Natural Product Synthesis

Spirocycloisomerization of Tethered Alkylidene Glycocyamidines: 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*.[1] 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 immunosuppressive 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**)[2] and massadine (**3**)[3].

Polycyclic bisguanidines **1**–**3** are members of a larger alkaloid family whose precise biosynthetic origin is a subject of speculation.[1b,4,5] Until recently, imidazole **4** was considered likely feedstock for the group.[4a,c] New observations challenge that idea.[6] However, from the synthetic perspective,[7] casting structures **1**–**3** in terms of **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 stereochemistries 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.[4a] 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.[4a] 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**.[8] The guanidine units in **5** are now both part of glycocyamidine[9] rings. The right-hand spirocycle is reminiscent of an intermediate proposed in the oxidative synthesis of dibromophakellin from dihydrooroidin by Büchi and Foley.[5] 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 glycocyamidine 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 *t*BuOCl in glacial AcOH, epimeric vicinal chloroacetoxylation products **14** were produced efficiently. Angular acetates **14** are themselves unstable, although methanolysis affords isolable 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 glycocyamidine **12** could be dehydrogenated to alkylidene **13** with SeO_2[14] (Scheme 3). Performing this reaction twice on tethered bisglycocyamidine **16** appeared a means to access target **17** (Scheme 4 A). 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

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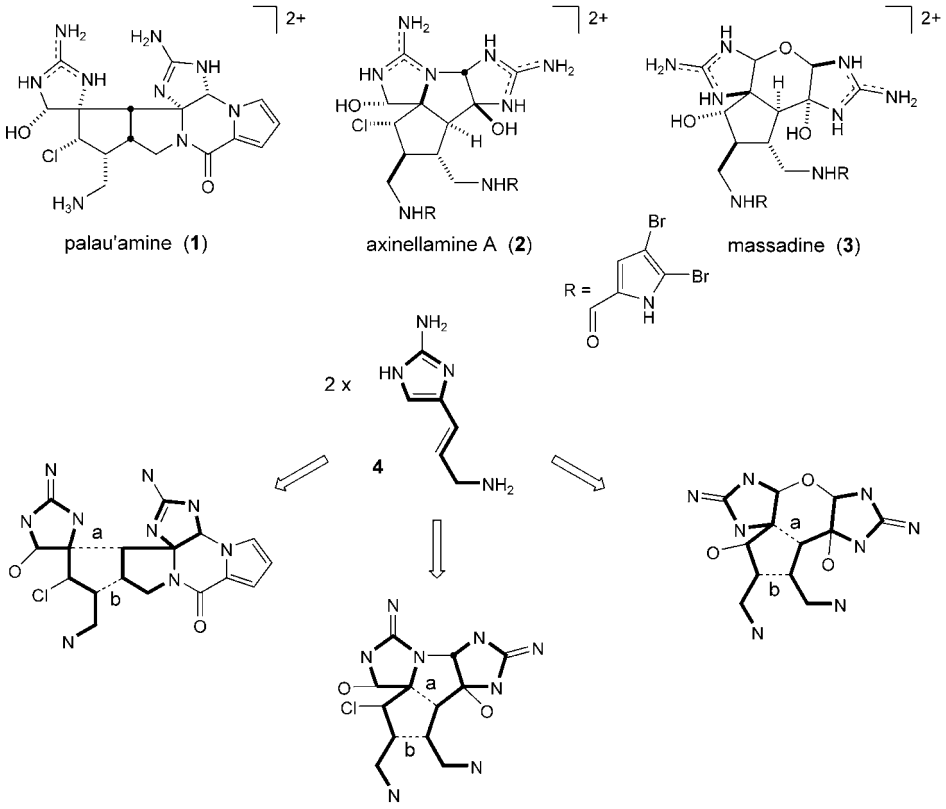
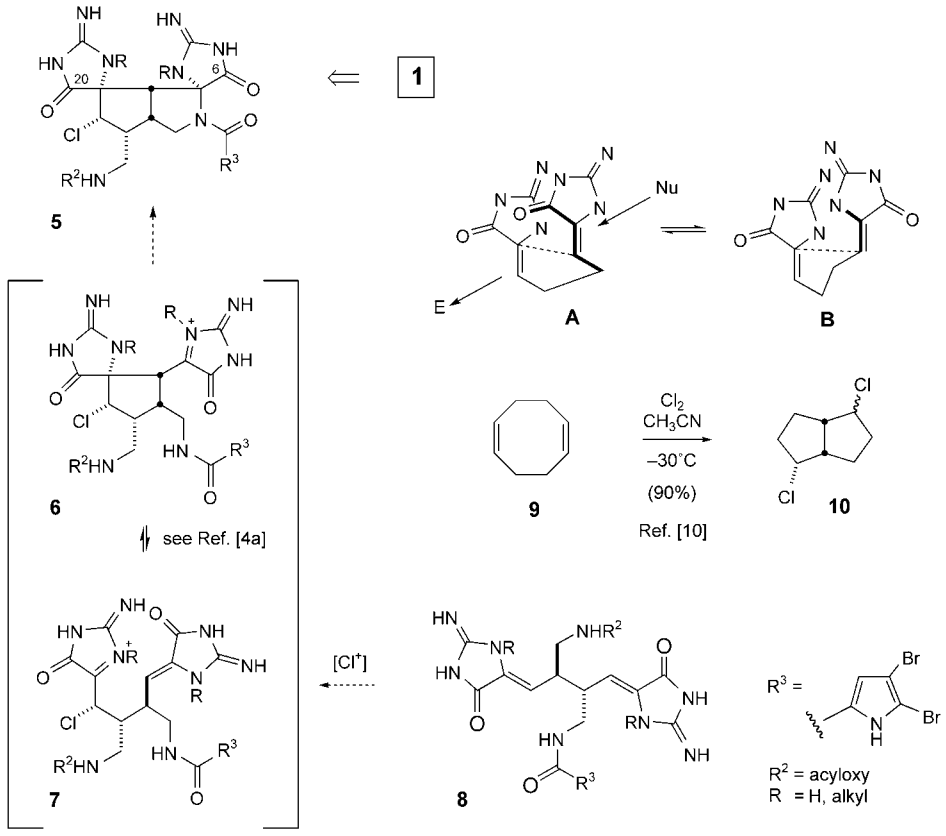
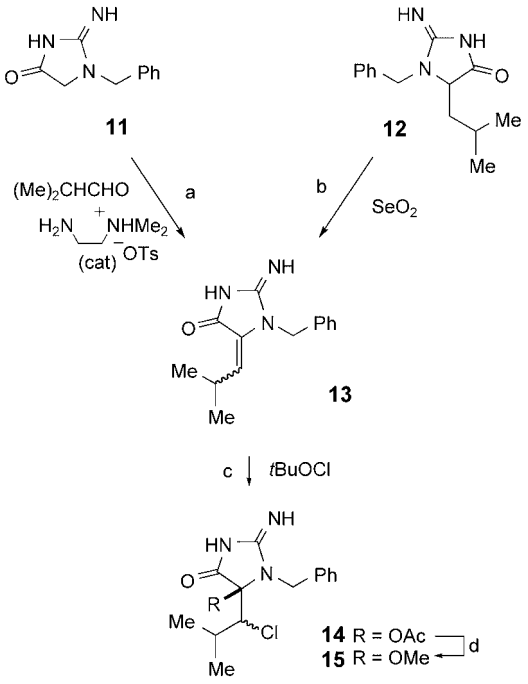


