

## 11-Step Total Synthesis of Araiosamines

Maoqun Tian,<sup>§</sup> Ming Yan,<sup>§</sup> and Phil S. Baran\*

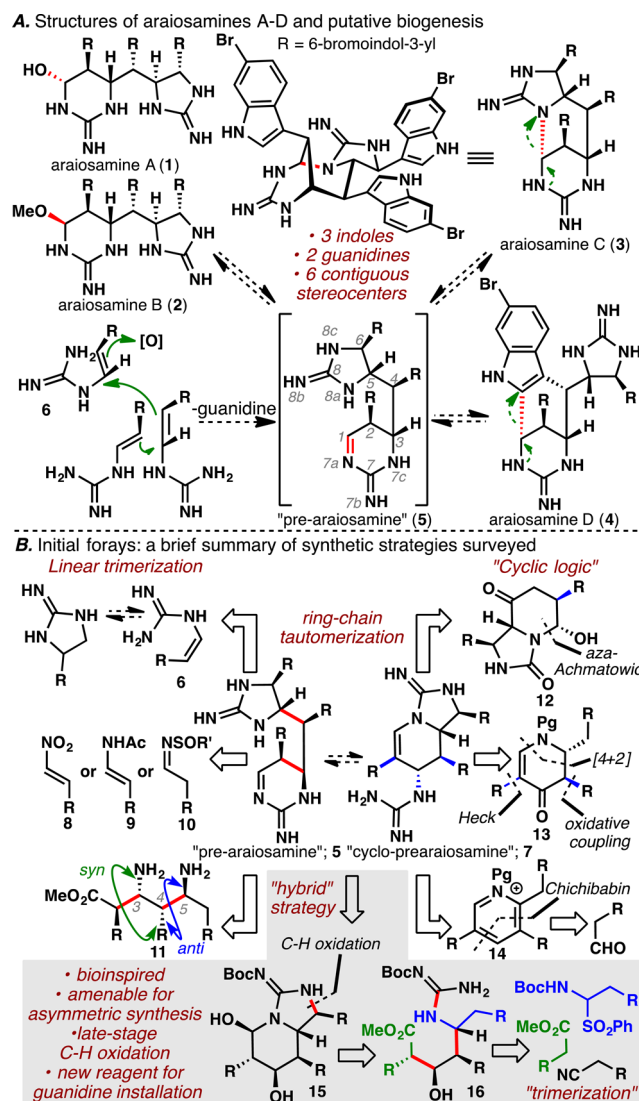
Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

## Supporting Information

**ABSTRACT:** A concise route to a small family of exotic marine alkaloids known as the araiosamines has been developed, and their absolute configuration has been assigned. The dense array of functionality, high polarity, and rich stereochemistry coupled with equilibrating topologies present an unusual challenge for chemical synthesis and an opportunity for innovation. Key steps involve the use of a new reagent for guanidine installation, a remarkably selective C–H functionalization, and a surprisingly simple final step that intersects a presumed biosynthetic intermediate. Synthetic araiosamines were shown to exhibit potency against Gram-positive and -negative bacteria despite a contrary report of no activity.

The marine environment is a constant source of exotic and even mystifying new molecular architectures.<sup>1</sup> In 2011 the Ireland group reported the isolation of araiosamines A–D (1–4, Figure 1A),<sup>2</sup> remarkable structures entangled by two guanidine units and decorated by three bromoindole heterocycles. These highly polar species feature six contiguous stereocenters and, in the case of 3 and 4, unique bicyclo[4.3.1] architectures. It was assumed in the isolation report that 1–4 originate from the same biosynthetic precursor, dubbed “pre-araiosamine” (5),<sup>2</sup> followed by addition of water (1) and methanol (2), and *N*-cyclization (3) or Pictet–Spengler cyclization (4). Past experience in the area of guanidine-containing marine natural product synthesis has taught us that much unique chemistry can be learned by pursuing concise routes to such densely functionalized and practically challenging molecules.<sup>1b,3</sup> This realization coupled with their captivating structure fueled our endeavor toward araiosamines, even though they were reportedly devoid of significant bioactivities.<sup>2</sup> In this Communication, a short pathway to araiosamines loosely modeled after biosynthesis is presented leading to the assignment of their absolute configuration and a new chemoselective reagent for guanidine installation.

