

Preparation of a Psammaplysene-Based Library

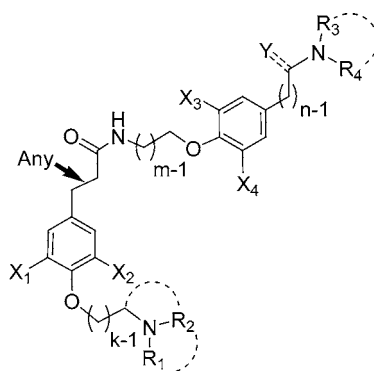
Savvas N. Georgiades and Jon Clardy*

Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115

jon_clardy@hms.harvard.edu

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ABSTRACT



A 28-member focused library, based on the pseudosymmetric template of the marine alkaloids psammaplysenes, was prepared from combinations of components that were, in turn, derived from 4-iodophenol.

Synthetic libraries based on natural product templates have emerged as important sources of structurally diverse small-molecule probes of biological function.¹ In this spirit, we have extended our work on psammaplysenes A and B (Figure 1a), two closely related pseudosymmetric bromotyrosine-derived alkaloids, originally isolated from the marine sponge *Psammaplysilla* sp.² They were initially identified in a high-throughput screen as inhibitors of FOXO1a nuclear export in cells with PTEN loss-of-function mutations.³ By interacting with a still unknown target in the PI3K/PTEN/Akt signaling pathway, they enhance the nuclear localization of the FOXO1a transcriptional regulator and, in effect, counteract inappropriate PI3K-generated stimulatory signals that arise due to the deficiency of tumor suppressor phosphatase PTEN. Because of the possible implications of modulating

this pathway and the limited supply of material from sponge collections, we recently developed an efficient synthesis of these two compounds⁴ in a way that could readily accommodate the synthesis of analogues and probes, especially a focused library that would help define structure–activity relationships.

As was the case for psammaplysenes A and B (Figure 1a), we set off to prepare a pool of acid and amine building blocks that could be combined to provide a number of analogues (Figure 1b). Variations of the original synthetic pathway that led from a common starting material, 4-iodophenol, to the two nonidentical halves of these pseudosymmetric molecules were used to assemble a 28-member collection of psammaplysene analogues, described herein. The compounds we elected to prepare bear a single modification compared to the most potent of the original structures, psammaplysene A (IC₅₀ = 5 μM).

The first set of building blocks comprises acids with alternative halogen ring substituents. A variety of aromatic

(1) Breinbauer, R.; Vetter, I. R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2879.

(2) Schroeder, F. C.; Kau, T. R.; Silver, P. A.; Clardy, J. *J. Nat. Prod.* **2005**, *68*, 574.

(3) Kau, T. R.; Schroeder, F.; Ramaswamy, S.; Wojciechowski, C. L.; Zhao, J. J.; Roberts, T. M.; Clardy, J.; Sellers, W. R.; Silver, P. A. *Cancer Cell* **2003**, *4*, 463.

(4) Georgiades, S. N.; Clardy, J. *Org. Lett.* **2005**, *7*, 4091.

