A Three-Step Entry to the Aspirochlorine Family of Antifungal Agents**

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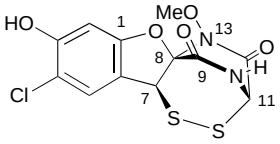
Dedicated to Professor Yoshito Kishi

Our laboratory has been studying a variety of natural products containing diketopiperazines (DKP) in the setting of indole alkaloid structures.[1] It was in this context that aspirochlorine (**1**), a bacterially derived metabolite isolated from various *Aspergillus* species, first caught our attention.[2] While initial reports on the biological properties of aspirochlorine had not been particularly encouraging, a recent disclosure from the Lepetit Research Center[3] indicated that this compound is a rather selective and potent inhibitor of fungal protein synthesis.



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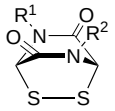

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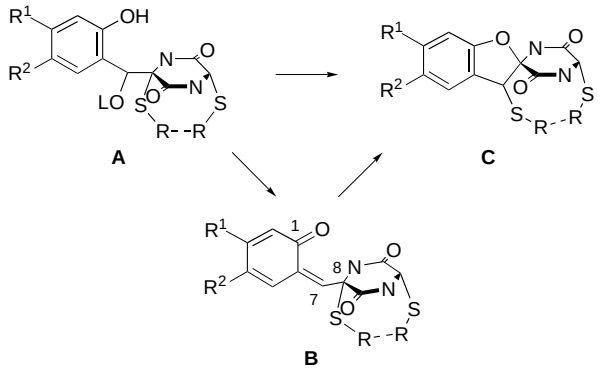
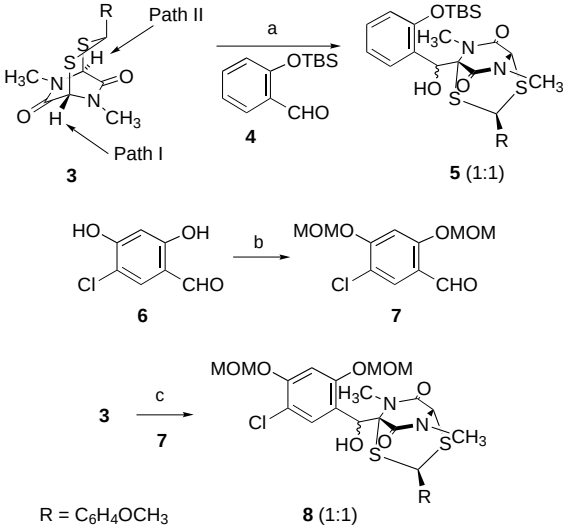
In addition to its increasingly attractive biological profile, aspirochlorine exhibits several structural features of particular interest. The epidithiodiketopiperazine (EDKP) moiety **2** is certainly well known in other natural products.[4] However, in the case of aspirochlorine one of the sulfur atoms is anchored not to the piperazine, but to the C(7) position of a spiro-fused dihydrobenzofuran substructure. Moreover, the two nitrogens of the DKP present novel structural characteristics as well. One of these nitrogens, N(13), bears a most unusual *N*-methoxy substituent, which is rarely present in DKP natural products. The other nitrogen atom is present in the form of a free NH linkage bearing a geminal sulfur atom. As such, there could well be concern over the possibility of a low energy, but destabilizing, pathway leading to acyl iminium character at C(11).[5]

These structural complexities notwithstanding, a total synthesis of aspirochlorine was accomplished by Williams and Miknis.[6] Our interest in revisiting the aspirochlorine problem, by a route quite different than that used in the previous synthesis, arose from a provocative, albeit unsupported, conjecture (Scheme 1). The thought was that the ring-enlarged dithio system present in **1** could arise from the rearrangement[7] of a more typical type of EDKP precursor **A**.[8] The electrophilic character that promotes rearrangement to **C** might arise directly upon heterolysis of the leaving group (OL) in **A**. Alternatively, loss of HOL from **A** might give rise to quinomethide **B**, which could serve as the active electrophile.[9] The ultimate hope in this case was that the sulfur migration step, though in principle reversible, might be followed by attack of the oxygen attached at position C(1) upon the now electrophilic C(8) bridgehead, thereby giving rise to the dihydrobenzofuran core of our target, **C**. While direct rearrangement of **A** to **C**, or rearrangement of **A** to **C** via **B**, implicitly raises issues of stereoselectivity at the migration terminus C(7), we postpone consideration of this interesting question until the results of the research are presented.