Initial forays toward the araiosamines were propelled by the intriguing hypothesis that guanidinylenamine (6) could serve as a precursor to 5 via a dramatic linear trimerization event (Figure 1B).<sup>2,4</sup> Generation of 6 through condensation or ring–chain tautomerization (of the corresponding 2-aminoimidazolidine) was examined, albeit with little success. Attempts to trimerize 8, 9, or 10 were thwarted by their predisposition to uncontrolled polymerization. A stepwise approach through sequential Mannich reactions with ester enolates forged the skeleton expediently. Unfortunately, the desired stereochemical outcome, in particular the C-3–C-5 stereotriad, was untenable on acyclic systems; only epimeric derivatives of 11 were obtained (see SI). With the failure of the linear trimerization strategy, approaches

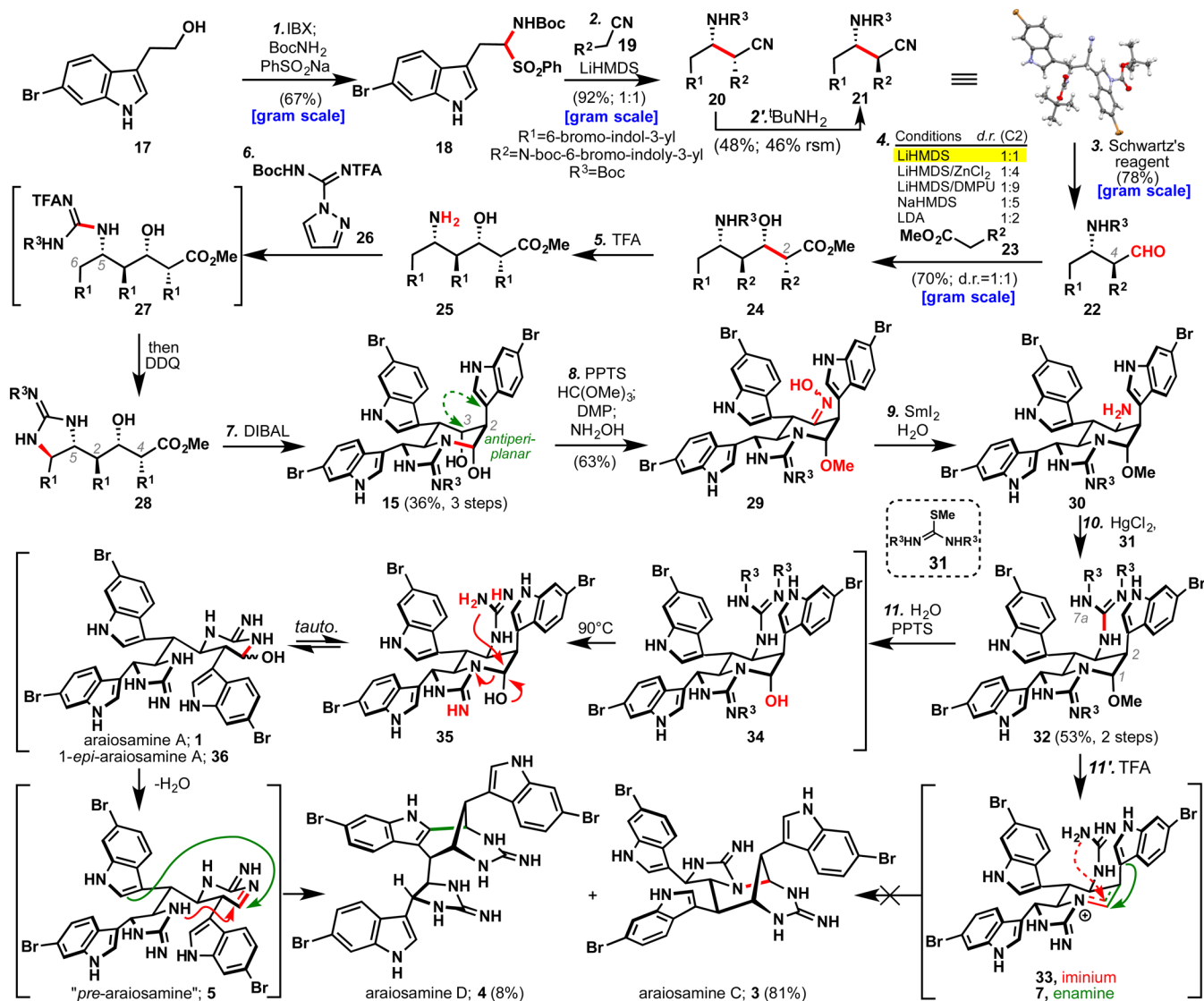


**Figure 1.** (a) Putative biogenesis of araiosamines and (b) evolution of synthetic strategies.

toward a bicyclic tautomer of 5, herein referred to as “cyclo-prearaiosamine” 7, were pursued based on stereocontrolled functionalizations of a pyridine/piperidine core (cyclic logic, Figure 1B). Direct construction of such a tris-indolyl-pyridinium (14) through the Chichibabin pyridine synthesis was foiled by the instability of indolylacetaldehyde derivatives.<sup>5</sup> Although variants

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Scheme 1. Total synthesis of araiosamines<sup>a</sup>