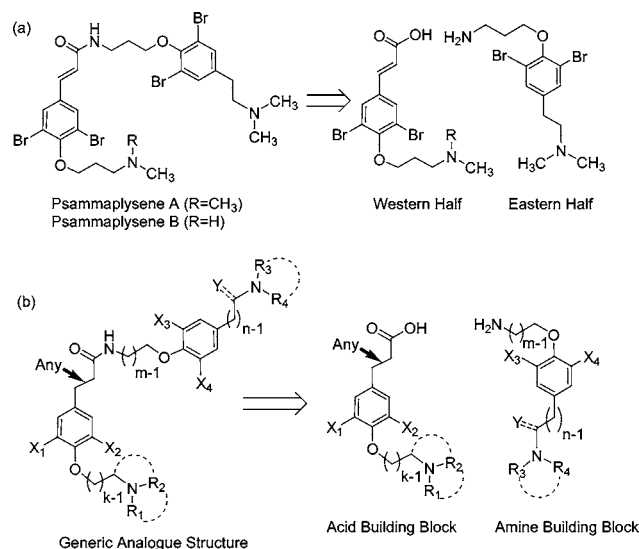
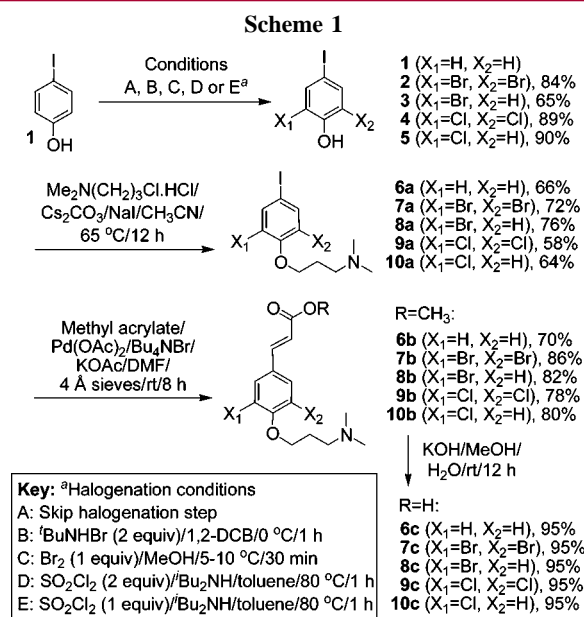


Figure 1. Main retrosynthetic disconnection for the original psammaplysenes and each library member.

electrophilic substitution conditions on 4-iodophenol (**1**) led to compounds **2–5** (Scheme 1). Dibrominated phenol **2**, a



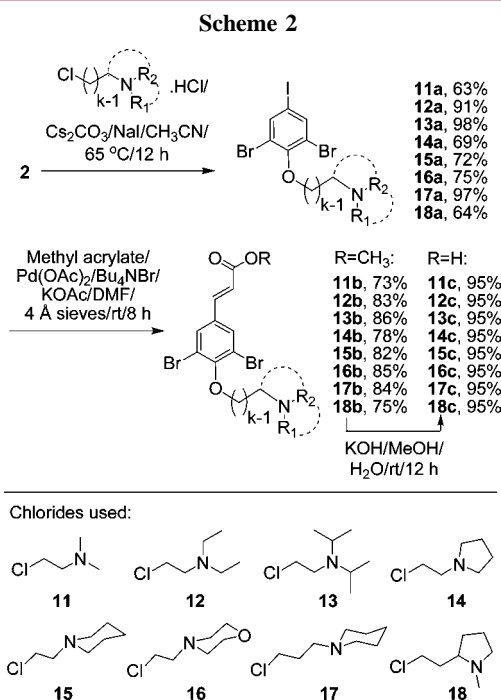
precursor to the natural products, was prepared using 2 equiv of *N*-bromo-*tert*-butylamine in 1,2-dichlorobenzene.^{5,6} Monobrominated phenol **3** was obtained using 1 equiv of Br₂ in MeOH. The dichlorinated and monochlorinated compounds, **4** and **5**, were formed using 1 and 2 equiv of SO₂Cl₂ in

(5) For the preparation of ^tBuNHBr, see: Boozer, C. E.; Moncrief, J. W. *J. Org. Chem.* **1962**, *27*, 623.

(6) For ortho-directed bromination of unsubstituted phenol with ^tBuNHBr, see: Jpn. Kokai Tokyo Koho, 09291053, November 11, 1997, Heisei.

toluene, respectively, in the presence of catalytic di-*iso*-butylamine.⁷ The unsubstituted counterpart, 4-iodophenol, was used directly in the next step. O-Alkylation of **1–5** with 1-chloro-3-(dimethylamino)-propane hydrochloride in CH₃CN, in the presence of Cs₂CO₃ and catalytic NaI, led to intermediate iodides **6a–10a**, respectively. These were subsequently converted to the corresponding methyl esters **6b–10b** via a Heck reaction with methyl acrylate in DMF, by means of a Pd(OAc)₂/^tBu₄NBr/KOAc system.⁸ The esters were hydrolyzed with KOH in MeOH/H₂O to give zwitterionic acids **6c–10c**.⁹

Another set of acid building blocks was chosen to have the same ring substitution as the natural product but variable chain lengths and different tertiary amine heads (Scheme 2).



