Spirocycloisomerization of Tethered Alkylidene Glycocyanamides: Synthesis of a Base Template Common to the Palau’amine Family of Alkaloids**

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In 1993 Scheuer, Kinnel, and co-workers described the structural elucidation of palau’amine (1), an antimicrobial principle isolated from extracts of the marine sponge Stylotella aurantium.[11] This substance inhibits both bacterial and fungal growth. It has the additional ability to block stimulated T-cell proliferation in vitro, yet remains relatively innocuous toward resting lymphocytes. The mechanism(s) underlying this immunsospressive property is not known. As a step toward the preparation of molecules useful for its exploration, we describe herein a new spirocyclization process—one with potential to support a synthesis of palau’amine as well as its constitutional relatives axinellamine (2) and massadine (3).[9]

Polycyclic bisguanidines 1–3 are members of a larger alkaloid family whose precise biosynthetic origin is a subject of speculation.[12–14] Until recently, imidazole 4 was considered likely feedstock for the group.[12a,c] New observations challenge that idea.[9] However, from the synthetic perspective,[7] casting structures 1–3 from 4 remains a useful exercise. Substructure 4 can be traced twice within polycycles 1–3 (Scheme 1). In each instance, the monomers are oriented head-to-head with bonds a and b forming a common embedded cyclopentane. The relative stereochemicals of substituents that emanate from this core differ in 1–3. Such spatial variations offer a rationale for how conserved events, initiated oxidatively after or during formation of the cyclopentane ring, could diverge to the observed ring systems—those similarly constituted but alternately linked.[14] We report herein a core substrate type prone to form bond a in a spirocyclization applicable to all three targets.

Scheme 2 details how the reaction could operate in the palau’amine case. This specific example parallels the general biosynthetic postulates of Al-Mourabit and Potier.[16] The natural product is thought to be accessible from intermediate 5, in which reductions at C20 and C6 and a net dehydration to install the C6 diaminal would be required to produce 1.[9] The guanidine units in 5 are now both part of glycocyanamide[9] rings. The right-hand spirocyclic is reminiscent of an intermediate proposed in the oxidative synthesis of dibromophakellin from dihydrooroidin by Büchi and Foley.[13] Analogously, albeit at a higher oxidation state, this portion of the palau’amine structure could arise from internal trapping of C-acyl iminium ion 6 (as indicated). Notably, ion 6 may be in equilibrium with fragmented species 7, itself another C-acyl iminium ion. The latter could be formed by the action of chloronium ion on pseudosymmetric bisalkylidene 8. If this were possible, hypohalite oxidations of 8 could initiate the formation of two rings and four new stereocenters in a single operation (8–5).

The stereochemical outcome of such a process depends on several factors. However, our initial goal was to validate the construction itself. Spirocyclization within intermediate 7 requires its tethered heterocycles to stack in parallel, which forces both the external electrophile and internal nucleophile to approach from trajectories peripheral to this self-assembled unit (A/B). Carbon–carbon bond formation would necessarily intervene. The reactivity sought is analogous to that observed in the oxidation of 1,5-cyclooctadiene with halogen to give bicyclooctane products (9–10, Scheme 2).[10] In that case, the olefins are spatially constrained and communicate transannularly during the reaction. In our case, substrate conformation would be relied upon to dictate comparable results.

We first needed to assess the behavior of an isolated alkylidene glycocyanamide toward electrophilic halogen. Heterocycle 11[11] was condensed with isobutyraldehyde in the presence of N,N-dimethylethylene diamine monotosylate as catalyst[12] to afford alkylidene 13 (Scheme 3). When this material was treated with tBuOCl in glacial AcOH, epimeric vicinal chloroacetoxyltation products 14 were produced efficiently. Angular acetates 14 are themselves unstable, although methanolyisis affords isolaole congeners 15—materials that have been fully characterized. These results confirm a desired “enamine” type reactivity of the alkylidene in 13 towards hypohalite.[13]

We next examined if similar chemistry executed on a dimeric substrate would result in spirocyclization. The original plan was to retain the substitution pattern of 13 in this dimer. The condensation of 11 with dialdehydes was unproductive. However, we did observe that glycocyanamide 12 could be dehydrogenated to alkylidene 13 with SeO2.[14] (Scheme 3). Performing this reaction twice on tethered bisglycocyanamide 16 appeared a means to access target 17 (Scheme 4A). A synthesis of 16 was developed that begins with 1,4-dibromo-2-butyne and elaborates symmetrically in two directions.[15] Interestingly, with 16 in hand, it was apparent that the properties of this molecule were not those intended. The substance readily formed insoluble aggregates. Under conditions in which dehydrogenation to 17 was possible, both materials were almost completely insoluble. Conversion was low and the isolation of even small quantities...
Scheme 1. Palau’amine (1) and its constitutional relatives axinellamine A (2) and massadine (3) can be viewed as dimeric composites of conserved subunit 4.[4a]

