Published in final edited form as:

Org Biomol Chem. 2017 October 18; 15(40): 8634–8640. doi:10.1039/c7ob02297b.

Synthesis of monoalkylidene diketopiperazines and application to the synthesis of barettin†

Elizabeth W. Kelley, Skylar G. Norman, and Jonathan R. Scheerer

Department of Chemistry, The College of William & Mary, P.O. Box 8795, Williamsburg, Virginia 23187, USA

Abstract

The synthesis of barettin, a selective serotonin receptor inhibitor and potent antibiofouling natural product, is described. The synthesis starts with the diketopiperazine nucleus intact and the side chains are installed using iterative aldol condensations. The route represents a general strategy for synthesis of a wide array of mono-alkylidene diketopiperazine structures, including those derived from non-canonical amino acid residues.

Introduction

Both 2,5-diketopiperazines (DKPs), the cyclic dipeptides of α -amino acids, and α,β -dehydroamino acids are widely distributed in nature, show many promising bioactivities, and have been the focus of several reviews.^{1,2} The DKP and dehydroamino acid structural elements can reside in the same molecule. Often termed alkylidene diketopiperazines, these molecules are a medicinally privileged scaffold found in several natural products. Construction of alkylidene diketopiperazines has often been established by combining traditional peptide coupling methods and classic strategies for dehydroamino acid synthesis.^{2,3} The synthesis of alkylidene DKPs derived from unnatural amino acid precursors can be somewhat more arduous due to construction of the requisite precursors. A selection of monoalkylidene natural products (1–3) are illustrated that have been the focus of major synthetic efforts.^{4,5}

The isolation of the cytotoxic natural product phenylahistin (3) provided the lead identification⁶ that has attracted the attention of several medicinal chemistry programs in academia and the pharmaceutical industry. While the mono-alkylidene natural product 3 has been prepared several times,⁷ medicinal chemistry and the structure-activity relationships were advanced using bis-alkylidene derivatives.⁸ This structural modification not only improved stability and enhanced the tubulin-stabilizing bioactivity but also greatly simplified the synthesis and enabled rapid generation of many unsaturated non-natural amino acid derivatives for evaluation. The construction of bis-alkylidene DKP structures is

†Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of new compounds and synthetic barettin. See DOI: 10.1039/c7ob02297b

Correspondence to: Jonathan R. Scheerer.

Conflicts of interest

There are no conflicts to declare.

now well established and can be easily accomplished through iterative aldol condensations using bisacetoxylglycine anhydride (**5**) and aromatic aldehydes (see Fig. 1, eqn (1)).⁹ This specialized aldol condensation requires very mild reaction conditions owing to the rapid N → O acyl transfer facilitating the elimination of acetate. The simplified analog plinabulin (**4**) was prepared in this manner and has progressed to phase III clinical trials for non-small cell lung cancer.¹⁰

We were inspired by the direct access to bis-alkylidene structures such as **4** and sought to apply a related iterative aldol strategy for the synthesis of mono-alkylidene DKP structures. Beginning with the DKP feature intact and using **5** as the starting material, we hoped to construct the side chains through an aldol condensation, reduction, aldol condensation sequence. Key to the sequence is whether the derived reduction intermediate **6** can effectively engage in a second aldol condensation (Fig. 1, eqn (2)) to form the desired mono-alkylidene product **7**. Literature precedent suggested that substituted diketopiperazines related to **6**, substrates derived from both natural¹¹ and unnatural¹² bis-acetoxy DKP substrates, could undergo aldol condensations; however, the mono-acyl DKP intermediate **6** has several more enolizable protons and effective regioselectivity and reactivity was not apparent from precedent. Although a modest hypothesis, if our synthesis plan could be reduced to practice, we reasoned that it would serve as a direct and general strategy for the synthesis of many mono-alkylidene DKP structures, including derivatives with non-natural amino acid substituents.

