Natural Products

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Synthesis of 1,9-Dideoxy-pre-axinellamine**

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Dimeric pyrrole imidazole alkaloids[1] such as the massadines,[2] axinellamines,[3] and palau'amines,[4] are marine-derived natural products that represent a great opportunity to advance fundamental chemical synthesis (Figure 1).[5] At the heart of their structure is a daunting stereochemical puzzle embedded in a fully substituted cyclopentane framework with spiro-fused and pendant guanidine-containing heterocycles. The extremely high nitrogen content of these molecules tests the limits of chemoselectivity control in synthesis. Their diverse and ornate architectures notwithstanding, the biochemical pathways to these interesting alkaloids may well be intimately related. The existence of such an interrelationship, if unearthed, could potentially simplify an approach to their chemical synthesis. It was recently postulated[1] that all of the members of this natural product family can be traced back to the same hypothetical progenitor: "pre-axinellamine" (**4**, Figure 1), by varying modes of ring closure. Herein we delineate a simple pathway to arrive at 1,9-dideoxy-pre-axinellamine (**5**, axinellamine numbering used herein[3]), a reduced form of that key intermediate (i.e. **4**), which represents the complete carbogenic skeleton of natural products **1**–**3**.

Lessons learned during the total synthesis of simpler dimeric pyrrole-imidazole alkaloids and forays into a purely biomimetic route[6] to **5** led us to target the trihalogenated building block **6**. As outlined in Figure 1, this simplified core is pre-programmed with all of the requisite functionality and stereochemistry for elaboration to **5**. In essence, construct **6** can be viewed as a minimal foundation for the synthesis of the carbogenic skeleton of **1**–**4**. The experimental validation of this vision is documented in Scheme 1.

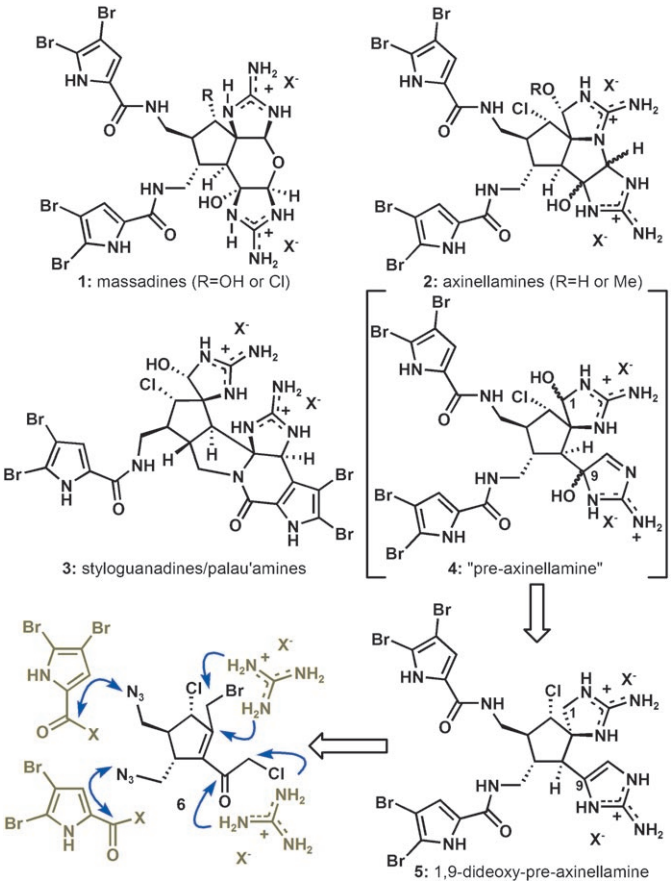

Figure 1. Selected dimeric pyrrole-imidazole alkaloids and retrosynthetic analysis of the hypothetical biogenetic precursor "pre-axinellamine" (**4**).

A Diels–Alder reaction between dimethyl fumarate and diene **7**[7] (>95%, directly carried to the next step) set three of the key stereochemical relationships (verified by X-ray crystallographic analysis of **8**) that would eventually manifest themselves in the cyclopentane core. Functional group interchanges involving conversion of the ester groups to azides and deprotection of the silyl group (64% over five steps) afforded allyl alcohol **9**. Installation of the PMB group (**10**) and ozonolytic scission of this tetra-substituted olefin led to the bis-methyl ketone **11** (85% over two steps), which was immediately converted into its bis-enol ether (TMSOTf, iPr$_2$NEt), brominated with NBS, and cyclized via an intramolecular aldol reaction on dry silica gel to furnish dibromide **12** in 57% overall yield.[8] The reactivity of α-bromo ketone **12** was attenuated by conversion to its α-chloro congener using LiCl—a maneuver necessary to enable its conversion to