The 4-fold difference in IC₅₀ values between psammaplysenes A and B³ indicates some sensitivity at this site. Precursor **2** was alkylated with chlorides of chain lengths *k* = 2–3 and different alkyl substituents on the nitrogen, including rings, to yield compounds **11a–18a**. In most cases where bulky substituents increased the steric requirement, a shorter chain was used to offset this effect. A few large substituents were used together with a longer chain to give a sense of the steric limits. Heck reaction, followed by ester hydrolysis, gave acids **11c–18c**.

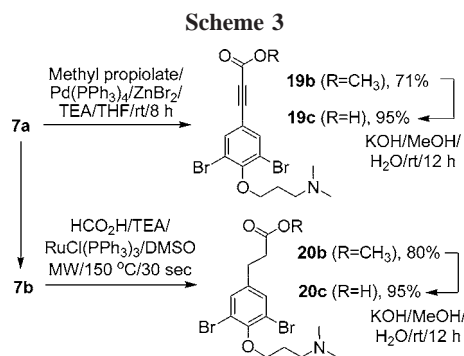
The trans double bond in psammaplysenes constitutes a distinguishing feature compared to other alkaloids of the

(7) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **1995**, *36*, 3893.

(8) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(9) Significant shifts downfield for the peaks corresponding to the methyl and methylene protons on carbons directly attached to the nitrogens of the acid building blocks suggest that the tertiary amines are protonated. Therefore, the building blocks must be overall zwitterionic, given that they are prepared and isolated in nonacidic conditions. Such pH-dependent shifts are expected for strongly basic systems.

same family. Because its significance is unknown, building blocks were prepared in which it was replaced by a triple or a single bond (Scheme 3). By carrying out a zinc-mediated



Negishi cross-coupling¹⁰ with methyl propiolate and Pd(PPh₃)₄ in TEA on **7a** instead of a Heck reaction with methyl acrylate, we obtained triple-bond-containing ester **19b**, which by nature is more linear than its analogue, **7b**. To obtain a compound with higher flexibility, **7b** was reduced under microwave-assisted conditions with formic acid/TEA/Wilkinson's catalyst in DMSO.¹¹ The fully saturated counterpart, **20b**, was obtained in good yield after 30 s at 150 °C. Both **19b** and **20b** gave the corresponding acids after ester hydrolysis.

The pseudosymmetric psammaphysene skeleton allows the use of the same key precursors, **1–5**, as the starting point for forming primary amine building blocks. Amines bearing various halogen substitution patterns were first prepared (Scheme 4). O-Alkylation of **1–5** with *N*-Boc-3-bromopropylamine afforded intermediates **21a–25a**. By treating only **2** with *N*-Boc-2-bromoethylamine, we prepared one single building block with a shorter central linker (**26a**, *m* = 2). Iodides **21a–26a** were submitted to standard Sonogashira¹² cross-coupling with alkynyl–trimethylsilane to form TMS-protected alkynes **21b–26b** in excellent yields. A highly efficient silver-catalyzed desilylative bromination with NBS in acetone¹³ converted the latter to bromoacetylides **21c–26c**. Aminolysis with dimethylamine in THF/CH₃CN, followed by reduction with NaBH₄ in MeOH, led to amines **21d–26d**. In the aminolysis reaction, the dihalogenated precursors appeared considerably more reactive than their monohalogenated and nonhalogenated counterparts,¹⁴ suggesting the reaction is sensitive to stereoelectronic factors.

(10) Anastasia, L.; Negishi, E.-I. *Org. Lett.* **2001**, *3*, 3111.

