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Scalable, Stereocontrolled Total Syntheses of (±)-Axinellamines A and B

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Supporting Information

ABSTRACT: The development of a simple, efficient, scalable, and stereocontrolled synthesis of a common intermediate en route to the axinellamines, massadines, and palau'amine is reported. This completely new route was utilized to prepare the axinellamines on a gram scale. In a more general sense, three distinct and enabling methodological advances were made during these studies: (1) an ethylene glycol-assisted Pauson–Khand cycloaddition reaction, (2) a Zn/In-mediated Barbier-type reaction, and (3) a $TfNH_2$-assisted chlorination–spirocyclization.

The axinellamines (**1**, **2**), massadines (**3**, **4**), and palau'amine (**5**) reside at the upper limit of structural complexity within the bioactive pyrrole–imidazole marine alkaloid (PIA) family (Figure 1).[1] As such, extensive effort has been expended toward their total chemical synthesis.[2] Although the feasibility of generating **1**–**5** in a laboratory setting on a milligram scale was demonstrated over the past three years,[2a,3] the ultimate challenge of procuring large quantities of these alkaloids, a prerequisite for any serious biological follow-up, has yet to be met. The center of inefficiency in the Scripps route to **1**–**5**[2a,3] lies in the preparation of common progenitor spirocycle **6**, which is synthesized by a lengthy 20-step sequence in 1% overall yield (40% ideality[4]) that proceeds without stereocontrol at C-7 (ca. 1:1 ratio formed). Only 4–6 additional steps are required to controllably convert **6** into **1**–**5**. In this Communication, the development of a simple, efficient, scalable, and stereocontrolled synthesis of **6** is reported, leading to the preparation of axinellamines on a gram scale. In a more general sense, three distinct and enabling methodological advances were made during these studies, as outlined in detail below.

At the heart of the retrosynthetic plan (Figure 1) of spiroaminoketone **6** is the speculation that allylic guanidine **7** may undergo a stereoselective chlorination–spirocyclization process, presumably due to the steric interaction between the Cl^+ source and the neighboring methylene azide functionality. This disconnection clears the two most challenging stereocenters of the fully substituted cyclopentane framework. Allylic guanidine **7** may arise from the stereoselective condensation of a putative allylic anion intermediate **8** with an appropriate side-chain segment. The strategic inclusion of this C_2-symmetric intermediate in the synthetic design is advantageous and fully exploits the hidden symmetry in this class of natural products,[5] as it not only eliminates the regioselectivity issue during the side-chain installation step but also renders the stereochemistry of the corresponding allylic chloride **9** irrelevant. Allylic chloride **9** could arise from

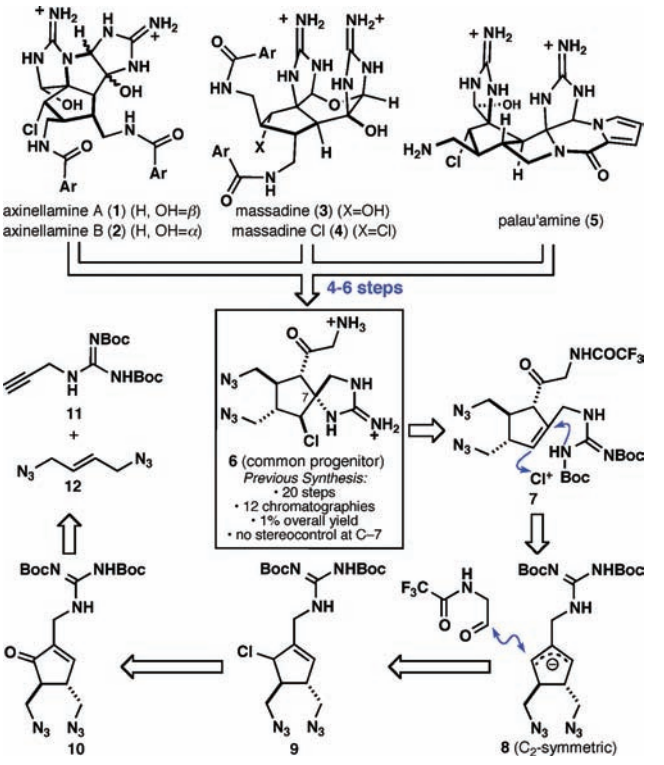

Figure 1. Structures of axinellamines A and B, massadine, massadine chloride, and palau'amine and retrosynthetic analysis.

cyclopentenone **10**, which in turn could be accessed via a Pauson–Khand cycloaddition between propargyl guanidine **11** and bis-allylic azide **12**.