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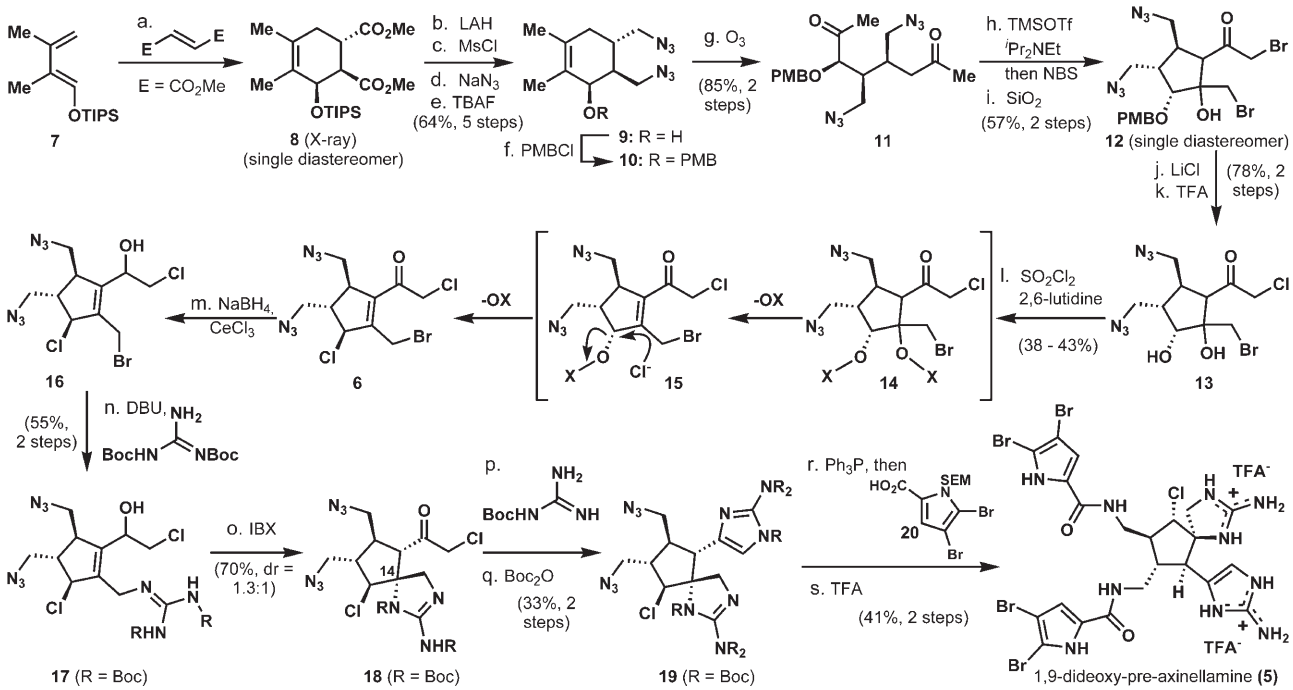

Scheme 1. Synthesis of 1,9-dideoxy-pre-axinellamine (**5**). Reagents and conditions: a) Dimethyl fumarate (0.95 equiv), diene **7** (1.0 equiv), 150 °C, 1 h; b) $LiAlH_4$ (3.0 equiv), THF, 0 °C, 30 min; c) MsCl (4.0 equiv), pyridine, starting temperature 0 °C, 30 min to 23 °C, 30 min; d) NaN_3 (6.0 equiv), DMF, 100 °C, 11 h; e) TBAF (1.05 equiv), THF, 23 °C, 55 min, 64% over five steps; f) NaH (2.0 equiv), PMBCl (1.05 equiv), TBAI (0.1 equiv), DMF, 0 °C starting temperature to 23 °C, 2 h; g) ozone, methanol, −78 °C, 30 min, then dimethyl sulfide, 5 h to 23 °C, 85% over two steps; h) TMSOTf (4.0 equiv), Hünig's base (6.0 equiv), DCM, 0 °C starting temperature, 1.5 h to 23 °C, 1.5 h, NBS (2.0 equiv), THF; i) silica gel, 47 °C, 12 h, 57% over two steps; j) LiCl (3.25 equiv), DMF, 23 °C, 1.5 h; k) anisole (2.0 equiv), TFA/DCM (1/10), 0 °C, 25 min, 78% for two steps; l) SO_2Cl_2 (9.0 equiv), 2,6-lutidine (5.0 equiv), MS 3 Å, DCM, 0 °C, 30 min, 38–43%; m) $NaBH_4$ (1.0 equiv), $CeCl_3 \cdot 7H_2O$ (0.5 equiv), MeOH, 0 °C, 20 min; n) *N*,*N*′-bis-Boc guanidine (2.0 equiv), DBU (1.5 equiv), DMF, −10 °C, 2.75 h, 55% over two steps; o) IBX (2.0 equiv), benzene, 83 °C, 10 h, 70% (d.r. 1.3:1 in favor of the desired diastereomer); p) Boc guanidine (4.0 equiv), THF, 55 °C, 24 h; q) $(Boc)_2O$ (15.0 equiv), NEt_3 (20.0 equiv), DMAP (cat), DCM, 23 °C, 3 h, 33% over two steps; r) PPh_3 (4.1 equiv), CH_3CN, 40 min, 60 °C, then H_2O, 1.5 h, then compound **20** (6.1 equiv), EDCI (10.2 equiv), NEt_3, 1.5 h, 23 °C, 45%; s) TFA/DCM (2/1), 23 °C, 3 h, 90%. TIPS = triisopropylsilyl, THF = tetrahydrofuran, MsCl = methanesulfonyl chloride, DMF = *N*,*N*-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride, PMBCl = *p*-methoxybenzyl chloride, TBAI = tetra-*n*-butylammonium iodide, TMSOTf = trimethylsilyl trifluoromethanesulfonate, DCM = dichloromethane, NBS = *N*-bromosuccinimide, TFA = trifluoroacetic acid, DBU = 1,8-diazabicycloundec-7-ene, IBX = 2-iodoxybenzoic acid, Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, SEM = 2-(trimethylsilyl)ethoxymethyl.