Scheme 1. Proposed sulfur rearrangement.

To evaluate the feasibility of such a functional group reorganization in a model system, we synthesized the known bicyclic thioacetal **3** (Scheme 2).[10] We were well aware of the



Scheme 2. Preparation of alcohols **5** and **8**. Conditions: a) BuLi, THF, then **4**, −78 °C, 40 %; b) MOMCl, *i*Pr$_2$NEt, DMF, 0 °C → RT, 95 %; c) BuLi, THF, then **7**, −78 °C, 67 %. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, RT = room temperature.

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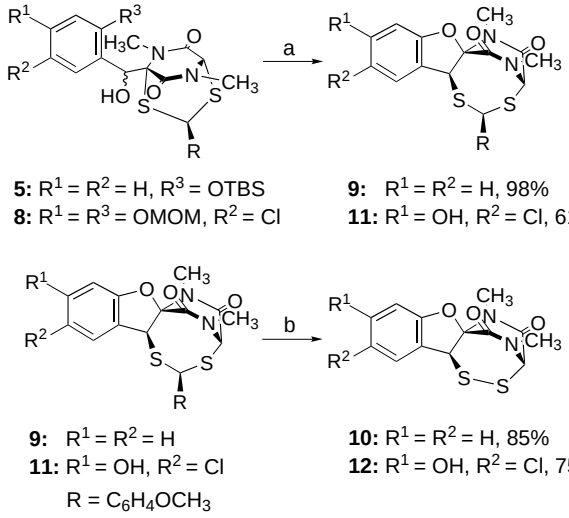
penetrating studies of Kishi and co-workers[11] which served to demonstrate that, in a system of this sort, deprotonation of the seemingly similar bridgehead protons may well occur with high diastereotopic selectivity. Indeed, based on the precedents of Kishi et al., it might be expected that deprotonation would follow the course suggested by Path I in preference to Path II. For our purposes it would be necessary to extend such findings to aldol-like reactions of such anions.[12]

Accordingly, we wondered about base-induced condensation of **3** with substituted benzaldehydes, such as **4**, with the expectation of reaching precursors of type **A**. Indeed, exposure of **3** to butyl lithium, at low temperature, followed by addition of **4** gave the corresponding alcohols **5** (Scheme 2). In a similar vein, a more realistic aldehyde **7** was prepared by protection of **6**[13] as the bis methoxymethyl ether. The condensation procedure was then executed to combine the anion of **3** with **7** and give the expected alcohols **8**. In each of these cases, NMR analysis indicated the formation of a two-component (1:1) mixture of products. At the time, we could not be certain whether the components of the mixture reflected stereochemical randomness in the deprotonation or in the C–C bond formation process. Nonetheless, we moved to the next phase of the synthesis.

We chose to start with simple acidolysis of the benzylic alcohol (Scheme 3). Remarkably, the action of anhydrous trifluoromethanesulfonic acid in acetonitrile on **5** furnished



