J|A|C|S COMMUNICATIONS

Published on Web 04/17/2009

Enantiospecific Total Syntheses of Kapakahines B and F

Timothy Newhouse, Chad A. Lewis, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received February 28, 2009; E-mail: pbaran@scripps.edu

The kapakahines are a family of cyclic peptides isolated from the marine sponge *Cribrochalina olemda* by Scheuer and co-workers in 1995. The first member of the family to be isolated, kapakahine B (**1**, Figure 1), has shown modest anti-leukemia activity ($IC_{50} = 5.4\ \mu M$, P388 murine leukemia cells), while the structurally related kapakahine F (**2**), lacking a single phenylalanine residue, is inactive.[1] Isolation of limited quantities of these natural products (0.3 and 0.8 mg of **1** and **2** isolated from 840 g and 4.0 kg of sponge material, respectively) has prevented a complete understanding of their bioactivity and mode of action. Structurally, they feature a heptacyclic ring system containing a *twisted*[2] 16-membered macrocycle, a hindered quaternary center linking two tryptophan residues, and a strained α-carboline.[3] Herein we report enantiospecific total syntheses of kapakahines B (**1**) and F (**2**) wherein all but the penultimate steps are executed on a gram scale. This level of practicality is enabled by a diastereoselective, oxidative N−C bond formation and a late-stage shift of structural topology.

Ring D of the strained A−D tetracycle was identified for initial disconnection due to its anticipated sensitivity.[4] The essence of our retrosynthetic plan hinged on a speculation that the resulting α-carboline portion (rings A−C), expressed as the hypothetical isomer **B**, could be constructed simultaneously with the twisted E-ring *via* a dynamic equilibration of the more easily accessible pyrroloindoline architecture in isomer **A**. A Curtin−Hammett scenario was envisioned, wherein, regardless of the steady-state distribution of constitutional isomers **A** and **B**,[5] the latter would react faster than the former under irreversible amide-bond-forming conditions. This hypothesis could be tested in short order by constructing isomer **A** via direct indole−aniline coupling.[6] The carbon framework of **1** and **2** could therefore be derived from dipeptide **3**, *o*-iodoaniline, and tripeptide **4**.

The preparation of tripeptide **4**, as depicted in Scheme 1, utilizes Knochel's method to convert serine-derived **5** to the silyl alkyne **6**.[7] Tripeptide **4** was prepared on decagram scale by hydrolysis of **6**, followed by coupling with H_2N-Ala-Leu-OBn.[8] The total synthesis of **1** and **2** was completed as shown in Scheme 2. Thus, protected dipeptide **3** is reacted with *o*-iodoaniline and *N*-iodosuccinimide in the absence of an acid-scavenger to afford the indole−aniline coupled product **7** in 65% yield as a single diastereomer. Neither racemization nor the undesired *endo* diastereomer was detected by the limits of crude ^1H NMR.[9] Next, Larock annulation[10] with tripeptide **4** provided the pentameric peptide **8** in 49% yield after recrystallization.

With all of the necessary amino acids incorporated, attention turned to the pivotal isomerization of the pyrroloindoline contained within **8** to the desired α-carboline expressed in the kapakahines (i.e., **11**). Exposure of the C- and N-termini occurred smoothly under reductive conditions (Pd/C, H_2), and the crude amino acid (**9**/**10**) was subjected to EDC and HOAt under base-free conditions to afford macrocycle **11** in 64% yield, along with 6% of the undesired, but separable, constitutionally isomeric macrocycle **12**.

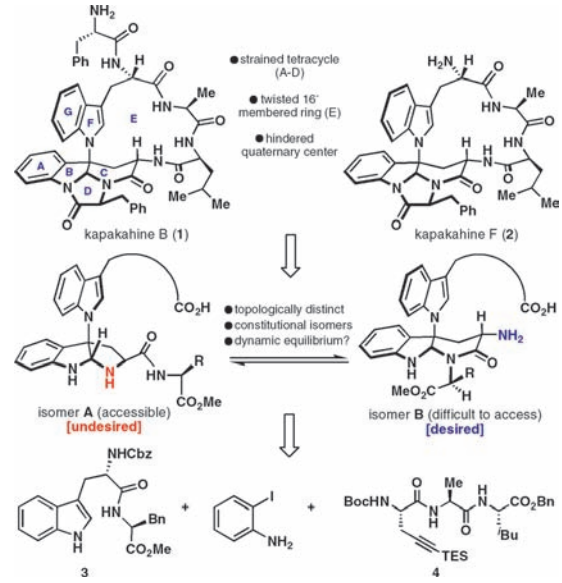
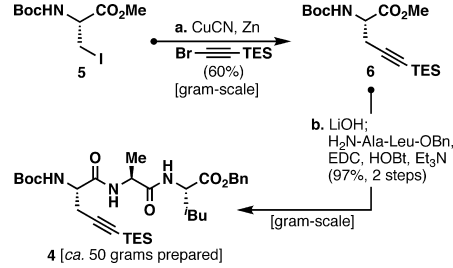


Figure 1. Retrosynthetic analysis of kapakahines B (**1**) and F (**2**).