17. The PMB group was then excised by brief exposure to TFA to afford diol **13** in 78% overall yield. At this point, all that was required to form **6** was elimination of the tertiary alcohol and displacement of the secondary alcohol with chloride. The surprising resistance of the tertiary alcohol to dehydration confounded this seemingly straightforward task until a cascade reaction was developed which addressed both problems in a single step. Thus, treatment of **13** with five equivalents of 2,6-lutidine in the presence of nine equivalents of SO_2Cl_2 and molecular sieves at 0 °C generated enone **6** in 38–43% yield (multigram-scale). This cascade reaction is believed to proceed via either the bis-chlorosulfonate ester or cyclic sulfate **14**, followed by elimination to **15** and chloride inversion to yield **6**. Roughly 15% yield of each of 13-*epi*-**6** and **21** (see Figure 2) were routinely isolated in this reaction. The twelve-step route to enone **6** from diene **7** is robust, scalable, and reliable.

While model studies on 13-deschloro-**6** suggested that **6** could be converted to **5** by direct condensation with a suitable guanidine surrogate followed by acylation, issues of chemo- and stereoselectivity necessitated a less direct approach. In practice, this task was akin to balancing on a thin tight rope, and after extensive experimentation a simple and reliable seven-step sequence to **5** from **6** was developed. Luche reduction[9] of **6** furnished the allylic alcohol **16** and allowed a chemoselective displacement of the allylic bromide with *N*,*N*′-bis-Boc guanidine and DBU leading to **17**. This choice of

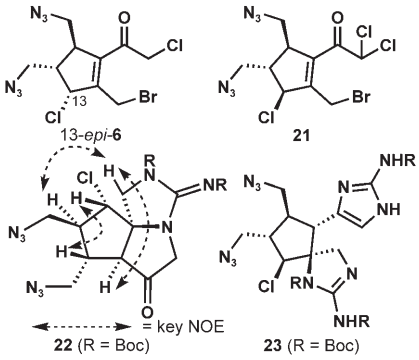

Figure 2. Informative by-products en route to **5**.

conditions proved critical to avoid intramolecular epoxide formation and/or cyclization of the newly appended guanidine onto the C-17 allylic chloride (both clear dead-ends). While several oxidative attempts on allylic alcohol **17** at room temperature or below gave exclusively the wrong spirodiasteromer at C-14 (after intramolecular conjugate addition), it was found that using IBX in refluxing benzene furnished a slight excess of the correct diastereomer **18**[10] (1.3:1, 70%). Installation of the final 2-amino imidazole heterocycle was also not without incident since nearly all conditions attempted led to tricyclic compound **22**[10] (Figure 2), resulting from intramolecular displacement of the chloride by the neighboring spiro-fused guanidine. Notably, this "by-product" represents the key ring system expressed in the axinellamines and can be easily accessed if desired (using most bases).[11]

Addition of N-Boc guanidine (4 equiv) in THF (no added base) provided **19**[10] (after global Boc introduction to facilitate purification) and proved essential to avoid the formation of **22**. In contrast, **23** (Figure 2) was easily accessed from 14-*epi*-**18** using N-Boc guanidine. The sequence **6** → **18**/**19** suffers from a non-strategic oxidation state fluctuation,[12] which was found to be essential since the direct conversion of **6** to **18** or **19** was unsuccessful. The synthesis of **5** was completed by a one-pot Staudinger reduction/acylation with dibromopyrrole **20**, followed by global deprotection (41% yield over the two steps).

Elements of symmetry recognition, clues from probable biogenetic relationships, a desire to harness innate reactivity, and extensive in-house empirical findings are among the ingredients that constitute the underlying logic of the present route to **5** via **6**. The synthesis of **5** represents the first report of a fully functionalized carbocyclic core of a polycyclized dimeric pyrrole-imidazole alkaloid with all of the correct stereochemical relationships.[13] With useful quantities of this complex intermediate available, the stage is now set to explore the fascinating oxidation pathways that should, in principle, afford a family of natural products via "pre-axinellamine" (**4**). While studies on the conversion of **5** to **4** are well underway, the findings reported herein have enabled the first total synthesis of the axinellamines.[11]

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[13] See Supporting information for full characterization and copies of spectra for all isolated intermediates. CCDC 680899 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

