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VIP **Synthetic Methods**

Synthetic (±)-Axinellamines Deficient in Halogen**

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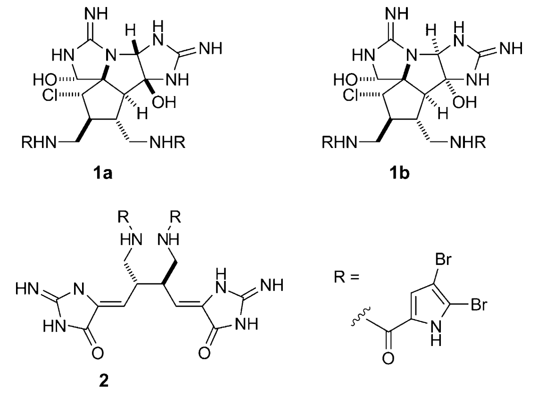
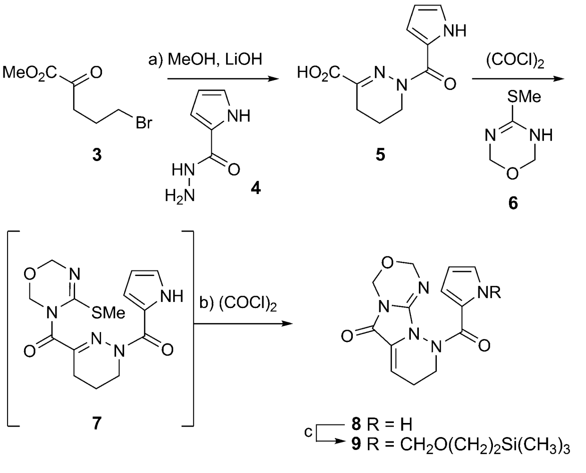
Pyrrole/imidazole alkaloids isolated from marine organisms have drawn attention from laboratories worldwide. Their structures, biosynthetic origins, preliminary biochemical activities, and chemical syntheses form an extensive literature.[1] This family of compounds contains hundreds of members, often 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 co-workers synthesized axinellamines[3] (**1**, Scheme 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 research group.[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, and oxidative desymmetrization of which with hypochorite 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 a higher oxidation state, and targeted a dispacamide dimer, for example **2**, as our key intermediate. The intention was to initiate oxidative spirocyclization at this stage and subsequently diverge to **1** and related structures. Herein, 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, thus providing new synthetic variants of the natural products that may prove useful in medicinal and biochemical research.



Scheme 1. Axinellamines A (**1a**) and B (**1b**) and hypothetical dispacamide dimer **2**.

Methyl-5-bromo-2-oxopentanoate (**3**, Scheme 2) is available on a mole scale by degrading carboethoxylated γ-butyrolactone with HBr/AcOH and esterifying the resultant α-ketoacid by the Fisher protocol.[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 thiouron-derived methylisothiourea **6**.[11] In



Scheme 2. Reagents and conditions: a) **4**, HOAc/MeOH, 0 °C; **3**, 0 °C to RT, 1 h; adjust to pH 6 (aq K_2CO_3 (3 M)) 65 °C, 1 h; LiOH (2.0 equiv), THF/H_2O, −10 °C, 45 min, 89 %. b) **5**, $(COCl)_2$ (1.0 equiv), DMF (1 mol %), CH_2Cl_2, RT, 3 h; **6** (1.8 equiv), Et_3N (1.8 equiv), CH_3CN, RT, 5 h; $(COCl)_2$ (1.0 equiv), 45 min, RT, 55 %. c) **8**, [18]crown-6, KO*t*Bu, THF, −10 °C, 3 min; $ClCH_2OCH_2CH_2Si(CH_3)_3$ (1.1 equiv), −10 °C, 5 min, 60 %.

