

Scalable, Stereocontrolled Total Syntheses of ($\pm$)-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 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 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% ideality⁴) 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 C₂-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

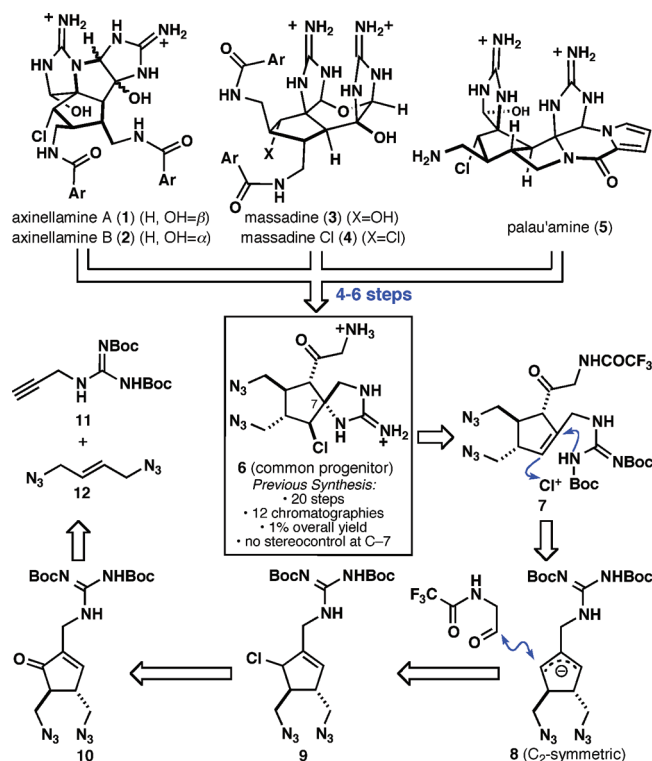


Figure 1. Structures of axinellamines A and B, massadine, massadine chloride, and palau'amine and retrosynthetic analysis.

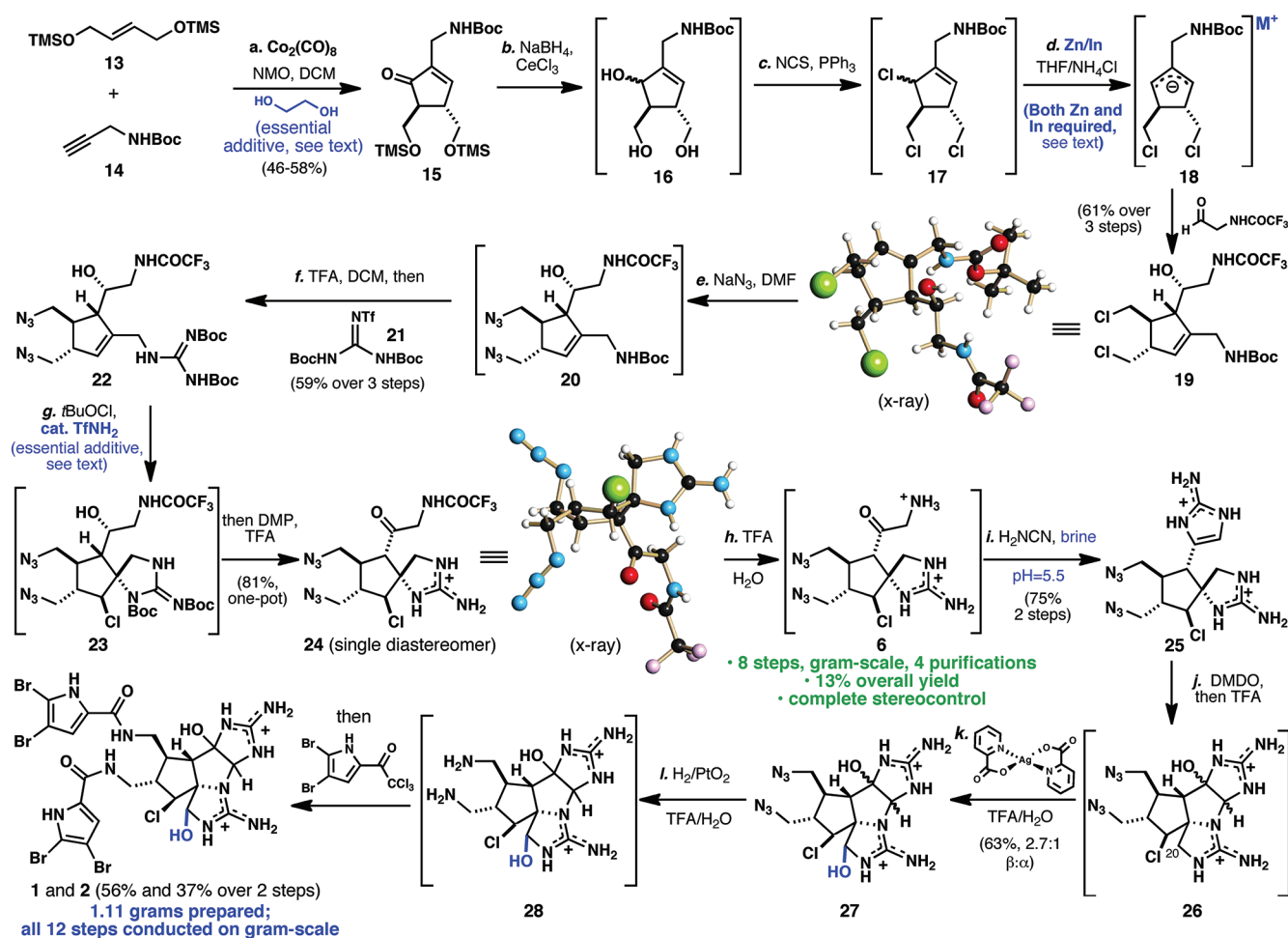
cyclopentenone 10, which in turn could be accessed via a Pauson–Khand cycloaddition between propargyl guanidine 11 and bis-allylic azide 12.

