H), 7.03−7.14 (m, 4H), 7.16−7.29 (m, 3H), 7.35 (m, 1H), 7.44 (m, 2H).

the complex adduct **13** in a gratifying, albeit unoptimized 59% yield.[24] Analysis of **13** by RP-HPLC or chiral HPLC on Chiracel AD revealed two peaks (ratio ≈ 1.6:1), indicating formation of one diastereomeric pair at the newly created α-acyloxy center. Therefore, the integrity of all four original chiral centers was preserved during the course of the reaction.

Acid-catalyzed *N*-Boc cleavage of **13** afforded the corresponding stable vicinal *O*-acyloxyamine hydrochloride salt quantitatively. Dissolution of this salt in methanol and adjustment of the solution pH to ~9 with triethylamine led, via facile *O*- to *N*-acyl migration, to the desired advanced intermediate **14** in practically quantitative overall yield (cf. **5** to **6** in Figure 2).[25] Model compound **14** constitutes the N(10)−C(17) region of CtA (**1a**) and CtB (**1b**) and may be deemed a suitable precursor for their total synthesis.[26] We envision that application of this three-step sequence to the appropriately protected isonitrile derivative of D-phetyr(vinyl), argininal, and diaminopropionyl-proline components would lead directly to the entire acyclic skeleton of **1a** and **1b**.

Our approach to the advanced cyclotheonamide intermediate **14** via the key Passerini reaction−deprotection−acyl migration strategy is convergent and highly efficient. Proceeding in just eight steps (longest linear sequence) and in 33% overall yield from a commercially available tyrosine derivative, it is complementary to other current multistep routes to similar intermediates.[9a,10]

In conclusion, the utility of this technology for the rapid construction of relatively complex α-ketoamide natural product precursors is highlighted by the concise synthesis of **14**, which serves as a model for the N(10)−C(17) segment of CtA (**1a**) and CtB (**1b**). The key Passerini reaction, deprotection, and *O*- to *N*-acyl migration steps proceed in moderate to high yields and under mild conditions. Other noteworthy features include operational simplicity and high atom-economy. Interest in efficient synthetic approaches to linear[3,17] and cyclic α-ketoamide protease inhibitors[2,11] leads us to speculate on alternate intramolecular variants that might directly provide advanced macrocyclic intermediates, thus further expanding the utility of this atom-economical process.[27] Numerous applications of this new technology to the synthesis of α-ketoamide natural products and protease inhibitors are envisioned and will form the basis of forthcoming publications from our laboratories.

Acknowledgment. Stimulating discussions with R. F. Nutt, T. K. Brunck, O. E. Levy, S. Y. Tamura, and K. E. Pryor are gratefully acknowledged.

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(25) **Experimental Details for 14.** To a solution of **13** (675 mg, 0.666 mmol) in anhydrous methanol (5 mL) at 0 °C was added freshly prepared 5 N HCl in anhydrous methanol (10 mL, 50 mmol). After 40 min at 0 °C the solvent was removed in vacuo. The residue was dissolved in fresh 10 mL portions of anhydrous acetonitrile, re-evaporated (repeated twice), and then evaporated once from a 10 mL portion of dichloromethane. High vacuum pumping for several hours afforded 645 mg (102% of theory, ~quantitative yield) of the corresponding *O*-acyloxyamine hydrochloride as a pale tan foam, which was used in the following reaction. To a solution of amine salt (625 mg, 0.658 mmol) in anhydrous methanol (3.3 mL) was added Et_3N (134.6 mg, 1.33 mmol, 185 mL). The solution was stirred at ambient temperature for 2 h, during which time a thick yellow slurry formed. The solvent was removed, and the residue was dissolved in 200 mL of ethyl acetate, extracted successively with 20 mL portions of 1 N HCl, saturated $NaHCO_3$ solution (2×), water, and brine, and then dried over anhydrous $MgSO_4$. Filtration, solvent removal, and filtration through a short silica gel column using dichloromethane/2-propanol 9:1 as eluent gave 588 mg (97.9% yield) of product **14** as a nearly colorless, amorphous solid. RP-HPLC analysis (Vydac 5 m C18, 5−75% CH_3CN, H_2O with 0.1% TFA): t_R = 19.1 and 19.5 min, 1.6:1 ratio at diastereomeric α-hydroxy center. TLC: (silica gel; dichloromethane/2-propanol 9:1) R_f = 0.5; (ethyl acetate) R_f = 0.2, 0.25; UV, PMA visualization. MS: $[MH]^+$ 914.8, $[MNa]^+$ 936.8. ^1H NMR (400 MHz, CD_3OD): δ 1.30−1.45 (br m, 1H), 1.48−1.75 (br m, 3H), 1.94 (m, 2H), 2.07 (m, 1H), 2.32 (br m, 1H), 2.70−3.04 (complex m, 3H), 3.07−3.28 (complex m, 3H), 3.48−3.62 (m, 2H), 3.67 (m, 1H), 3.70 + 3.72 (2s, 3H), 4.05−4.13 (m, 1H), 4.37−4.57 (m, 2H), 4.60−4.78 (complex m, 3H), 5.18−5.40 (complex m, 2H), 5.23+ 5.25 (2s, 2H), 5.86 + 5.96 (minor + major m, 1H), 6.96 (m, 2H), 7.05−7.30 (m, 7H), 7.35 (m, 1H), 7.43 (m, 2H).

(26) Elaboration of **14** to the corresponding protected vinylogous tyrosine (v-Tyr) intermediate could proceed via the following sequence of reactions: (a) TBDMSCl, imidazole, DMF, room temperature; (b) $LiBH_4$, THF, EtOH, 0 °C to room temperature; (c) SO_3·Pyr, DMSO, Et_3N, 5 °C to room temperature; (d) Ph_3PCHCO_2t-Bu, CH_2Cl_2, 0 °C to room temperature. Alternatively, construction of the corresponding v-Tyr analogue of **12** followed by application of the Passerini reaction, deprotection, and *O*- to *N*-acyl migration sequence may also be a viable approach to this intermediate.

(27) For application of MCR to synthesis of macrocyclic peptides and natural products, see: Doemling, A. *Comb. Chem. High Throughput Screen.* **1998**, *1*, 1 and references therein.