Scheme 1. Palau'amine (**1**) and its constitutional relatives axinellamine A (**2**) and massadine (**3**) can be viewed as dimeric composites of conserved subunit **4.**[4a]



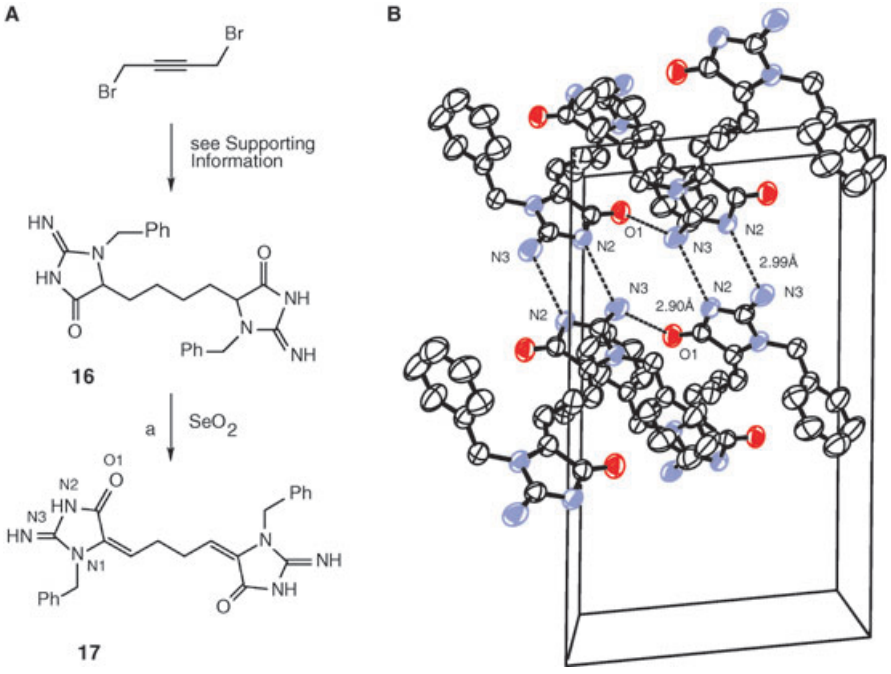
Scheme 2. Retrosynthesis of palau'amine identifies a core spirocyclization relevant to structural types **1**–**3**.