<sup>a</sup>Reagents and conditions: (1) 17 (1 equiv), IBX (1.5 equiv), MeCN, 82 °C, then *tert*-butyl carbamate (1 equiv), sodium benzenesulfinate (1.1 equiv), THF/H<sub>2</sub>O/formic acid, 25 °C (67%, one pot); (2) 19 (3 equiv), LiHMDS (3 equiv), THF, -78 °C (92%, 1:1); (2') MeOH/<sup>t</sup>BuNH<sub>2</sub> (10:1); (3) Schwartz's reagent (2.6 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C (78%); (4) 23 (3 equiv), LiHMDS (4 equiv), THF, -78 °C (70%, d.r. = 1:1); (5) TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:3) 0 to 25 °C; (6) 26 (1 equiv), THF, 25 °C then DDQ (1.5 equiv), MeCN, 25 °C; (7) DIBAL (ca. 3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C (36%, over 3 steps); (8) PPTS (1 equiv), MeOH/HC(OMe)<sub>3</sub> (2:1), 25 °C; DMP (2 equiv), THF, 25 °C then NH<sub>2</sub>OH·HCl (11 equiv), NaOAc (5.5 equiv), EtOH, 50 °C (63%, one pot); (9) SmI<sub>2</sub>, THF/H<sub>2</sub>O (6:1), 25 °C; (10) *N,N'*-Di-Boc-*S*-methylisothiourea (31) (2.4 equiv), HgCl<sub>2</sub> (2.9 equiv), DMF, 25 °C (53%, 2 steps); (11') TFA/CH<sub>2</sub>Cl<sub>2</sub> (1:1), (11) PPTS (4.4 equiv), MeCN/H<sub>2</sub>O (1:2), 25 °C to 90 °C (3, 81%; 4, 8%, one pot); IBX = 2-iodoxybenzoic acid, LiHMDS = lithium bis(trimethylsilyl) amide, Schwartz's reagent = ZrCp<sub>2</sub>(H)Cl, TFA = trifluoroacetic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL = diisobutylaluminum hydride, PPTS = pyridinium *p*-toluenesulfonate, DMP = 1,1,1-triacetoxy-1,1-dihydro-1,2-benzodioxol-3(1*H*)-one

of the cyclic core (e.g., 12 and 13) were furnished stereoselectively via a Diels–Alder reaction or an Achmatowicz rearrangement,<sup>6</sup> such endeavors were plagued by the extraneous functionalities associated with the ring-forming reactions.

