Published in final edited form as:

Angew Chem Int Ed Engl. 2012 April 27; 51(18): 4340–4343. doi:10.1002/anie.201200205.

Synthetic (±)-Axinellamines Deficient in Halogen**

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Keywords

axinellamines; pyrrole/imidazole alkaloids; spirocycloisomerization; glycoamidine reduction; dispacamide

Marine organism derived pyrrole/imidazole alkaloids have drawn attention from laboratories worldwide. Their structures, biosynthetic origins, preliminary biochemical activities and chemical syntheses form an extensive literature.^[1] The family contains hundreds of members, often grouped based upon their oroidin content.^[2] So-called monomers, dimers and dimers of dimers are known. Further diversity derives from oxidative transformations of the monomeric and/or dimeric units. The most intricate polycyclic ‘dimers’ are uniquely challenging synthetic targets and, despite numerous efforts, have been prepared by one group. In a tactical tour-de-force, Baran and coworkers synthesized axinellamines^[3] (**1** – Figure 1), massadines and palau’amine from a common intermediate.^[4] This work evolved in stages, and beautifully leveraged collaborative re-interpretation of data on natural samples to confirm a uniform stereochemistry for the set.^[5] A refined synthesis of (±)-axinellamines A and B has also been reported by the Baran lab.^[6]

Among the creative ways envisioned to prepare structures **1**^[7], a strategy reminiscent of early biosynthetic proposals^[8] was attractive to us. The core of the molecules would derive from a homodimeric precursor, whose oxidative desymmetrization with hypochlorite would install the halogenated spirocycle.^[9] Notwithstanding the tenuous and challenging prospect of carrying two basic guanidine units intact through the synthesis, this approach was intuitive and direct. For reasons discussed previously^[9], we chose to work with an oroidin synthon at higher oxidation state and targeted a dispacamide dimer (e.g. **2**) as our key intermediate. The intention was to initiate oxidative spirocyclization at this stage and subsequently diverge to **1** and related structures. Here we report a unique system wherein alkylidenes of type **2** actually exist as an alternate set of equilibrating structural isomers. The full ensemble spirocycloisomerizes with ease under non-oxidative conditions. This has allowed us to synthesize axinellamines in partially halogenated forms – providing new synthetic variants of the natural products that may prove useful in medicinal and biochemical research.

**Funding provided by the NIH (RO1-GM60591), the Donald J. & Jane M. Cram Endowment, the Foote Family Endowment (fellowship to A.G.R.) and a major instrumentation grant from the National Science Foundation (CHE-1048804). We are grateful to Dr. Saeed Khan (UCLA) for X-ray crystallographic analyses. We thank the Garcia-Garibay laboratory for access to instrumentation. We are grateful to Dr. Paul B. Hurley and Robert S. Jordan for experimental assistance.

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Methyl-5-bromo-2-oxopentanoate (**3** – Scheme 1) is available on mole scale by degrading carboethoxylated γ -butyrolactone with HBr/AcOH and Fisher esterifying the resultant α -ketoacid.^[10] When **3** is condensed with pyrrole-2-carboxylic acid hydrazide (**4**) and the product saponified *in situ*, we obtain tetrahydropyridazinecarboxylic acid **5** in high yield. The acid chloride derived from **5** is then used to N-acylate thiourea derived methylisothiourea **6**.^[11] In developing this procedure, we observed that crude product **7** was often contaminated with small amounts of **8** – the desired product from what was to be the next step in our sequence. Control experiments established that pure **7** was cleanly converted to **8** when treated with oxalyl chloride alone. This allowed us to develop a one-pot procedure wherein **5** is transformed to **8** via the intermediacy of **7** (Scheme 1). Ring closure occurs *in situ* via net expulsion of methylmercaptan^[12] to afford tricyclic glycoamidinium **8** in good overall yield. We are not aware of the ring systems in **7** and **8** being reported previously.