Scheme 3. Regioselective vicinal chloroacetoxylation of an alkylidine glycocyamidine. Reaction conditions: a) isobutyraldehyde (1.2 equiv), *N*,*N*-dimethylethylene diamine (30 mol%), *p*TsOH (30 mol%), DMF, microwave heating (150°C), 50 min (41%, *E*/*Z* = 5:1); b) SeO_2, *t*BuOH, 75°C, 2 h (75%); c) *t*BuOCl (1.1 equiv, neat), glacial AcOH, room temperature, 1 h (>80%-^{1}H NMR); d) silica gel, MeOH, room temperature, 6 h (95%). Ts = toluene-*p*-sulfonyl; DMF = *N*,*N*-dimethylfomamide.

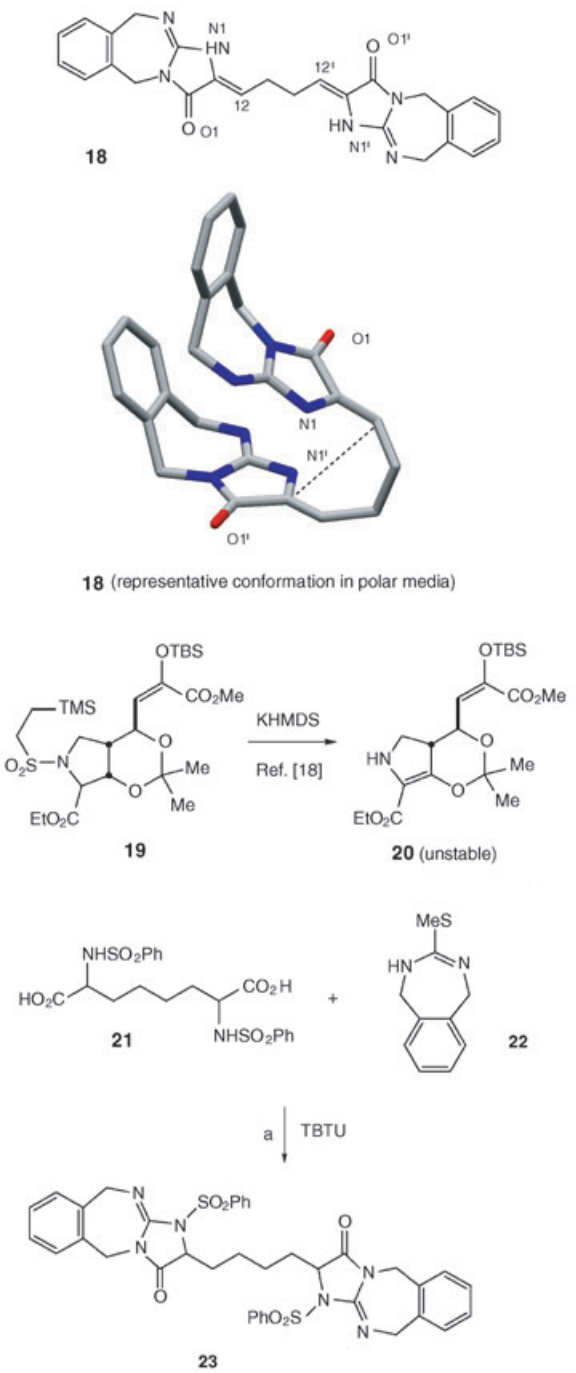
of **17** in pure form was a painstaking exercise. Compound **17** has the functionality to test our key idea, but is otherwise a poor model. The goal was a substrate whose heterocyclic termini could associate internally to facilitate the cyclization illustrated in Scheme 2. Treatment of **17** with 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 $C2_1/c$), each in extended conformation with their glycocyamidine 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**.[15] 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.



Scheme 4. Bisalkylidene **17** forms highly insoluble aggregates and proves to be an intractable model system. A) Reaction conditions: a) SeO_2 (1.4 equiv), *t*BuOH, 70°C, 4 h (5–7%). B) X-ray crystallography indicates the glycocyamidine rings in **17** associate bimolecularly through extensive hydrogen bonds. Partial unit-cell occupancy is shown (space group $C2_1/c$) in ORTEP format (50% probability thermal ellipsoids, hydrogen atoms omitted for clarity).