Initial forays based on this blueprint revealed that **11** possessed only marginal reactivity under the most common Pauson–Khand reaction conditions and **12** completely decomposed for most of the cases (perhaps due to the known rearrangement of allylic azides[6]). Thus, bis-allylic trimethyl silyl ether **13** and propargyl amine **14** were employed (Scheme 1). Initial trials under thermal conditions with cyclohexylamine,[7a] BuSMe,[7b] DMSO,[7c] and water[7d] as additive only led to decomposition of the Co complex of **14**.

Under the mediation of *N*-oxides such as NMO[7e] and TMANO,[7f] the desired product **15** was produced in only 15–25% yield. After extensive experimentation,[8] it was identified that the combination of ethylene glycol and NMO dramatically improved

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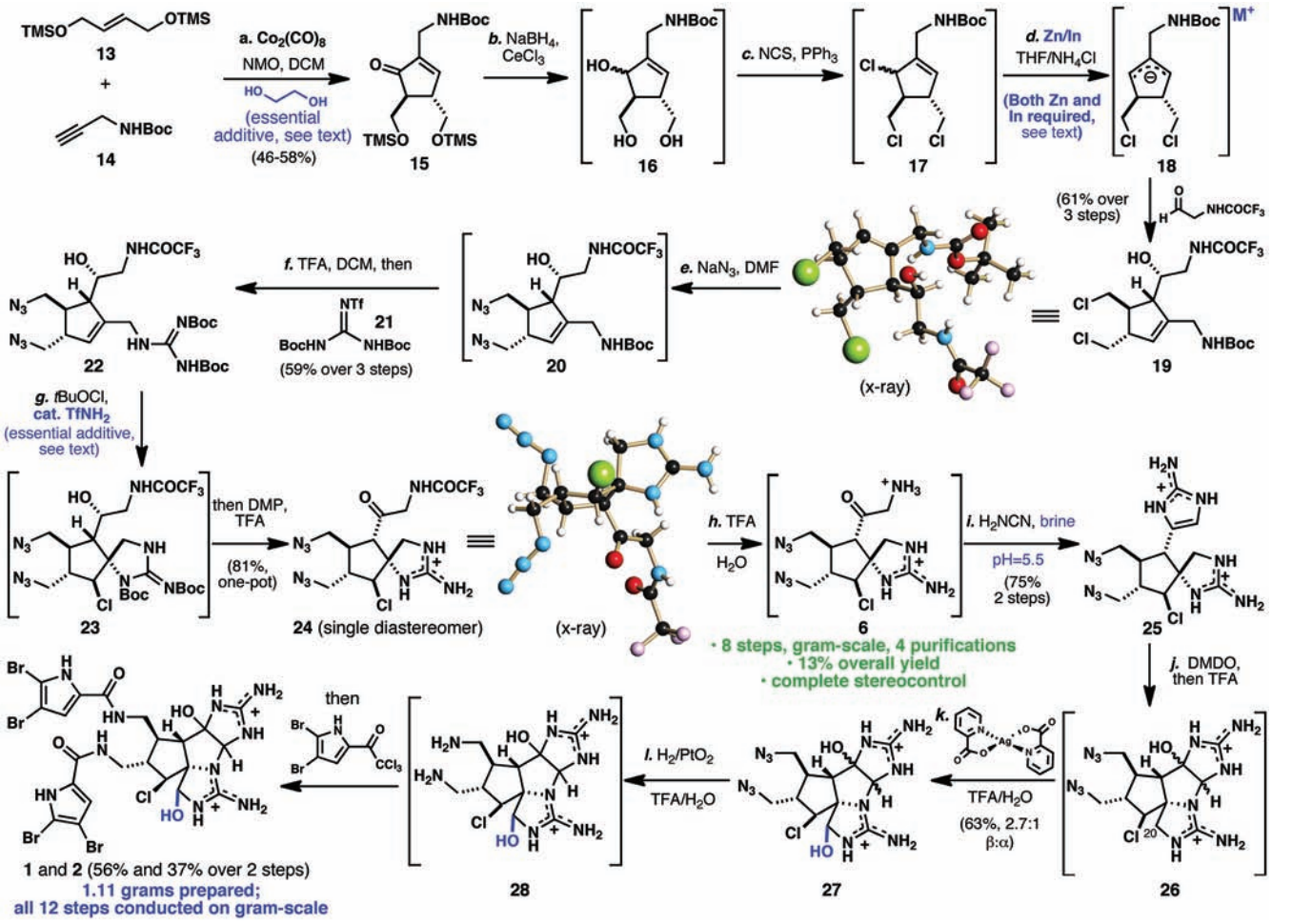
Scheme 1. Stereocontrolled, Gram-Scale Synthesis of the Axinellamines 1 and 2[a]