The combined lessons from these extensively explored strategies led to a hybrid approach. Hemiaminal 15 was targeted as a viable precursor to 5. It was postulated that 15 could be synthesized concisely via 16 through controlled linear oligomerization<sup>7</sup> of simple building blocks, while its rigid bicyclic structure would confer stereocontrol over the final guanidine installation, thereby combining strategic elements of linear/cyclic approaches.

Scheme 1 depicts the successful synthesis of the araiosamines, commencing with the preparation of carbamoylsulfone<sup>8</sup> 18: 6-bromo-tryptophol (17, commercially available from numerous suppliers or prepared in two steps from 6-bromoindole) was oxidized to the corresponding aldehyde, which was subjected to a three-component coupling with BocNH<sub>2</sub> and PhSO<sub>2</sub>Na to furnish the stable acylimine precursor (18).

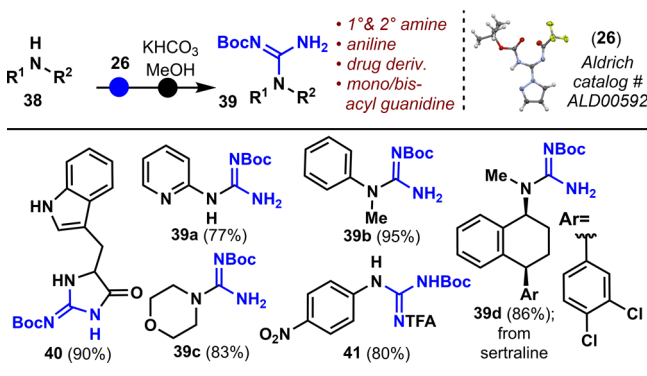
Mannich reaction of lithiated *N*-Boc-6-bromoindolyacetonitrile (19) with the *in situ* derived imine from 17 afforded the desired *anti*-adduct 21 (assigned by X-ray) alongside the *syn*-diastereomer 20, which could be easily epimerized with <sup>t</sup>BuNH<sub>2</sub>.<sup>8</sup> Reduction of the nitrile in 21 was examined next. The use of

conventional reductants such as DIBAL led to low yields (ca. 20%) and substantial C-4 epimerization, but hydrozirconation using Schwartz's reagent delivered ample amounts of the desired aldehyde **22** with minimal stereochemical erosion.<sup>9</sup>

Subsequent aldol reaction between **22** and the lithium enolate of **23** forged the entire carbon skeleton of araiosamines, albeit without stereocontrol as the desired product, **24**, was formed in equal amounts with its C-2 epimer. Extensive attempts to improve the diastereoselectivity met with little success as variations of nucleophiles (see SI for details) and bases or additions of chelating agents and Lewis acids universally favored the undesired diastereomer. Nevertheless, the conciseness of the sequence still allowed us to procure ample amounts of **24**.

Treatment of **24** with TFA unveiled the free amine, setting the stage for the installation of the first guanidine. Several guanidinylation reagents<sup>10</sup> were surveyed: Goodman's reagent<sup>11</sup> failed to react with **25** even at elevated temperatures presumably owing to steric effects, while reaction with **31**<sup>12</sup> only proceeded in the presence of mercuric chloride, forming substantial amounts of side products. Even *N,N*-bis-Boc-guanylpiprazole<sup>13</sup> was completely unreactive with **25**. To address this problem, *N*-Boc,*N'*-trifluoroacetyl-guanylpiprazole (**26**) was synthesized; it was surmised that the TFA group would impart the carboximidamide moiety adequate reactivity to engage hindered or electron deficient amines. Indeed, **26** exhibited considerable reactivity toward an assortment of substrates (Table 1), including electron