We selected baretin (**8**) as a model target in which to evaluate the general synthetic strategy.¹³ Although baretin could presumably be prepared in biomimetic fashion from arginine and tryptophan, we sought to access the structure by eschewing amino acids as starting materials. Baretin (**8**) was isolated¹⁴ in 1986 from the sponge *Giodia barretti* and, more recently, the potent antibiofouling activity of **8** (ED₅₀ 0.9 μM) was revealed.¹⁵ The antifouling activity is reversible and non-lethal; **8** prevents settlement of the cyprid larvae and metamorphosis into the barnacle adult. Baretin is a selective serotonin 5-HT receptor ligand and this attribute is putatively responsible for the observed antifouling activity (Fig. 2).¹⁶

Biofouling, the attachment of aquatic organisms to submerged infrastructure such as ship hulls and water purification facilities, causes significant economic costs.¹⁷ The use of antifouling tributyltin oxides (TBT) over the past 40 years, while effective at mitigating biofouling (LD₅₀ ca. 0.15 μM), has produced negative health and environmental consequences and has led to bioaccumulation of toxic organotin reagents in marine ecosystems.¹⁸ The UN ban on organotin additives in paints took effect in 2008 and, as a result, natural products with anti-biofouling properties such as **8** have received renewed attention.¹⁹

Results and discussion

Our synthesis plan for the construction of baretin was to engage the bisacetoxylglycine anhydride precursor **5** with β-guanidinyl aldehyde **9** (Scheme 1). The resulting aldol condensation product **10** could undergo reduction and a second aldol condensation with the

required 6-bromoindole carboxaldehyde. We envisioned carrying the basic guanidine residue as the bis-boc protected variant, which would both facilitate purification by normal phase conditions and enable acid mediated cleavage as the final operation.

In order to initiate the synthesis, the required β -guanidinyaldehyde **9** was prepared by Dess-Martin oxidation of hydroxy-propyl guanidine **12** (Scheme 2).²⁰ The resulting aldehyde **9** proved to be a sensitive substrate and was not stable to chromatography; silica gel promoted elimination of the guanidine residue, perhaps an unsurprising event, given the acidity of bis-boc- β -guanidine ($pK_a < 11$).²¹ Nonetheless, the β -guanidinyaldehyde **9** could be used directly without purification in the subsequent aldol condensation with bisacetoxylglycine anhydride (**5**). Although several bases (including *t*-BuOK, DBU, and NEt₃) have been effective in related condensations using **5** with more simple aldehydes, we found that use of Cs₂CO₃ (1.05 equiv.) in DMF (23 °C, 2 hours) was the mildest and gave optimal results in our case with β -guanidinyaldehyde **9**. The resulting aldol condensation product **10** exhibited similar sensitivity to aldehyde **9**. Prolonged reaction times or exposure to silica promoted degradation of **10**, leading to elimination of bis-boc- β -guanidine residue. In order to avoid decomposition, the unpurified aldol condensation product **10** was submitted directly to catalytic hydrogenation (H₂, Pd/C). The resulting reduction product **13**, obtained in 67% yield over the three steps from aldehyde **9**, was stable and could be manipulated using standard practices. Overall, the success of the specialized aldol condensation between **5** and aldehyde **9** is a testament to the mild reaction conditions, which appear to tolerate delicate β -heteroatom functionality prone to elimination.

With an expeditious and serviceable route to diketopiperazine **13** established, we turned our attention to the second aldol condensation to install the alkylidene feature extending from C6 (Scheme 3). Despite our efforts, we were unable to determine conditions that led to productive bond formation at C6. In our hands, attempted aldol reactions on **13** only provided a small amount of bond formation at C3 of the DKP. We concluded that the greater acidity of the imide proton at C3 in DKP substrates such as **13** does not permit effective enolization and reaction at the less acidic C6 position. In order to activate C6, we converted the lactam in **13** to the derived imide **14** by acylation with di-*t*-butyl dicarbonate. Careful control of reagent stoichiometry, as well as minimizing the amount of base and reaction time, was required to prevent formation of Claisen condensation products (at C6 of **14**). Overall, we determined that the combination of Boc₂O (1.05 equiv.), DMAP (0.05 equiv.) in MeCN for 15 minutes reliably delivered the desired imide **14** in good yield (85%) and high purity (no chromatography required).