[a] Reagents and conditions: (a) $Co_2(CO)_8$, NMO, ethylene glycol, 4 Å molecular sieves, DCM, rt, 12 h, 46−58%; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C to rt, 12 h; (c) PPh_3, NCS, DCM, 0 °C to rt, 12 h; (d) Zn, In, 2,2,2-trifluoro-*N*-(2-oxoethyl)acetamide, THF, 6% aq NH_4Cl, rt, 3 h, 61% for three steps; (e) NaN_3, DMF, 85 °C, 16 h; (f) TFA, DCM, rt; then **21**, Et_3N, DCM, rt, 12 h, 59% for three steps; (g) ^{t}BuOCl, $TfNH_2$ (0.25 equiv), DCM, 0 °C; then DMP, TFA:DCM = 1:10, rt, 12 h, 81%; (h) TFA:H_2O = 1:1, 70 °C, 36 h, quantitative if isolated, carried to next step directly; (i) H_2NCN, brine, NaOH (pH 5.5), 70 °C, 4 h, 75% for two steps; (j) DMDO, TFA:H_2O = 5:95; then TFA:DCM = 1:1, rt, 24 h; (k) silver(II) picolinate, TFA:H_2O = 1:9, rt, 1.5 h, 63% yield over two steps, 2.7:1 β:α; (l) H_2, Pt_2O, TFA:H_2O = 5:95, 1 h; then 2,3-dibromo-5-trichloroacetylpyrrole, DIEA (pH 8.0), MeCN, rt, 24 h, 56% and 37% over two steps for **1** and **2**

the performance of this transformation, generating the desired cyclopentenone **15** reproducibly in 46−58% yield (6.2 g scale). In light of the fact that intermolecular Pauson−Khand reactions of unactivated alkenes are rare and involve reaction partners without useful functional groups,[7,8] the discovery of this ethylene glycol-assisted condition is notable. Studies are underway to evaluate both the scope and mechanistic origin of this new protocol.

With the scalable formation of cyclopentenone **15** secured, subsequent Luche reduction was performed to effect the 1,2-reduction and desilylation in one pot (6.2 g scale). The resulting triol **16** (not purified) was converted to the corresponding trichloride **17** as an inconsequential mixture (2:1) of diastereomers. After filtration through a short silica plug, trichloride **17** was determined to be pure enough for the subsequent side-chain installation without additional purification. At this juncture, conditions for the speculative desymmetrizing Barbier reaction to access **19** needed to be developed. While initial trials using Zn, In, Sn, and Fe under anhydrous conditions[9a] failed to produce any desired product, it was discovered that the combination of Zn and saturated NH_4Cl[9b] successfully produced **19**, albeit in low yield. After extensive optimization, it was found that the combination of Zn, In, and NH_4Cl (6% aqueous solution) dramatically increased the reaction yield (61% overall from diol **16**, 4.1 g scale) while reducing the required reaction time. Control studies using In or $InCl_3$ without Zn or employing Zn/Cu only produced complex mixtures or recovered starting material. To our knowledge, the synergistic combination of In and Zn in a Barbier reaction is without precedent, and this and related reactions warrant further investigation.