Table 1. Scope of the Guanidinylation Reaction



deficient anilines (**39a**, **41**) and drug molecules (**39d**). The bis-acyl guanidine product could be isolated (**40**); alternatively, the TFA group could be removed in the same pot upon treatment with methanolic  $\text{KHCO}_3$  to afford monoacylguanidines.<sup>14</sup> Reaction between **25** and **26** proceeded chemoselectively to yield the guanidinylation product (**27**). Subsequent treatment with DDQ in the same pot enabled a "Yonemitsu-type" oxidation<sup>15</sup> of the C-6 indole to elicit a cyclization with complete chemo- and stereoselectivity.<sup>16</sup> Notably, two other unprotected indoles were unscathed during this formal C–H functionalization process. The chemoselectivity may be ascribed to steric hindrance at C-2 and the electron-withdrawing ester group at C-4; the stereoselectivity is most likely dictated by the C-5 stereocenter.

Reduction of crude **28** afforded hemiaminal **15** where direct displacement of the C-3 hydroxyl would install the final guanidine in the correct stereochemistry. However, as the C-2 indole resides in an antiperiplanar conformation,<sup>17</sup> anchimeric displacement prevailed when nucleophilic substitutions were attempted on derivatives of **15**, leading to overall stereoretention.<sup>18</sup> The hemiaminal **15** was converted into its *N,O*-acetal, which was immediately subjected to Dess–Martin oxidation; direct

reductive amination of the ensuing ketone with ammonium salts was unsuccessful. Oxime **29** was thus prepared in a single-flask sequence. As anticipated, reduction of the oxime in **29** was a highly challenging undertaking: not only is the oxime moiety sterically encumbered by two adjacent indole nuclei; other functionalities such as the *N,O*-acetal or three aryl bromides are conceivably more prone toward reduction. Indeed, the oxime was unreactive toward lithium aluminum hydride and sodium; various combinations of sodium borohydride and metal salts led to debrominations (see SI). A combination of  $\text{SmI}_2$  and  $\text{H}_2\text{O}$  was singularly successful:<sup>19</sup> **29** was reduced to primary amine **30** stereoselectively. The second guanidine was appended onto crude **30**, yielding **32** and setting the stage for the pivotal N-7a/C-1 cyclization.

Intriguingly, exposure of **32** to TFA did not elicit the logically expected outcome. Instead, the resulting iminium **33** spontaneously tautomerized to enamine **7** ("cyclo-*pre*-araiosamine"), which failed to cyclize under various acidic media. Hydrolysis of **32** with aqueous PPTS gave **34** whereupon activation ( $\text{MsCl}$ /pyridine) of the hemiaminal also led to **7**. It was reasoned that the C-2 indole readily and reversibly engages the iminium to shield the top face from N-7a cyclization (*vide supra*). To surmount this vexing neighboring group effect and the enamine dead-end, aqueous conditions were selected that might encourage equilibration. Toward this end, **32** was first hydrolyzed to **34** at ambient temperature; heating this mixture to 90 °C removed the Boc groups, thus liberating **35**, which was found to exist in equilibrium with araiosamine A (**1**) and 1-*epi*-araiosamine A (**36**) through ring–chain tautomerization. While isolated **1** reverted back to a tautomeric mixture containing **35** and **36** over several hours, continued heating of this mixture yielded araiosamines C (**3**) and D (**4**) through the intermediacy of "*pre*-araiosamine" (**5**).

Since the absolute configuration of these natural products was not known, the racemic path to **1**, **3**, and **4** was adapted to answer this lingering question. This could be easily achieved by utilizing Ellman's auxiliary<sup>20</sup> in the initial Mannich step (Figure 2).