Scheme 1. Synthesis of Tripeptide **4**[a]

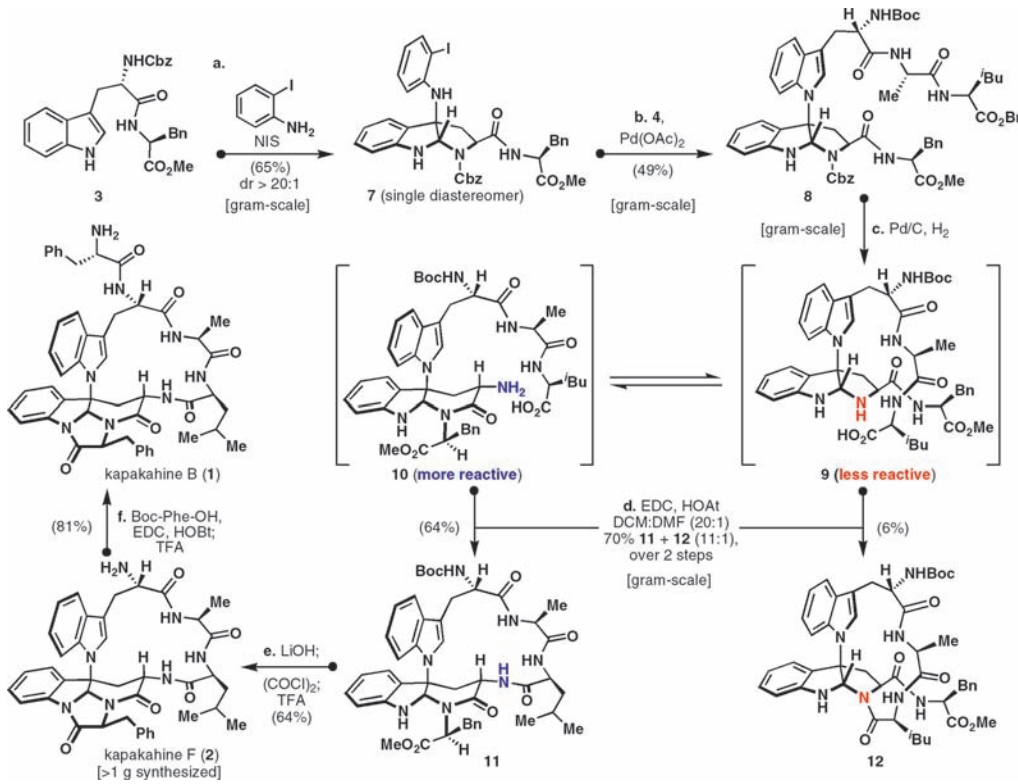


[a] Reagents and conditions: (a) CuCN (0.9 equiv), LiCl (1.8 equiv), Zn (3.6 equiv), TMSCl (0.1 equiv), $Br(CH_2)_2Br$ (0.2 equiv), DMF, −20 → 23 °C, 11 h, 60%; (b) LiOH (1.2 equiv), 1:1 THF/H_2O, 0 °C, 0.5 h; H_2N-Ala-Leu-OBn (1.1 equiv), EDC (1.2 equiv), HOBt (1.4 equiv), THF, 0 → 23 °C, 10 h, 97% (two steps).

In accord with the planning stages of this work (Figure 1), the selectivity obtained in favor of α-carboline **11** can be ascribed to the relative reactivity of the two presumed equilibrating amines **9** (isomer **A**) and **10** (isomer **B**). The greater reactivity of the primary amine **10**, relative to that of the less reactive secondary amine **9**, leads to selective macrocyclization to the desired product **11**. Several experiments support the existence of such an equilibrium. For instance, the cyclic peptides **11** and **12** are unreactive when resubjected to the reaction conditions. Alternative reaction conditions (e.g., DMF as solvent, DIPEA as base, etc.) led to near-exclusive formation of the undesired product **12**. The difference in the relative rates of reaction between **9** and **10** likely determines the ratio of products, **11** and **12**, rather than the position of equilibrium between the two isomers.[5] Alternatively, it is conceivable that the open-chain imine tautomer of **9** and **10** is the reactive