Starting with bis-chloride **19**, azide installation, Boc removal with TFA, and subsequent guanidine installation using **21** as guanidine source[10] occurred smoothly to produce allylic guanidine **22** in 59% yield over three steps with only one chromatography (3.2 g scale). The critical spirocyclization−chlorination step required extensive study. Initial attempts to convert **22** to **23**

using a variety of chlorinating agents were frustratingly variable—with results differing on the batch of **22**. It was eventually discovered that residual $TfNH_2$, formed during installation of the guanidine moiety in the preceding step with reagent **21**, played an enabling role in the ensuing reaction with ^tBuOCl, delivering spirocycle **23** as a single diastereomer (ca. 85% carried in crude form to the subsequent step after solvent removal). Interestingly, in the absence of $TfNH_2$ or with excess of $TfNH_2$, complex mixtures were obtained. Intrigued by these observations, we carried out additional studies to understand this transformation. In a ^{19}F NMR experiment, addition of ^tBuOCl to a mixture of $TfNH_2$ and CD_2Cl_2 led to no observable shift of the CF_3 group, which indicated that the formation of TfNHCl was unlikely. Whereas mixing of $TfNH_2$ with allylic guanidine **22** led to no spectroscopic changes, the addition of $TfNH_2$ to the spiro product **23** induced a dramatic shift of most of the proton signals (see SI for details). Studies are underway to further understand the origin of this dramatic effect.

Spirocycle **23** could be processed in crude form and in the same reaction vessel to ketone **24** using DMP with 10:1 DCM/TFA as solvent (81% yield from **22** to **24**, 2.4 g scale). Further treatment of purified **24** with TFA in the presence of water produced spiro-aminoketone **6** in a total of eight steps with four chromatographic purifications and in 13% overall yield from **13** and **14**. By comparison to our previous synthesis of **6**, this route reduced the number of steps by more than half and increased the overall yield by >10-fold (63% ideality). It is worth mentioning that 2.5 g of **6** was prepared by one chemist in a single batch within two weeks, which surpassed the entire amount of **6** that was produced during our previous studies toward this family of PIAs (~2 g over a three-year period).

Finally, in order to demonstrate that complicated tetracyclic PIAs can be prepared in large quantities with intermediate **6**, the syntheses of axinellamines A and B were completed. Thus, reaction of **6** with cyanamide in brine at pH 5.5 led to **25** in 75% yield over two steps (1.9 g scale). Oxidation of the 2-aminoimidazole with DMDO and subsequent dehydrative cyclization with TFA furnished **26** that was processed in crude form to **27**-α and **27**-β with silver(II) picolinate in 63% yield over two steps (1.26 g scale, 2.7:1 β:α). Conversion of the azide groups to the acylpyrrole side chains was accomplished in a one-pot sequence involving PtO_2-mediated reduction followed by acylation with 2,3-dibromo-5-trichloroacetylpyrrole to furnish **1** and **2**. Over 1 g of the axinellamines (0.89 and 0.22 g of **1** and **2**, respectively) has been prepared by this route—dramatically surpassing both the efficiency of our previous synthesis and isolation from natural sources.

Notable features of the stereocontrolled syntheses of **1**, **2**, and **6** (12 and 8 steps, 4 and 7 purifications, respectively), representing formal total syntheses of **3**−**5**, include (1) the robustness, simplicity, and practicality of the route despite the sheer complexity of **1** and **2**—all steps are conducted on a gram scale, none require cryogenic temperatures, and most proceed without intermediate purification or an inert atmosphere; (2) an ethylene glycol-assisted Pauson−Khand cycloaddition reaction; (3) a chemoselective In/Zn-mediated Barbier-type reaction; and (4) a $TfNH_2$-assisted chlorination−spirocyclization.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all reactions and products, including ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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