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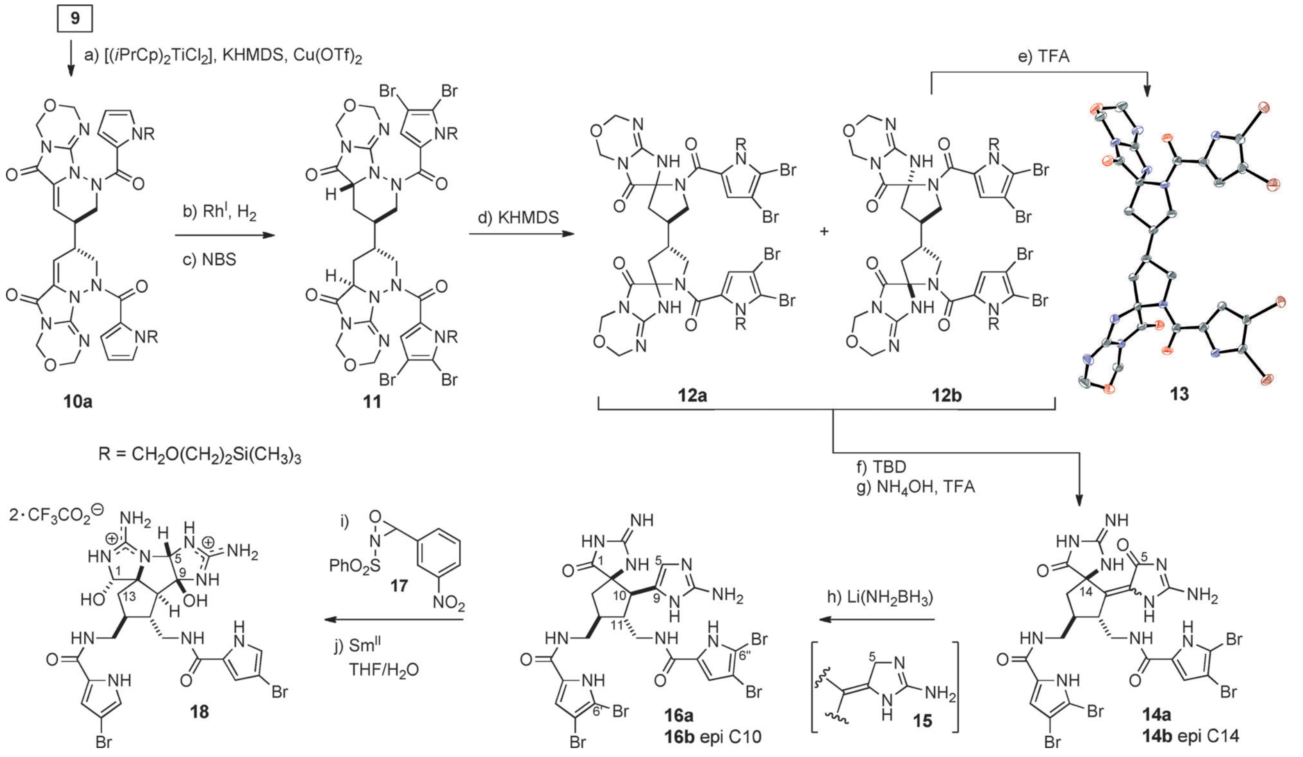
developing this procedure, we observed that crude product **7** was often contaminated with small amounts of **8**, the desired product from what was to be the next step in our sequence. Control experiments established that pure **7** was cleanly converted into **8** when treated with oxalyl chloride alone. This allowed us to develop a one-pot procedure wherein **5** is transformed to **8** via the intermediacy of **7** (Scheme 2). Ring closure occurs in situ by the net expulsion of methylmercaptan[12] to afford tricyclic glycocyamidine **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 derivatized with 2-(trimethylsilyl)ethoxymethyl chloride to increase solubility. Product **9** is then mixed with diisopropyltitanocene dichloride in THF and cooled to −78 °C prior to treatment with potassium hexamethyldisilazide (KHMDS, Scheme 3). 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. ca. 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 *N*-bromosuccinimide (NBS) to afford **11**. When **11** is added to a solution of [18]crown-6 containing a two-fold excess of KHMDS at −78 °C, both hydrazide N−N bonds undergo cleavage.[9b] Presumably this occurs by 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 bisalkylidene of type **2** (Scheme 1) would form in this reaction. Inexplicably, no such material is detected. Rather, we isolate two separable fractions of bisspiroaminal 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 and subsequently 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 room temperature, 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 and Et_3N/