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 azides⁶). Thus, bis-allylic trimethyl silyl ether 13 and propargyl amine 14 were employed (Scheme 1). Initial trials under thermal conditions with cyclohexylamine,^{7a} BuSMc,^{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

Received: July 4, 2011

Published: August 16, 2011

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

^a Reagents and conditions: (a) $\text{Co}_2(\text{CO})_8$, NMO, ethylene glycol, 4 Å 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 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) $t\text{BuOCl}$, TfNH_2 (0.25 equiv), DCM, 0 °C; then DMP, $\text{TFA}:\text{DCM} = 1:10$, rt, 12 h, 81%; (h) $\text{TFA}:\text{H}_2\text{O} = 1:1$, 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, $\text{TFA}:\text{H}_2\text{O} = 5:95$; then $\text{TFA}:\text{DCM} = 1:1$, rt, 24 h; (k) silver(II) picolinate, $\text{TFA}:\text{H}_2\text{O} = 1:9$, rt, 1.5 h, 63% yield over two steps, 2.7:1 $\beta:\alpha$; (l) H_2 , PtO_2 , $\text{TFA}:\text{H}_2\text{O} = 5:95$, 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 source¹⁰ 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 $^t\text{BuOCl}$, 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 $^t\text{BuOCl}$ 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

S 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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■ ACKNOWLEDGMENT

Financial support for this work was provided by the NIH/NIGMS (GM-073949), the NSF (predoctoral fellowship to R.A.R.), Amgen, and Bristol-Myers Squibb. We thank Prof. A. Rheingold and Dr. Curtis E. Moore for X-ray crystallographic measurements.

■ REFERENCES

- (1) (a) Urban, S.; Leone, P. d. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731–735. (b) Nishimura, S.; Matsunaga, S.; Shibasaki, M.; Suzuki, K.; Furihata, K.; Van, S. R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255–2257. (c) Grube, A.; Immel, S.; Baran, P. S.; Koeck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6721–6724. (d) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377. (e) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281–3286. For a review, see: (f) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594.
- (2) For a comprehensive listing of studies towards the PIA family, see ref 1f and (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098. For recent studies, see: (b) Namba, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett.* **2010**, *51*, 6557–6559. (c) Feldman, K. S.; Nuriye, A. Y.; Li, J. *J. Org. Chem.* **2011**, *76*, 5042–5060. (d) Chinigo, G. M.; Breder, A.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 78–81. (e) Ma, Z.; Lu, J.; Wang, X.; Chen, C. *Chem. Commun.* **2011**, *47*, 427–429.
- (3) (a) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581–3583. (b) Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3578–3580. (c) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491. For the full account, see: (d) Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jorgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Kock, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011** in press (DOI: 10.1021/ja2047232).
- (4) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657–4673.
- (5) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem.* **2009**, *74*, 5909–5919.
- (6) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444–13445.
- (7) (a) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem.—Eur. J.* **2001**, *7*, 1589–1595. (b) Brown, J. A.; Janecki, T.; Kerr, W. J. *Synlett* **2005**, 2023–2026. (c) Chung, Y. K.; Lee, B. Y. *Organometallics* **1993**, *12*, 220–223. (d) Sugihara, T.; Yamaguchi, M. *Synlett* **1998**, 1384–1386. (e) Shambayati, S.; Crowe, W. E.; Schrieber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289. (f) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204.
- (8) For some recent reviews on the Pauson–Khand reaction, see: (a) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318–344. (b) Strübing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, *18*, 165–178. (c) Pérez-Castells, J. *Top. Organomet. Chem.* **2006**, 207–257. (d) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037. (e) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795–9833. (f) Blanco-Urgoiti, J.; Anorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32–42. (g) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2004**, 3377–3383. (h) Rivero, M. R.; Adrio, J.; Carretero, J. C. *Eur. J. Org. Chem.* **2002**, 2881–2889. (i) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**,

56, 3263–3283. (j) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657–1668.

(9) (a) Blomberg, C. *The Barbier reaction and related one-step processes*; Springer-Verlag: Berlin, 1993. (b) Breton, G. W.; Shugart, J. H.; Hughey, C. A.; Conrad, B. P.; Peralá, S. M. *Molecules* **2001**, 6, 655–662.

(10) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, 63, 3804–3805.