11-Step Total Synthesis of Araiosamines

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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. 1 In 2011 the Ireland group reported the isolation of araiosamines A–D (1–4, Figure 1A), 2 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), 2 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. 1b, 3 This realization coupled with their captivating structure fueled our endeavor toward araiosamines, even though they were reportedly devoid of significant bioactivities. 2 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 guanidinyl enamine (6) could serve as a precursor to 5 via a dramatic linear trimerization event (Figure 1B). 4 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 expeditiously. 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 toward a bicyclic tautomer of 5, herein referred to as “cyclo-prearaiosamine” 7, 4 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 indolylacetaldheyde derivatives. 5 Although variants

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

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of the cyclic core (e.g., 12 and 13) were furnished stereoselectively via a Diels−Alder reaction or an Achmatowicz rearrangement, 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 oligimerization of simple building blocks, while its rigid bicyclic structure would confer stereocntrol 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 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 BocNH2 and PhSO2Na to furnish the stable acylimine precursor (18).

The Mannich reaction of lithiated N-Boc-6-bromoindolylacetronitrile (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 ’BuNH2. Reduction of the nitrile in 21 was examined next. The use of

“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/H2O/formic acid, 25 °C (67%, one pot); (2) 19 (3 equiv), LiHMDS (3 equiv), THF, −78 °C (92%, 1:1); (2′) MeOH/’BuNH2 (10:1); (3) Schwartz’s reagent (2.6 equiv), CH2Cl2, 25 °C (78%); (4) 23 (3 equiv), LiHMDS (4 equiv), THF, −78 °C (70%, d.r. = 1:1); (5) TFA/CH2Cl2 (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), CH2Cl2, −78 °C (36%, over 3 steps); (8) PPTS (1 equiv), MeOH/H2O (2:1), 25 °C; DMP (2 equiv), THF, 25 °C then NH2OH·HCl (11 equiv), NaOAc (5.5 equiv), EtOH, 50 °C (63%, one pot); (9) SmI2, THF/H2O (6:1), 25 °C; (10) NN’-Di-Boc-S-methylisothiourea (31) (2.4 equiv), HgCl2 (2.9 equiv), DMF, 25 °C (53%, 2 steps); (11) TFA/CH2Cl2 (2:1), (11) PPTS (4.4 equiv), MeCN/H2O (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 = ZrCp2(H)Cl, TFA = trifluoroacetic acid, DIBAL = diisobutylaluminum hydride, PPTS = pyridinium p-toluenesulfonate, DMP = 1,1,1-triacetoxy-1,2-dihydro-1,2-benziodoxol-3(1H)-one.
deficient anilines (39a, 41) and drug molecules (39d). The bisacyl guanidine product could be isolated (40); alternatively, the TFA group could be removed in the same pot upon treatment with methanolic KHCO₃ to afford monoaacylguanidines. 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 of the C-6 indole to elicit a cyclization with complete chemo- and stereoselectivity. 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 antiplanar conformation, anchimeric displacement prevailed when nucleophilic substitutions were attempted on derivatives of 15, leading to overall stereoretention. The hemiaminal 15 was converted into its N₃O-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 N₃O-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 SmI₂ and H₂O was singularly successful; 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 (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 auxiliary20 in the initial Mannich step (Figure 2).

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 carbamoylation 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

Table 1. Scope of the Guanidinylation Reaction

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|---------------------------------------------|
| ![Image](https://example.com/table1.png) |

Figure 2. Synthesis of (+)-araiosamine C (see SI for conditions).
mixture with 35 and 36), 3, and 4 seem to attest further to their
treatment in a surprising

Table 2. Cytotoxic and Antibacterial Activities (MIC in μg/mL)

| Compound number | BT-474 (human carcinoma cell line) | HCC1595 (hepatoma cell line) | Streptomyces aureus (gram positive) | E. Coli (gram negative) |
|-----------------|-----------------------------------|-------------------------------|-----------------------------------|------------------------|
| (±)-1, 35, 36   | not active                        | not active                    | 1                                 | 2                      |
| (±)-3           | not active                        | not active                    | 1                                 | 8                      |
| (±)-4           | not tested                        | not tested                    | not active*                        | not tested             |
| Nat. 3, 4       | axinellamine A                    | not tested                    | not tested                        | >2                     |
| Ciprofloxacin   | not tested                        | not tested                    | 2                                 | 2                      |

*Result from the original isolation report [ref 2].

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. 
When 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-approach, which capitalized on this innate property, the invention 
tautomerization add an additional layer of complication. Pivotal 
motifs, the di 
have surfaced as antibacterial agents. Marine isolates like 
considered activities against both 
Gram-positive and Gram-negative bacteria, in stark contrast to the 
original report.22 Scalable total syntheses have allowed us to 
identify natural products with erroneously reported potency.22 
This study, much akin to the axinellamines,3c 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, 

![Image]

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