The succeeding aldol condensation between *N*-Boc-*N*-acetoxyl DKP **14** and 6-bromoindole aldehyde **15** was first attempted using standard condensation conditions with Cs₂CO₃ (Scheme 3, entry 1). Full consumption of DKP **14** was noted, however, none of the desired aldol condensation product **16** was obtained; rather, exclusive formation of the rearrangement product **17** was observed in 80% yield. Formation of **17** can be rationalized by enolization at C3 and transannular addition to the C5 carbonyl resulting in ring contraction to the observed 5-membered ring product **17**. A related aza-Chan rearrangement²² has been previously observed on bis-Boc DKP substrates using *t*-BuOK.²³

When we employed an organic base (entry 2, DBU, 23 °C), we again observed rearrangement product **17**, but a small amount of the desired aldol condensation product **16** was also identified (ratio 86 : 14). Lowering the reaction temperature to 0 °C (entry 3, DBU) provided a more equitable ratio of **16** and **17** (33 : 67), although the desired aldol condensation was still the minor pathway. Enolization with LiHMDS (1.0 equiv., entry 4) at –78 °C followed by warming to 0 °C led to exclusive formation of the desired aldol condensation; the resulting product mixture contained only **16** and unreacted starting materials (which complicated purification to homogeneity). By increasing the amount of LiHMDS (1.25 equiv., entry 5), full conversion was observed and the desired aldol condensation product **16** was obtained in 72% isolated yield. The success of LiHMDS as a base in this aldol operation is presumably attributable to slower equilibration of the kinetic enolate at C6, which permitted the desired bimolecular process to proceed. The final operation, removal of the carbamate protecting groups with trifluoroacetic acid, occurred without event. In this way, (±)-bare-ttin (**8**) was isolated as the mono trifluoroacetate salt. The spectroscopic properties of our synthetic material **8** agree favorably with previously published data (see ESI[†] for NMR comparison table).^{12b}

Conclusions

In summary, we have prepared the natural product barettin, a sponge isolate with promising antibiofouling properties, in 6 total steps (1 chromatographic separation) and 41% overall yield starting from a protected hydroxypropyl guanidine derivative. In the course of the synthesis, we have validated a simple synthetic strategy toward mono-alkylidene diketopiperazines starting from bisacetoxylglycine anhydride (**5**). We anticipate that the key 4-step sequence comprised of two aldol condensations, a reduction, and lactam *N*-acylation is a general reaction sequence that may find application in the synthesis of a broad range of mono-alkylidene diketopiperazines, a significant class of natural products and related derivatives that possess diverse and promising biological activities.

Experimental section

General experimental considerations

All reactions were carried out under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring unless otherwise indicated. Acetonitrile, THF, toluene, and Et₂O were degassed with argon and purified by passage through a column of molecular sieves and/or a bed of activated alumina. Dichloromethane was distilled from CaH₂ prior to use. All reagents were used as received unless otherwise noted. Flash column chromatography was performed using silica gel (230–400 mesh). Analytical thin layer chromatography was performed on 60 Å glass plates. Visualization was accomplished with UV light, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, or ninhydrin, followed by heating. ¹H NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm) or tetramethylsilane (0.00 ppm). Proton-decoupled ¹³C NMR spectra were recorded on a 400

[†]Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra of new compounds and synthetic barettin. See DOI: 10.1039/c7ob02297b

MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). Mass spectra data analysis was obtained through positive electrospray ionization (ICR-MS w/NaCl). All compounds were judged to be homogeneous (>95% purity) by ¹H and ¹³C NMR spectroscopy unless otherwise noted as mixtures. The asterisk in the names for all new compounds indicates that the compound is present as a racemic mixture.

1,3-Di-*t*-butylcarbamate-2-(3-oxopropyl)guanidine (9)

The following procedure is modified from the literature.¹⁸ A flask was charged with hydroxypropylguanidine **12** (2.00 g, 6.30 mmol), dissolved in CH₂Cl₂ (11.0 mL) and pyridine (3.06 mL, 37.8 mmol) was added. Dess-Martin periodinane (DMP) (3.48 g, 8.19 mmol) was taken up in CH₂Cl₂ (30.0 mL) in a separate flask. The solution of **12** containing pyridine was added to the DMP solution dropwise over 5 min using a syringe. Additional CH₂Cl₂ (6.0 mL) was used to rinse the flask and syringe. After 1 h, 1 M NaOH (75 mL, 75 mmol) and Et₂O (30 mL) were added, and the biphasic reaction mixture was rapidly stirred for 15 min. The reaction mixture was extracted with additional Et₂O (100 mL), washed with H₂O (3 × 50 mL), dried (Na₂SO₄), filtered and concentrated to afford aldehyde **9** (1.86 g, 5.89 mmol, 93% yield) as a gummy yellow residue. The material was used in the subsequent reaction without further purification. A portion of **9** was purified by flash column chromatography for analytical purposes. The spectral data of **9** is in agreement with published data.¹⁸