Scheme 2. Retrosynthesis of palau’amine identifies a core spirocyclization relevant to structural types 1–3.
of 17 in pure form was a painstaking exercise. Compound 17 has the functionality to test our key idea, but is otherwise a poor model. The goal was a substrate whose heterocyclic termini could associate internally to facilitate the cyclization illustrated in Scheme 2. Treatment of 17 with hypochlorite initiated no such event,[16] probably reflecting, as does its solubility profile, an unwanted preference for bimolecular association. The arrangement of 17 in the crystalline state supports this idea. The unit cell contains four molecules of 17 (8 asymmetric units, space group C21/c), each in extended conformation with their glycocamidine rings interacting bimolecularly through multiple H bonds (Scheme 4B).[17]

Another design was needed—one in which the guanidine units are more properly managed. As a means to disrupt bimolecular hydrogen bonding, we considered repositioning the N1 benzyl unit on each heterocycle to N2. Alone, the change was synthetically awkward, but the incorporation of both N2 and N3 into a 2,4-benzodiazepine appeared workable. Compound 18 (Scheme 5) became the target. Computer simulations suggested this molecule would adopt compact globular forms in polar solvents, positioning the alkylidene units appropriately for subsequent oxidative spirocyclization. With N1 unsubstituted, Z-alkylidene geometry in 18 was expected to be thermodynamically favored. How to install this unsaturation was the pivotal question. We eventually adopted an approach based on basic degradation of sulfonamides. Overman and Trenkle had shown that a potassium enolate of 19 fragments with loss of the 2-trimethylsilylethylsulfinate ion, affording an imine product that tautomerizes to enamine 20 in situ.[18] A related transformation, executed twice on bissulfonamide 23, was considered a method to produce 18. Whereas the ring system in 23 was unknown, it could be prepared concisely. The route used to synthesize 16 was adapted to access the 2,7-diaminosuberic acid derivative 21.[19] Condensing this material with a twofold excess of o-xylyldiamine-derived methylisothiourea 22[19] provided 23 directly. The seco amides presumably formed transiently in the reaction cyclized spontaneously, with ejection of methanethiol at each end of the molecule.

With 23 available, we examined its response to base. Exposure to KHMDS caused degradation. However, when the compound was treated with DBU in DMF, monoalkylidene 26 formed rapidly (Scheme 6). This material was isolated without incident. When 26 was reexposed to DBU, two new products emerged in high yield. Surprisingly, neither was found to be bisalkylidene 18. Rather, they proved to be geometric isomers of spirocyclization product 24.[17] When the reaction was per-
formed in [D]-DMF and monitored periodically by $^1$H NMR spectroscopy (Scheme 6 inset), a progression of events became evident. Within 10 minutes, DBU converted 23 into 26. During the next hour, a second olefinic triplet ($\delta = 5.23$ ppm) became more prominent, although concurrently with signals corresponding to rearrangement products 24. The system siphoned completely to the latter within 10 h.

We noted that the ratio of isomers 24 changed during the experiment. It was likewise possible that the second alkene signal reflected equilibration of 26 with an isomeric monoalkylidene and that target bisalkylidene 18 was not observed, or perhaps even formed, under these conditions. To address this question, we synthesized nonsymmetric monosulfonamide 25 and subjected it to identical elimination conditions. Like 23, 25 rapidly converted into a monoalkylidene (namely, 27). Notably, carbamate 27 was inert to further degradation and did not equilibrate with a second product over time, which implies the second olefinic signal in the original experiment is itself reflective of symmetric bisalkylidene 18.

This is precisely the behavior we had hoped to see. Whereas 18 was designed to participate in a spirocyclization initiated by hypohalite, the molecule is apparently so well-poised for the reaction that a proton is sufficient provocation. Compound 18 cannot be isolated, and available data does not distinguish whether carbon–carbon bond formation occurs through: 1) C directly, perhaps catalyzed by salt 28; 2) imino tautomer D; or 3) inner salt E, the product of net proton transfer from C12 to C12' within D. Nevertheless, the outcome validates the central tenet of our approach to 1–3 (Scheme 1 and Scheme 2). Moreover, the markedly different reactivities of bisalkylidenes 17 and 18, with the former showing no inclination to cycloisomerize (Scheme 4), suggest the propensity for cyclization is tunable. In substrates substituted appropriately to complete the natural products, there should be ample opportunity to initiate analogous spirocyclization through chlorination (or oxygenation in the case of 3). Attempts to synthesize such substrates while attending to stereochemical parameters associated with the larger problem are ongoing.

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Scheme 6. Elimination of phenylsulfonic acid (2 equiv net) from 23 initiates a high-yielding spirocyclosomerization in situ. Real-time monitoring of the reaction by \(^1\)H NMR spectroscopy (DBU (2.2 equiv), one portion at \(t = 0\) min, 70 \(\mu\)M in [D\(_7\)]DMF, 400 MHz, 35 °C) implicates the successive intermediacy of 26 and 18. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

[9] Glycocyanamide nomenclature refers to cyclic anhydrides of α-guanidino carboxylic acids; the prototype is derived from glycine: C. Lempert, Chem. Rev. 1959, 59, 667–736; the equivalent IUPAC designation is 2-amino-1H-5-imidazolone.
[16] Treatment of 17 with tBuOCl in AcOH/CF\(_3\)CH\(_2\)OH provides vicinal bifunctionalization products in low yields, analogous to those generated from monomer 13 (Scheme 3) under similar conditions.
[17] Crystallographic data (excluding structure factors) for 17 and (Z)-24 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 250890 and CCDC 250891. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).