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

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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. ethylene glycol-assisted Pauson-Khand cycloaddition reaction, 2. a Zn/In-mediated Barbier type reaction, and 3. a TfNH₂-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 towards 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% ideality⁴) that proceeds without stereocontrol at C-7 (ca. 1:1 ratio formed). Only four to six 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 C₂-symmetric intermediate in the synthetic design is advantageous and fully exploits the hidden symmetry in this class of natural products⁵ as it not only eliminates the regioselectivity issue during the sidechain installation step, but also renders the stereochemistry of the corresponding allylic chloride **9** irrelevant. Allylic chloride **9** could arise from cyclopentenone **10**, which in turn could be accessed *via* a Pauson-Khand cycloaddition between propargyl guanidine **11** and *bis*-allylic azide **12**.

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

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 azides⁶). Thus, *bis*-allylic trimethyl silyl ether **13** and propargyl amine **14** were employed. Initial trials under thermal conditions with cyclohexyl amine,^{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 the performance of this transformation, generating the desired cyclopentenone **15** reproducibly in 46-58% yield (6.2 gram 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 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 gram 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 sidechain 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 NH₄Cl^{9b} successfully produced **19**, albeit in low yield. After extensive optimization, it was found that the combination of Zn, In and NH₄Cl (6% aqueous solution) dramatically increased the reaction yield (61% overall from diol **16**, 4.1 gram scale) while reducing the required reaction time. Control studies using In or InCl₃ 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 further studies in 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 source¹⁰ occurred smoothly to produce allylic guanidine **22** with 59% yield over three steps with only one chromatography (3.2 gram 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 TfNH₂, formed during installation of the guanidine moiety in the preceding step with reagent **21** played an enabling role in the ensuing reaction with *t*BuOCl delivering spirocycle **23** as a single diastereomer (*ca.* 85% carried in crude form to subsequent step after solvent removal). Interestingly, in the absence of TfNH₂ or with excess of TfNH₂, complex mixtures were obtained. Intrigued by these observations, additional studies have been carried out to understand this transformation. In a ¹⁹F NMR experiment, addition of *t*BuOCl to a mixture of TfNH₂ and CD₂Cl₂ led to no observable shift of the CF₃ group, which indicated that the formation of TfNHCl was unlikely. Whereas mixing of TfNH₂ with allylic guanidine **22** led to no spectroscopic changes, the addition of TfNH₂ 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 gram scale).

Further treatment of purified **24** with TFA in the presence of water produced spiro-aminoketone **6** in a total of 8 steps with 4 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 grams 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 towards this family of PIAs (~2 grams 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 & 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 gram 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 picolinate in 63% yield over 2 steps (1.26 gram scale, 2.7:1 β : α). Conversion of the azide groups to the acylpyrrole sidechains was accomplished in a one-pot sequence involving PtO₂-mediated reduction followed by acylation with 2,3-dibromo-5-trichloroacetylpyrrole to furnish **1** and **2**. Over one gram of the axinellamines (0.89 and 0.22 grams of **1** and **2** respectively) have 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 **1–2**: All steps are conducted on a grams-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 TfNH₂-assisted chlorination-spirocyclization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Scheme 1.

Stereocontrolled, gram-scale synthesis of the axinellamines (**1** and **2**).

Reagents and Conditions: a) $\text{Co}_2(\text{CO})_8$, NMO, ethylene glycol, 4Å molecular sieves, DCM, rt, 12 h, 46-58%; b) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, 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 3 steps; e) NaN_3 , DMF, 85°C, 16 h; f) TFA, DCM, rt; then **21**, Et_3N , DCM, rt, 12 h, 59% for 3 steps; g) $t\text{BuOCl}$, TfNH_2 (0.25 eq), DCM, 0 °C; then DMP, TFA:DCM=1:10, rt, 12 h, 81%; h) TFA:H₂O=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 2 steps; j) DMDO, TFA:H₂O=5:95; then TFA:DCM=1:1, rt, 24 h; k) Silver(II)picolinate, TFA:H₂O=1:9, rt, 1.5 h, 63% yield over 2 steps, 2.7:1 $\beta:\alpha$; l) H_2 , PtO_2 , TFA:H₂O=5:95, 1 h; then 2,3-dibromo-5-trichloroacetylpyrrole, DIEA (pH=8.0), MeCN, rt, 24 h, 56% and 37% over 2 steps for **1** and **2**