(*Z*)-1-(3-(4-Acetyl-3,6-dioxopiperazin-2-ylidene)propyl) guanidine-1,3-di-*t*-butylcarbamate (10)

Bisacetoxyglycine anhydride (**5**) (1.17 g, 5.89 mmol) and aldehyde **9** (1.86 g, 5.89 mmol) were dissolved in DMF (14.2 mL). In one lot, Cs₂CO₃ (2.01 g, 6.18 mmol) was added and the reaction flask was repeatedly evacuated (50 torr) and backfilled with N₂. After stirring for 2 h at rt, the reaction mixture was diluted with H₂O (150 mL) and extracted with EtOAc (4 × 40 mL). A small quantity of saturated NaCl solution was added to mitigate emulsions. The combined organic layers were washed with sat. NaCl, dried (Na₂SO₄), filtered and concentrated under reduced pressure to afford **10** (2.73 g, quant recovery) as a colorless solid. The material was used in the subsequent reaction without further purification. A portion of **10** was purified by flash column chromatograph for analytical purposes: TLC in 40% EtOAc/Hex *R*_f: 0.46 (UV/CAM); IR (film) 1724, 1685, 1637, 1319, 1279, 1228, 1052, 1020, 775, 731 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 11.48 (s, 1H), 9.10 (s, 1H), 8.52 (t, *J* = 5.5 Hz, 1H), 6.30 (t, *J* = 8.4 Hz, 1H), 4.44 (s, 2H), 3.46 (dt, *J* = 5.9, 8.6 Hz, 2H), 2.60 (s, 3H), 2.57 (dt, *J* = 8.2, 8.7, 2H), 1.50 (s, 9H), 1.48 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) 8 168.5, 159.6, 159.3, 156.0, 152.4, 149.3, 125.4, 115.1, 79.5, 75.9, 42.1, 35.0, 24.2, 24.1, 23.2, 21.9; exact mass calc'd for C₂₀H₃₁N₅O₇Na [M + Na]⁺ 476.2116, found 476.2115.

1-(3-(4-Acetyl-3,6-dioxopiperazin-2-yl)propyl)guamdme-1,3-di-*t*-butylcarbamate (13)

Alkylidene DKP **10** (1.15 g, 2.54 mmol) was dissolved in EtOAc (10 mL), and 10% Pd/C (0.5 g, 50% water wet paste) was added in one portion. The reaction mixture was sparged with H₂ for 5 min and then left under an H₂ atmosphere. After stirring for 45 min, the reaction mixture was flushed with N₂, filtered and the filter pad was rinsed with several

portions of CH_2Cl_2 . The filtrate was concentrated under reduced pressure to afford **13** (0.83 g, 1.83 mmol, 67% yield over 3 steps from alcohol **12**) as an off-white crystalline solid: mp 203–206 °C; TLC (40% EtOAc in hexanes) R_f : 0.19 (UV/CAM); IR (film) 1730, 1708, 1685, 1650, 1364, 1329, 1271, 1225, 1162, 1134, 1099, 1050, 1024, 980, 740 cm^{-1} ; ^1H NMR (data is complicated by amide/carbamate rotamers, 400 MHz, CDCl_3) 11.41 (s, 1H), 8.45 (t, $J = 5.9$ Hz, 1H), 7.79 (d, $J = 2.4$ Hz, 1H), 4.49 (d, $J = 18$ Hz, 1H), 4.25 (m, 1H), 4.18 (d, $J = 18$ Hz, 1H), 3.51 (ddt, $J = 6.2, 6.7, 7.0$ Hz, 1H), 3.31 (ddt, $J = 6.2, 6.6, 6.8$ Hz, 1H), 2.56 (s, 3H), 1.84 (m, 4H), 1.47 (s, 18H); ^{13}C NMR (400 MHz, CDCl_3) 8 171.9, 169.3, 166.4, 166.3, 163.2, 156.6, 153.3, 83.5, 79.9, 79.8, 55.7, 45.7, 38.9, 38.8, 29.8, 28.2, 28.1, 27.3, 24.9; exact mass calc'd for $\text{C}_{20}\text{H}_{33}\text{N}_5\text{O}_7\text{Na}$ $[\text{M} + \text{Na}]^+$ 478.2272, found 478.2270.