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 spirocycloisomerization product **24**.[17] When the reaction was per-



Scheme 5. Compound **18** is designed to have a diminished hydrogen bonding capability, which allows the structure to adopt conformations more readily that facilitate the intended carbon–carbon bond formation. Reaction conditions for the formation of **23**: a) TBTU, $(i\text{Pr})_2\text{NEt}$, **22** (2.2 equiv), CH_2Cl_2, RT (35%). TBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; KHMDS = potassium hexamethyldisilazide.

formed in $[D_7]$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 (δ = 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**[15] 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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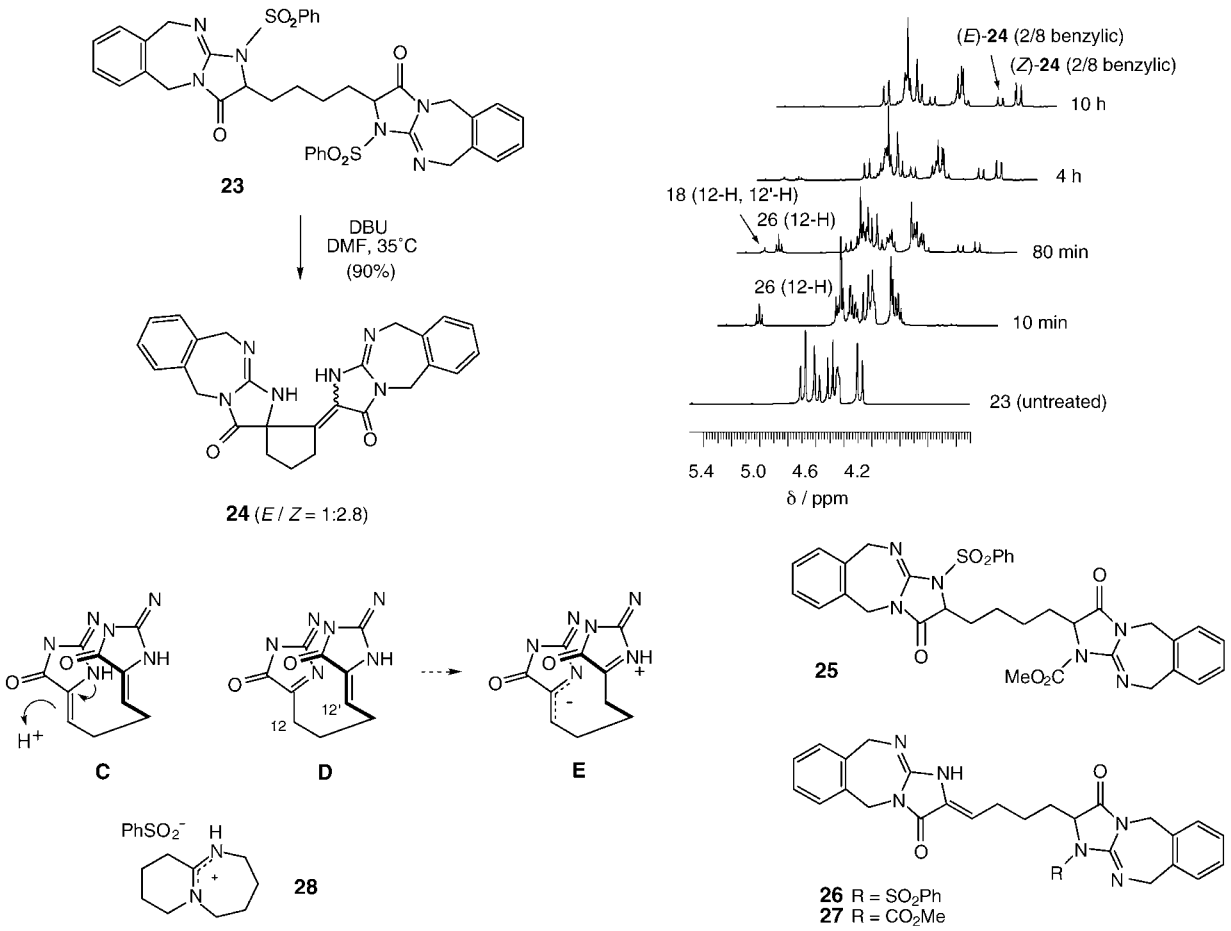

Scheme 6. Elimination of phenylsulfinic acid (2 equiv net) from **23** initiates a high-yielding spirocycloisomerization in situ. Real-time monitoring of the reaction by ^{1}H NMR spectrosopy (DBU (2.2 equiv), one portion at $t = 0$ min, 70 μM in [D_7]DMF, 400 MHz, 35 °C) implicates the successive intermediacy of **26** and **18**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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[16] Treatment of **17** with *t*BuOCl in AcOH/CF_3CH_2OH 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)..
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