Scheme 3. Reagents and conditions: a) **9**, $[(iPrCp)_2TiCl_2]$ (1.05 equiv), THF, −78 °C, 10 min; KHMDS (1.2 equiv), −78 °C, 30 min; $Cu(OTf)_2$ (1.5 equiv, slurry in THF), −78 °C, 3 h, 55 %, d.r. = 1.2:1 (C_2/*meso*). b) $[ClRh(PPh_3)_3]$ (0.6 equiv), H_2 (600 psi), THF, 40 °C, 3 d, 67 %. c) NBS (4.0 equiv), THF, 0°C, 45 min, 57 %. d) [18]crown-6 (3.5 equiv), KHMDS (4.0 equiv), 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 *i*PrOH/THF, see Ref. [16]). f) **12a** + **12b**, TBD (1.2 equiv), THF, RT, 1 h (see Ref. [18]). g) aq NH_4OH, 1,2-dimethoxyethane/H_2O (4:1), 120 °C, 90 min; TFA, CH_2Cl_2, RT, 1 h; Et_3N, MeOH; 43 % of **14a** over two steps after preparative HPLC. h) **14a**, excess $Li(NH_2BH_3)$, THF, 60 °C, 10 h; TFA/H_2O (1:9), 60 °C, 4 h, 13 % of **16a**, 26 % of **16b** (see the Supporting Information). i) **16a**, **17** (1.4 equiv), 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 %. Products from steps g)–j) were isolated by preparative HPLC as trifluoroacetate salts. Free-base forms of **14** and **16** are stable and are drawn for clarity.

MeOH, we obtain fully unmasked spirocyclic bisguanidines **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 solution of **14a** in THF is warmed with Myers' lithium amidotrihydroborate (LAB).[19] This gradually deoxygenates C5 to give an intermediate that has ^{1}H 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 step sequesters residual boron away from reaction products while migrating the alkene to afford an aminoimidazole. The bistrifluoroacetate 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 procedure initiates a net aminohydroxylation of the imidazole to provide a C9 angularly hydroxylated C5 aminal and its epi-C5,C9 diastereomer (compare **1a** versus **1b**) in roughly a 4:1 ratio after 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 SmI$_2$ rapidly and selectively debrominates at C6′ and C6″ and then more slowly reduces the C1 carbonyl group to the corresponding hemiaminal. Product **18**[24] uniquely combines a nonchlorinated axinellamine A core structure with the monobrominated pyrrole units common to sceptrins and ageliferins.

The total synthesis of nonchlorinated (±)-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 SmI$_2$ mediated glycocyamidine 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. In 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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Keywords: alkaloids · axinellamines · dispacamide · natural products · spiro compounds

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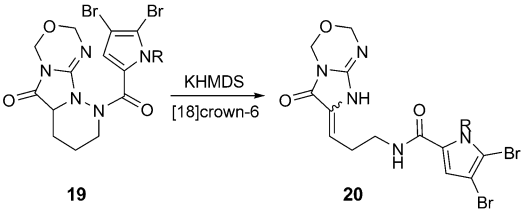
[11] Isothiourea **6** (m.p. 124–126 °C, *i*PrOH/hexanes) is prepared directly from thiourea, formalin, and methyl iodide using a modified protocol: C. D. Egginton, C. P. Vale, *Text. Res. J.* **1969**, *39*, 140–147. See the Supporting Information.

[12] Stoichiometric HgCl$_2$ was required to achieve a related ring closure in a previous series (Ref. [9b]).

[13] Of many oxidants examined, only the Livinghouse reagent [(CF$_3$CH$_2$O)V(O)Cl$_2$] provides **10** in a yield and with regiose-

lectivity comparable to reactions with $Cu(OTf)_2$: K. Ryter, T. Livinghouse, *J. Am. Chem. Soc.* **1998**, *120*, 2658–2659.