***tert*-Butyl 4-acetyl-2-(3-guanidinopropyl)-3,6-dioxopiperazine-1-carboxylate-1,3-di-*t*-butylcarbamate (**14**)**

DKP **13** (100 mg, 0.220 mmol) was dissolved in MeCN (0.88 mL) at rt. Boc_2O (49 μL , 0.23 mmol) was added as a liquid, followed by addition of DMAP (1.3 mg, 0.011 mmol). After 15 min, the reaction was complete as judged by TLC and the reaction mixture was diluted with EtOAc (10 mL) and washed sequentially with saturated NH_4Cl (5 mL) and saturated NaCl (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford DKP **12** (103 mg, 0.186 mmol, 85% yield) as a white powder that was used without further purification: mp 54–59 °C; TLC (40% EtOAc in hexanes) R_f : 0.53 (UV/CAM); IR (film) 1782, 1714, 1637, 1613, 1574, 1367, 1131, 727 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 11.48 (s, 1H), 8.36 (s, 1H), 5.05 (d, $J = 18.8$ Hz, 1H), 4.82 (t, $J = 7.6$ Hz, 1H), 3.97 (d, $J = 18.4$ Hz, 1H), 3.47 (m, 2H), 2.58 (s, 3H), 1.90 (m, 2H), 1.74 (m, 2H), 1.54 (s, 9H), 1.48 (s, 18H); ^{13}C NMR (400 MHz, CDCl_3) 8 171.3, 167.9, 164.0, 163.7, 156.4, 153.5, 150.1, 85.4, 83.5, 79.5, 60.1, 46.6, 39.9, 30.1, 28.4, 28.2, 28.0, 27.2, 25.8; exact mass calc'd for $\text{C}_{25}\text{H}_{41}\text{N}_5\text{O}_9\text{Na}$ $[\text{M} + \text{Na}]^+$ 578.2796, found 578.2795.

***tert*-Butyl (Z)-3-((1-acetyl-4-(*tert*-butoxycarbonyl)-5-(3-guanidinopropyl)-3,6-dioxopiperazin-2-ylidene)methyl)-6-bromo-1*H*-indole-1-carboxylate-1,3-di-*t*-butylcarbamate (**16**)**

A dry flask was charged with DKP **14** (50 mg, 0.090 mmol), flushed with N_2 for 15 min, dissolved in THF (0.30 mL), and cooled to -78 °C (15 min). In a separate flask, 6-bromoindole carboxaldehyde **15** (32 mg, 0.099 mmol) was dissolved in THF (0.26 mL) under a N_2 atmosphere. To the flask containing the solution of **14** was added 1 M LiHMDS (113 μL , 0.113 mmol). After stirring for 5 min at -78 °C, the solution containing aldehyde **15** was added to the flask dropwise over 5 min *via* syringe. The flask and syringe were rinsed with additional THF (0.23 mL). After stirring for 20 min at -78 °C, the reaction flask was transferred to an ice bath and allowed to warm to rt overnight. Approximately 20 h after beginning the procedure, the reaction mixture was diluted with saturated NH_4Cl (15 mL) and extracted with EtOAc (2×15 mL). The combined organic layers were washed with saturated NaCl (30 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (gradient elution: 0% $\rightarrow$ 10% EtOAc in CHCl_3) to afford desired product **16** (53 mg, 0.065 mmol, 72% yield) as a yellow crystalline solid: TLC (10% EtOAc in CHCl_3) R_f : 0.44 (UV/CAM); IR (film) 1714, 1638, 1616, 1366, 1228, 1146, 1131, 726 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 11.44 (s, 1H),

8.32 (m, 2H), 8.12 (br s, 1H), 7.88 (s, 1H), 7.48 (d, $J = 8.2$ Hz, 1H), 7.41 (dd, $J = 1.8, 8.5$ Hz, 1H), 7.22 (d, $J = 1.2$ Hz, 1H), 4.78 (t, $J = 7.1$ Hz, 1H), 3.44 (dt, $J = 7.1, 13$ Hz, 2H), 1.93 (m, 2H), 1.68 (m, 2H), 1.66 (s, 9H), 1.55 (s, 9H), 1.44 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) 8 166.3, 163.6, 159.1, 156.2, 153.2, 151.0, 148.8, 135.7, 128.3, 126.9, 125.8, 125.5, 120.4, 119.5, 118.7, 113.4, 110.5, 85.7, 84.7, 83.1, 79.3, 58.6, 40.0, 31.9, 28.3, 28.1, 28.0, 25.2; exact mass calc'd for $\text{C}_{37}\text{H}_{51}\text{BrN}_6\text{O}_{10}\text{H} [\text{M} + \text{H}]^+$ 819.2923, found 819.2924.