The pyrrole nitrogen in **8** is silylethylmethoxylated to increase solubility. Derivative **9** is then mixed with diisopropyltitanocene dichloride in THF and cooled to -78°C prior to treatment with potassium hexamethyldisilazide. The putative titanocene dienolate formed is oxidized *in situ* with cupric triflate to initiate regioselective homodimerization at the enolate γ position.^[13] C_2 symmetric product **10a** is separated from its *meso* counterpart (d.r. ~1.2:1) and hydrogenated in the presence of Wilkinson's complex to afford a four-electron reduction product in high diastereomeric excess. This material is then tetrabrominated using NBS to afford **11**. When **11** is added to a solution of 18-crown-6 containing a two-fold excess of potassium hexamethyldisilazide at -78°C , both hydrazide N-N bonds undergo cleavage.^[9b] Presumably this occurs via sequential or cascading enolate formation/ β -elimination pathways. Based on our own precedent as well as results found using a monomeric model^[14], we anticipated a bis-alkylidene of type **2** (Figure 1) would form in this reaction. Inexplicably, no such material is detected. Rather we isolate two separable fractions of bis-spiroaminal isomers **12**, wherein the tethered amides have 5-exo cyclized onto imino tautomers of the target alkylidenes. Analyses of crude reaction mixtures show one diastereomer of **12** predominates; yet several isomeric variants are present in lesser amounts. If one treats purified major isomer **12b** with TFA followed by workup with aqueous NaHCO_3 ^[15], X-ray crystallographic analysis of product **13** shows it to possess the relative stereochemistry we tentatively assign to **12b**.^[16]

Structural dynamics in this system are fascinating and can be channeled. Stirring **12a** or **12b** with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) at RT, either individually or as a mixture, initiates isomerization to common monoalkylidene-containing spirocycles (diagnostically fluorescent upon UV irradiation)^[9a]. When these materials are treated with aqueous NH_4OH ^[17] followed by TFA; $\text{Et}_3\text{N}/\text{MeOH}$, we obtain fully unmasked spirocyclic bis-guanidines **14** as a favorable mixture of C14 epimers.^[18]

After **14a** is isolated by preparative HPLC, advancement to the axinellamine ring system occurs in three carefully orchestrated steps. First, a THF solution of **14a** is warmed with Myers' lithium amidotrihydroborate (LAB).^[19] This gradually deoxygenates C5 to give an intermediate having ^1H NMR data consistent with an alkylidene aminoimidazoline (namely, **15**).^[20] This substance can be isolated (impure), but is typically not. Rather, the reaction is quenched and stirred with 10% aqueous TFA at 60°C for several hours. This sequesters residual boron away from reaction products while migrating the alkene to afford an aminoimidazole. The bis-trifluoroacetate salt of C10,C11 anti diastereomer **16a**^[21] is isolated by preparative HPLC and oxidized with 3-(3-nitrophenyl)-2-(phenylsulfonyl) oxaziridine **17** in aqueous THF.^[22,23] This initiates a net aminohydroxylation of the imidazole to provide a C9 angularly hydroxylated C5 aminal and its epi-C5,C9 diastereomer (confer **1a** vs **1b**) in roughly a 4:1 ratio following preparative HPLC purification on a fluorinated stationary phase. Attempts at similarly 'biomimetic' oxidations of related

substrates reduced at C1 were reported unsuccessful.^[4e] Here the oxidation proceeds smoothly. Low isolated yields reflect the difficulty in purifying individual diastereomers by HPLC. Exposing the major isomer to an excess of aqueous SmI₂ rapidly and selectively debrominates at C6' and C6'' and then more slowly reduces the C1 carbonyl to the corresponding hemiaminal. Product **18**^[24] uniquely combines a non-chlorinated axinellamine A core structure with the monobrominated pyrrole units common to sceptrins and ageliferins.

The total synthesis of non-chlorinated (±)-axinellamine A congener **18** occurs in 13 operations. The route is concise and features a host of unusual and unexpected reactions. The use of formaldehyde/thiourea composite heterocycle **6** as both a guanidine precursor and reactivity mask is new, as are the LAB and SmI₂ mediated glycoamidinium reductions. Notably, final oxidation state at both C1 and C5 in **18** derives from reductive events, rather than oxidation.^[4] The structural plasticity of dimers **12**, including the ease and fidelity with which they isomerize, holds considerable promise. As we learn to further manipulate these complex spiroaminals, there is potential to synthesize numerous additional members of this alkaloid family. Doing so, we are well positioned to evaluate the impact of core and peripheral halogenation on biological activities. Work along these lines is ongoing, as are efforts to improve stereocontrol in key steps and to generate optically active products.