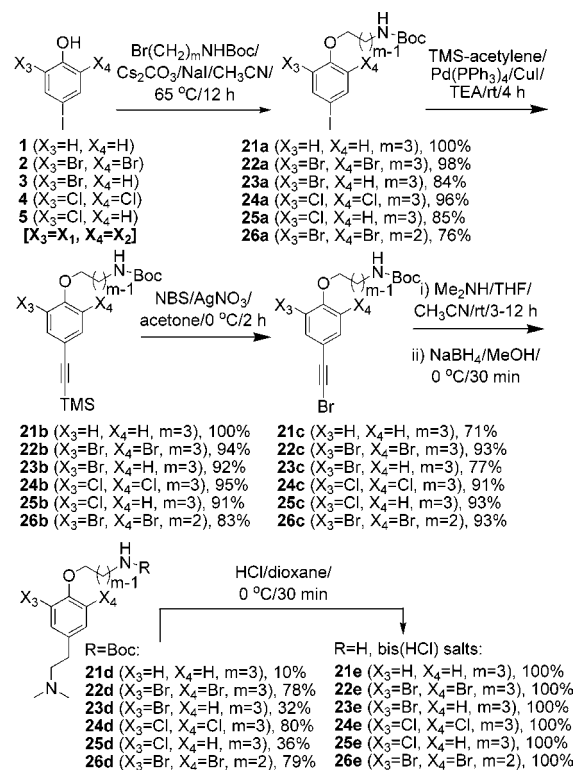
(11) Our method was a modification of the one described in: Desai, B.; Danks, T. N. *Tetrahedron Lett.* **2001**, *42*, 5963.

(12) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(13) (a) Bowles, D. M.; Anthony, J. E. *Org. Lett.* **2000**, *2*, 85. (b) Tobe, Y.; Nakagawa, N.; Kishi, J. Y.; Sonoda, M.; Naemura, K.; Wakabayashi, T.; Shida, T.; Achiba, Y. *Tetrahedron* **2001**, *57*, 3629. (c) Tobe, Y.; Utsumi, N.; Nagano, A.; Sonoda, M.; Naemura, K. *Tetrahedron* **2001**, *57*, 8075.

(14) Our stock of **21d** was supplemented by an independent pathway, alkylation of commercially available hordenine sulfate with *N*-Boc-3-bromopropylamine (50% yield), to compensate for the low yield obtained in the reductive aminolysis.

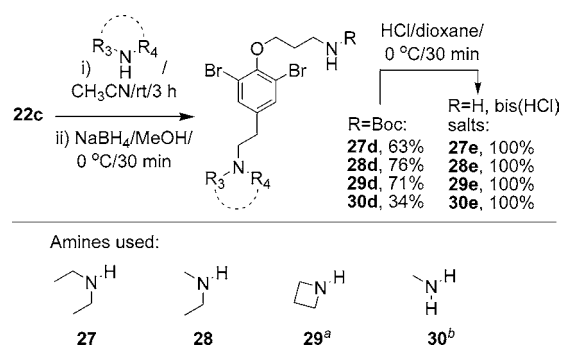
Scheme 4



Primary amines **21e–26e** were obtained as their dihydrochloride salts via Boc deprotection with HCl in dioxane.¹⁵

The net reductive amination of aryl bromoacetylides to saturated phenethylamine systems provided the means for preparing amine building blocks with various amine heads, other than dimethyl (Scheme 5). Four examples were tried.

Scheme 5

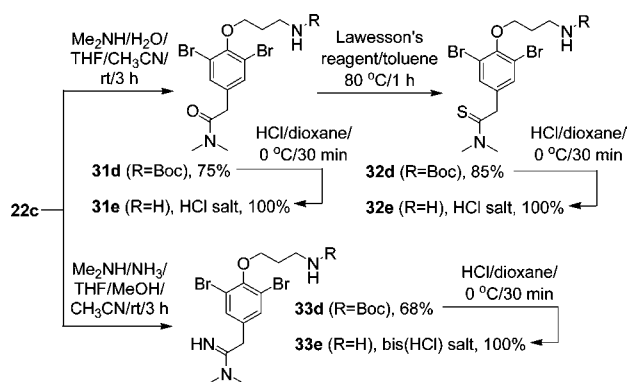


Key: ^aThis amine was used as the HCl salt, and an equimolar amount of TEA was added to the reaction mixture. ^bA mixed THF/CH₃CN solvent was used in this case.