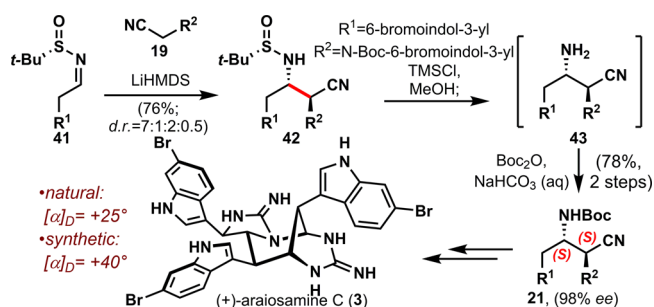


Figure 2. Synthesis of (+)-araiosamine C (see SI for conditions).

Subjecting imine **41** under similar conditions afforded a mixture of four diastereomers (7:1:2:0.5) favoring the desired **42**. Facile purification of this mixture was achieved after selective removal of the sulfonamide followed by the carbamylation of the primary amine, affording (*S,S*)-**21** (confirmed by X-ray) in high enantiomeric excess. Elaboration of this (*S,S*)-**21** through the sequence allowed the synthesis of (+)-araiosamine C (**3**), which was found to be the natural enantiomer based on its optical rotation.

With ample supplies of araiosamines secured, their biological activities were examined. Natural araiosamines were reported to be inactive against zebra fish embryos, *Staphylococcus aureus*, and HIV infection. Cytotoxic assays of synthetic **1** (as a tautomeric

mixture with 35 and 36), 3, and 4 seem to attest further to their bereft therapeutic value (Table 2). Nevertheless, in a surprising

**Table 2. Cytotoxic and Antibacterial Profiles (MIC in  $\mu\text{g}/\text{mL}$ )**

Compound number	BT-474 [human carcinoma cell lines]	HCC1954	<i>Staphylococcus aureus</i> [gram positive]	<i>E. Coli</i> [gram negative]
( $\pm$ )-1, 35, 36	not active	not active	1	2
( $\pm$ )-3	not active	not active	1	8
( $\pm$ )-4	not active	not active	2	16
Nat. 1, 3, 4	not tested	not tested	not active <sup>a</sup>	not tested
axinellamine A	not tested	not tested	2	2
Ciprofloxacin	not tested	not tested	>2	0.015

<sup>a</sup> result from the original isolation report [ref 2].

<sup>a</sup>Result from the original isolation report [ref 2].

turn, araiosamines exhibited considerable activities against both Gram-positive and Gram-negative bacteria, in stark contrast to the original report.<sup>21</sup> Scalable total syntheses have allowed us to identify natural products with erroneously reported potency.<sup>22</sup> This study, much akin to the axinellamines,<sup>3c</sup> represents a rare case where natural products reported to lack biological activities have surfaced as antibacterial agents. Marine isolates like 1, 3, and 4 are difficult to isolate or grow in a cell culture. To this end, chemical synthesis is ideally suited to procure these alkaloids for future biomedical evaluations.

The alternating indole-guanidine motifs present in 1–4, presumably assembled in nature by a seemingly simple trimerization, has been constructed concisely. Aside from the practical difficulty associated with such highly polar and sensitive motifs, the differing topologies accessible through ring–chain tautomerization add an additional layer of complication. Pivotal to the success of this endeavor was the evolution of a hybrid approach, which capitalized on this innate property, the invention of a powerful reagent for the installation of monoprotected Boc-guanidines (Aldrich catalog # ALD00592), and a remarkably chemo- and stereoselective C–H functionalization. Finally, the antibacterial activity of these structures is a welcome discovery that will be the subject of continued study.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09701.

Experimental procedures and analytical data (<sup>1</sup>H and <sup>13</sup>C NMR, MS) for all new compounds (PDF)

Compounds 39b (CIF); (S,S)-21 (CIF); 26 (CIF); 21 (racemic) (CIF); 18 (CIF); S4 (CIF); S3 (CIF); additional compounds found in SI PDF (CIF, CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*pbaran@scripps.edu

### Author Contributions

<sup>§</sup>These authors contributed equally.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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assistance with NMR spectroscopy, and Prof. A. L. Rheingold and Dr. C. E. Moore for X-ray analysis.

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