[14] Under identical reaction and work-up conditions, treatment of **19** with KHMDS affords solely alkylidenes **20**. It is not yet clear why corresponding dimers **12** exist in spiroaminal forms.



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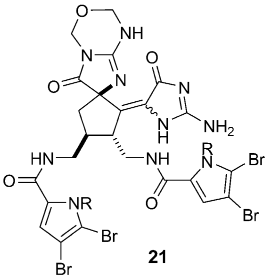
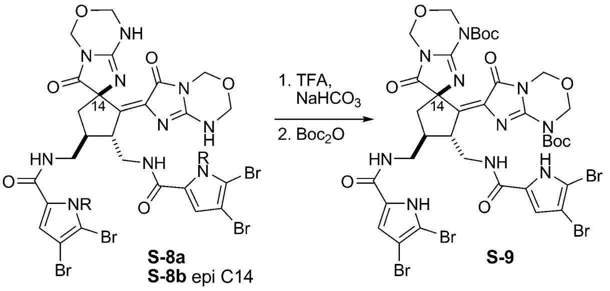
[16] CCDC 859078, 859079, 859080 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Initially we observed isomers **12** would convert into **21** upon prolonged heating in DMF (110°C). We speculated that trace Me_2NH was responsible for the oxadiazine degradation that occurred. Aqueous NH_4OH was subsequently found to promote full deprotection. This is in contrast with acidic hydrolyses in these systems, which afford largely hydantoin products.



[18] Treatment of aminals **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, then subsequently worked-up with aqueous base and the resultant material acylated with $O(CO_2t\text{Bu})_2$, X-ray crystallographic analysis shows the product to be **S-9** (Ref. [16]). Fully deprotecting **S-8a** in the manner shown in Scheme 3 (step g), affords two geometric isomers of **14a**, but no **14b**. Both isomers of **14a** are converted into products **16** upon LAB reduction. Consistent with their stereochemical assignments, **S-8b** is likewise converted into two isomers of **14b**, neither of which give **16a** or **16b** after LAB reduction.



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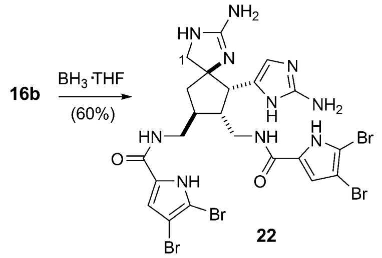
[20] Diastereotopic C5 methylene protons in **15** appear as a signature spectral pattern: (**15**, bis-TFA salt) ^{1}H NMR (600 MHz, CD_3OD): $\delta = 4.40$, 4.12 ppm (AB, $J_{AB} = 16.2$ Hz, 2H). This compares to the C1 methylene protons in borane reduction product **22** derived from **16b**: (bis-TFA salt) ^{1}H NMR (600 MHz, CD_3OD): $\delta = 3.70$, 3.55 ppm (AB, $J_{AB} = 11.2$ Hz, 2H).



[21] The C10,C11 *anti* stereochemistry in **16a** is assigned based upon ^{1}H NMR chemical shift and coupling constant data (C10H, $\delta = 3.28$ ppm, d, $J = 11.6$ Hz) as well as T-ROESY correlations relative to its C10,C11 *syn* counterpart (see the Supporting Information).

[22] A brief treatment with $KMnO_4$ (1 equiv, acetone/water, −30°C, < 1 min) also generates the axinellamine ring system from **16a**, albeit in lower yield.

[23] Oxaziridines are known to oxidize imidazoles and 2-amino-imidazoles: P. B. Koswatta, R. Sivappa, H. V. Rasika Dias, C. J. Lovely, *Synthesis* **2009**, 2970–2982.

[24] The ^{1}H NMR spectra of **18** closely resemble those of natural axinellamine A (Ref. [3]). Characteristic ^{1}H NMR (600 MHz, $[D_6]$DMSO) signals include $\delta = 4.81$ ppm (C1H, d, $J = 6.3$ Hz) and $\delta = 5.15$ ppm (C5H, s) and a diagnostic NOE correlation between C13H(β) and C5H. See the Supporting Information.