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- [18]. Treatment of amins 12 with TBD provides two spirocyclic products (S-8a, S-8b). We have discussed mechanistic possibilities for related transformations previously (ref. 9a). When the major isomer (S-8a) is exposed to TFA followed by aqueous base work-up and the resultant material acylated with $\text{O}(\text{CO}_2\text{tBu})_2$, X-ray crystallographic analysis shows the product to be S-9 (ref. 16). Fully deprotecting S-8a in the manner shown in Scheme 2 (step g), affords two geometric isomers of 14a, but no 14b. Both isomers of 14a convert to products 16 upon LAB reduction. Consistent with their stereochemical assignments, S-8b is likewise converted to two isomers of 14b, neither of which give 16a or 16b after LAB reduction.
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- [21]. C10, C11 anti stereochemistry in 16a is assigned based upon ^1H NMR chemical shift and coupling constant data (C10H, δ 3.28, d, $J = 11.6$ Hz) as well as T-ROESY correlations relative to its C10, C11 syn counterpart (see Supporting Information).
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Figure 1.

Scheme 1.

Reagents and conditions: a) **4**, HOAc/MeOH, 0°C; **3**, 0°C to RT, 1h; adjust to pH 6 (3M aq. K₂CO₃), 65°C, 1h; 2.0 eq LiOH, THF/H₂O, -10°C, 45 min, 89%; b) **5**, 1.0 eq (COCl)₂, 1 mol % DMF, CH₂Cl₂, RT, 3h; 1.8 eq **6**, 1.8 eq Et₃N, CH₃CN, RT, 5h; 1.0 eq (COCl)₂, 45 min, RT, 55%; c) **8**, 18-crown-6, KO^tBu, THF, -10°C, 3 min; 1.1 eq ClCH₂OCH₂CH₂Si(CH₃)₃, -10 °C, 5 min, 60%.

Scheme 2.

Reagents and conditions: a) **9**, 1.05 eq $[i\text{-PrCp}]_2\text{TiCl}_2$, THF, -78°C , 10 min; 1.2 eq KHMDS, -78°C , 30 min; 1.5 eq $\text{Cu}(\text{OTf})_2$ (slurry in THF), -78°C , 3 h, 55%, d.r. = 1.2:1 (*C*₂/*meso*); b) 0.6 eq $\text{CIRh}(\text{PPh}_3)_3$, 600 psi H_2 , THF, 40°C , 3 d, 67% c) 4.0 eq NBS, THF, -10°C , 45 min, 57%; d) 3.5 eq 18-crown-6, 4.0 eq KHMDS, THF, -78°C ; dilute with EtOAc, quench with phosphate buffer (pH 7.8), 15% of **12a**, 39% of **12b**; e) **12b**, TFA, CH_2Cl_2 , RT; sat. aq. NaHCO_3 , **13** (crystals from *n*PrOH/THF – see ref. 16); f) **12a** + **12b**, 1.2 eq TBD, THF, RT, 1 h (see ref. 18); g) aq. NH_4OH , DME/ H_2O (4:1), 120°C , 90 min; TFA, CH_2Cl_2 , RT, 1 h; Et_3N , MeOH; 43% of **14a** over two steps following preparative HPLC; h) **14a**, excess $\text{Li}[\text{NH}_2\text{BH}_3]$, THF, 60°C , 10 h; TFA/ H_2O (1:9), 60°C , 4 h, 13% of **16a**, 26% of **16b** (see Supporting Information); i) **16a**, 1.4 eq **17**, TFA/ H_2O (1:9), 55°C , 5 h, 26%, d.r. = 4:1; j) major isomer, excess SmI_2 , THF/ H_2O , -40°C to RT, 45%. KHMDS = potassium hexamethyldisilazide, TBD = 1,5,7-Triazabicyclo[4.4.0]dec-5-ene, DME = 1,2-Dimethoxyethane. Products from step (g) forward are isolated by preparative HPLC as trifluoroacetate salts. Free base forms of **14** and **16** are stable and are drawn for clarity.

Footnote_14.

Footnote_17.

Footnote_18.

Footnote_20.