Interestingly, the reaction proceeds not only for acyclic secondary amines but also for strained cyclic secondary amines and for primary amines, even though in the last case,

(15) Han, G.; Tamaki, M.; Hruby, V. J. *J. Pept. Res.* **2001**, *58*, 338.

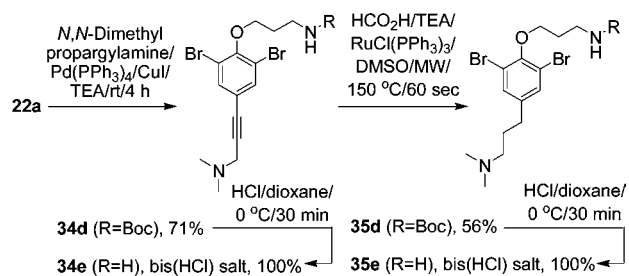
Scheme 6



not surprisingly, the yield is considerably lower. In all cases, LC-MS analysis suggested that the intermediates were ynamines or reversible bisamino adducts, in accord with our previous observations.⁴

The scope of the amine addition reaction was further studied to include examples where the amine was added in mixtures with other nucleophiles (Scheme 6). If dimethylamine was added to **22c** as a 1:1 mixture with H_2O , an adduct was formed that tautomerized to amide **31d**, in accord with a previous report.¹⁶ This amide was successfully converted to the corresponding thioamide (**32d**) with Lawesson's reagent in toluene.¹⁷ Upon addition of a 1:1 dimethylamine/ NH_3 mixture to **22c**, mixed aryl acetimidamide **33d** was obtained. Compounds **31d**–**33d** were deprotected to the free amines **31e**–**33e** without any observed degradation.

Scheme 7



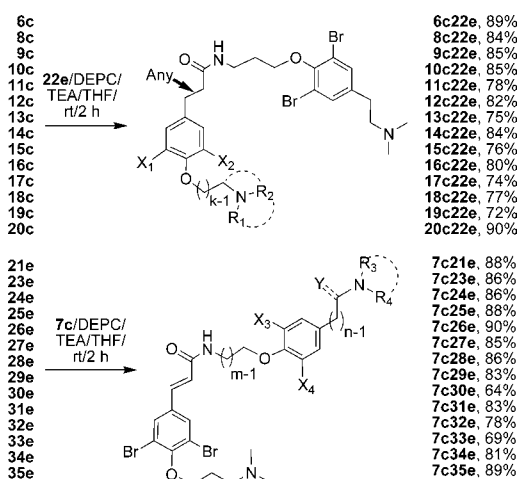
Finally, amine building blocks with a longer terminal linker were prepared (Scheme 7). A Sonogashira coupling

(16) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925.

(17) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061.

of iodide **22a** to propargyl dimethylamine afforded **34d**. This was reduced under microwave-assisted conditions developed above to give fully saturated **35d** ($n = 3$). Both compounds were converted to the free amines after Boc removal.

Amide coupling, using diethyl phosphocyanidate with TEA in THF, generated 28 new compounds, resulting from combining all the different acid building blocks with the primary amine eastern half of psammalydene A, **22e**, or combining all the different amine building blocks with the acid western half of psammalydene A, **7c** (Scheme 8).

Scheme 8^a

Key: ^aYields for final products were determined by LC-MS prior to purification. (Yields for all intermediates as shown in previous schemes are isolated yields.)

In conclusion, a focused library of psammalydene-like molecules has been prepared in solution by combining building blocks that derive via divergent pathways from a common precursor, 4-iodophenol. This library will be screened in diverse biological assays.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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