***tert*-Butyl (1-acetyl-3-(3-1,3-di-*t*-butylcarbamoylguanidinopropyl)-2,4-dioxopyrrolidin-3-yl)carbamate (17)**

A dry flask was charged with DKP 14 (50 mg, 0.090 mmol), bromoindole carboxaldehyde **15** (32 mg, 0.099 mmol), flushed with N_2 for 15 min, and dissolved in DMF (0.5 mL). Cs_2CO_3 (33 mg, 0.1 mmol) was added in one lot and the reaction vessel was repeatedly evacuated (50 torr) and backfilled with N_2 . After stirring for 1 h at rt, the reaction was diluted with sat. aq. NH_4Cl and extracted with EtOAc (3×10 mL). The combined organic layers were washed with saturated NaCl (30 mL), dried over Na_2SO_4 , and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (gradient elution: 10% $\rightarrow$ 40% EtOAc in CHCl_3) to afford desired product **17** (40 mg, 80% yield) as a colorless amorphous solid: TLC (40% EtOAc in hexanes) R_f : 0.55 (UV/CAM); IR (film) 3330, 1743, 1718, 1643, 1616, 1369, 1329, 1285, 1135 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) 11.5 (s, 1H), 8.36 (t, $J = 5.5$ Hz, 1H), 6.03 (s, 1H), 4.38 (d, $J = 19.2$ Hz, 1H), 4.21 (d, $J = 19.2$ Hz, 1H), 3.41 (q, $J = 5.8$ Hz, 2H), 2.63 (s, 3H), 1.82 (m, 2H), 1.68 (m, 2H), 1.499 (s, 9H), 1.496 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (400 MHz, CDCl_3) 8 202.7, 172.2, 170.4, 163.3, 156.3, 155.2, 153.3, 83.4, 81.8, 79.5, 63.9, 53.0, 39.8, 30.1, 28.2, 28.1, 28.0, 25.8, 22.8; exact mass calc'd for $\text{C}_{25}\text{H}_{41}\text{N}_5\text{O}_9\text{Na} [\text{M} + \text{Na}]^+$ 578.2797, found 578.2795.

(*Z*)-1-(3-(5-((6-Bromo-1*H*-indol-3-yl)methylene)-3,6-dioxopiperazin-2-yl)propyl)guanidine (8) (barettin)

The Boc-protected barettin **16** (34 mg, 0.041 mmol) was dissolved in anhydrous CH_2Cl_2 (0.91 mL). The reaction flask was cooled to 0 $^\circ\text{C}$ and sparged with argon prior to introduction of dry TFA (0.91 mL). After stirring for 1 h at 0 $^\circ\text{C}$, the reaction was warmed to rt and was concentrated under reduced pressure. Addition of PhMe and subsequent removal *in vacuo* was performed to aid removal of excess TFA. Following concentration, barettin ($\pm$)-8- HO_2CCF_3 (22 mg, 0.042 mmol, quant) was obtained as a flaky light yellow solid. The spectral data of our synthetic material is in agreement with published literature¹² and only minor differences are noted in the ^1H and ^{13}C NMR data. See SI for spectra as well as an NMR comparison table.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge primary support from the National Institutes of Health (R15 GM107702 to JRS). Support was also provided by the Camille and Henry Dreyfus Foundation (Henry Dreyfus Teacher-Scholar Award to JRS). The NSF MRI provided funds for the acquisition and upgrade of a 400 MHz NMR Spectrometer (award number 1337295).

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Fig. 1.
Mono-alkylidene diketopiperazine natural products 1–3 and plinabulin (4), a bis-alkylidene DKP synthetic analog.

Fig. 2.
Structure of baretin.

Scheme 1.
Barettin and proposed synthesis plan.

Scheme 2.
Aldol condensation with β -guanidinyaldehyde.

Scheme 3.
Completion of the synthesis of barettin.