10.1021/ja901573x CCC: $40.75

Scheme 2. Gram-Scale, Enantiospecific Total Syntheses of Kapakahines B (**1**) and F (**2**)[a]



[a] Reagents and conditions: (a) *o*-iodoaniline (1.2 equiv), *N*-iodosuccinimide (1.6 equiv), MeCN, −45 → −35 °C, 1 h, 65%; (b) $Pd(OAc)_2$ (0.20 equiv), NaOAc (7.0 equiv), LiCl (1.0 equiv), **4** (2.2 equiv), DMF, 100 °C, 24 h, 49%; (c) 10% Pd/C (0.20 equiv), H_2, MeOH, 1 h; (d) EDC (3.0 equiv), HOAt (6.0 equiv), DCM/DMF (20:1), 12 h, 70% (11:1); (e) LiOH, THF/H_2O/MeOH, 1 h; $(COCl)_2$ (4.0 equiv), Et_3N (1.0 equiv), DCM, 1 h; TFA/DCM, 1:10, 1 h, 64% (three steps); (f) Boc-Phe-OH (1.2 equiv), EDC (2.0 equiv), HOBt (1.8 equiv), Et_3N (3.0 equiv), DCM 1 h; TFA/DCM, 1:10, 1 h, 81% (two steps).

intermediate that, after ring closure, affords a mixture of the macrocyclic isomers.

Subsequent hydrolysis of the methyl ester **11** and imidizolone formation via the acid chloride, followed by Boc removal, afforded kapakahine F (**2**) in significant quantities (>1 g). Although synthetic and natural **2** were identical by HPLC co-injection, the limited data available for **2** complicated structural proof (^{13}C NMR data not reported for **2** and several non-identical ^1H NMR spectra reported with an unknown salt form; see Supporting Information for details). This situation was rectified by the conversion of **2** to **1**. Thus, coupling of **2** to Boc-Phe-OH and subsequent Boc deprotection afforded **1** in 81% yield, which was identical to natural **1** (HPLC co-injection, ^{13}C and ^1H NMR).

Concise, enantiospecific syntheses of kapakahines B (**1**) and F (**2**) have been completed in 12−14 steps (four chromatography events and one distillation) from acetylene and five naturally occurring amino acids. The overall yields of **1** and **2** from **3** are 10 and 12%, respectively, and nearly every step has been conducted on a gram scale. Only the final two stages have been performed on a smaller scale (**11** → **2**, 100 mg and **2** → **1**, *ca.* 50 mg) due to the sensitivity of functionality that requires immediate processing and our desire to create a series of analogues from this family. Two powerfully simplifying transformations underscore the logic of this approach: (1) stereocontrolled formation of a challenging quaternary center by direct indole−aniline coupling (**3** → **7**) and (2) a late-stage shift of topology by dynamic equilibration (**8** → **11** via **10**). The latter of these transformations illustrates a design principle that could facilitate the synthesis of twisted macrocyclic frameworks: *in situ* kinetic trapping in a dynamic equilibrium. A program to properly evaluate the biological potential of the kapakahine family has been initiated, and those details will be published in due course.

Acknowledgment. We are grateful to Dr. Kyle Eastman for early studies and to Dr. Yoichi Nakao for providing HPLC samples of **1** and **2**. Dr. D. H. Huang and Dr. L. Pasternack are acknowledged for NMR spectroscopic assistance. Financial support for this work was provided by an unrestricted grant from Bristol-Myers Squibb and a graduate fellowship (to T.N.).

Supporting Information Available: Detailed experimental procedures, all spectra, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Nakao, Y.; Yeung, B. K. S.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1995**, *117*, 8271–8272. (b) Yeung, B. K. S.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168–7173. (c) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387–1390.
(2) The kapakahines' name is derived from the Hawaiian "kapakahi", meaning "twisted".
(3) For studies toward the kapakahines and related structures, see: (a) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905–2908. (b) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027–5030. (c) Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895.
(4) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913–4915.
(5) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006.
(6) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887.
(7) (a) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799–4802. (b) IJsselstijn, M.; Kaiser, J.; van Delft, F. L.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Amino Acids* **2003**, *24*, 263–266. (c) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599–4602. (d) Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734–4741.
(8) Boggs, N. T.; Bruton, H. D.; Craig, D. H.; Helpern, J. A.; Marsh, H. C.; Pegram, M. D.; Vandenbergh, D. J.; Koehler, K. A.; Hiskey, R. G. *J. Org. Chem.* **1982**, *47*, 1812–1816.
(9) The stereochemistry of all the kapakahines corresponds to the stereochemistry of the *exo* diastereomer **7**.
(10) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690.

JA901573X