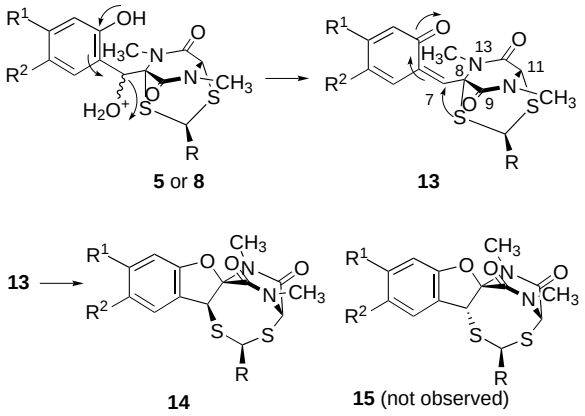
Scheme 3. Rearrangement of EDKPs **9** and **11**. Conditions: a) CF_3SO_3H, CH_3CN, RT; b) *m*CPBA, CH_2Cl_2, 0 °C; then Me_2S, then $HClO_4$ in MeOH, 0 °C → RT. *m*CPBA = *meta*-chloroperoxybenzoic acid.

exclusively a dehydration product as a single diastereomer and in near quantitative yield. We concluded that **5** was indeed a 1:1 mixture of hydroxy epimers. These had converged to a single product by sulfur migration and associated formation of the spiro linkage. That this product was in fact the desired compound **9** with the relative stereochemistry required for aspirochlorine was unequivocally established by crystallographic analysis.[14]

Having effected the desired rearrangement there remained the issue of removing the thioacetal and forming the disulfide bridge, as it is present in the natural product. Following the precedent of Kishi and co-workers[11] it might be expected that disulfide formation in a protected EDKP could be effected from a *p*-methoxybenzylidene dithioacetal by oxidation of one of the sulfur atoms to a sulfoxide. The conversion of a non-EDKP thioacetal of type **9** however, was not precedented. Happily, the action of *meta*-chloroperoxybenzoic acid followed by treatment of the monosulfoxide with perchloric acid cleanly converted **9** into the corresponding disulfide **10**.

It was important to test the applicability of this chemistry in a more realistic scenario. Upon applying anhydrous acid conditions to benzylic alcohols **8**, the rearranged product **11** was obtained as a single diastereomer. Moreover, application of the thioacetal deprotection sequence to produce **12** also proceeded smoothly, to give an advanced model of the natural product, which differs from aspirochlorine only in the substituents on the nitrogen atoms.[15]

Clearly the stereochemical outcomes at position C(7) in the rearrangements are independent of the configurations at this center in the starting alcohols **5** and **8** (Scheme 4). This finding rules out obligatory inversion at the migration terminus in the



Scheme 4. Mechanistic rationalization of the stereoselective rearrangement of **5** and **8**.

rearrangement but does not go into the question of the intermediacy of quinomethide (see **13**). We also note that the preference for sulfur migration to the β-face[16] of position C(7) (that is, *syn* to C(9)) cannot easily be interpreted as a consequence of least-motion considerations,[17] since the plane containing the bridgehead carbons C(8) and C(11), as well as the two sulfur atoms, appears to bisect the median plane of the DKP ring. Hence, the observed stereospecificity reflects an inherent preference of the sulfur to migrate *syn* to position C(9) rather than N(13). A possible, though certainly unproven, interpretation is that in the operative β-face pathway leading to **14**, the sulfur atom can maintain a favorable long-range interaction with the C(9) carbonyl center.[18] By contrast, movement from the α-face (leading to unobserved product **15**) might incur relatively unfavorable electronic or steric interactions with the N(13) methyl function.[19] Thus, it will be of interest, and of importance to the total synthesis, to learn whether this face selectivity is responsive to the nature of the substituent at position N(13).[20]

In summary, we have demonstrated an unprecedented sulfur migration in a protected EDKP. This rearrangement occurs in a highly stereoselective manner and in high yield. The amenability of this chemistry to produce structural

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diversity in a quest for superior antifungal agents is apparent on inspection. Efforts to implement this rearrangement as a key simplifying transformation in the total synthesis of the fully elaborated aspirochlorine system will be reported in due course.

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[8] At this stage we leave unspecified the nature of the R---R insert in structures **A**–**C**. The sulfur groups may be separated, directly connected, or connected through a linker.

[9] It is recognized that the species produced from protonation of the ketonic oxygen of quinomethide **B** formally converges with the product of **A** upon acid-induced heterolysis of OL.

[10] For the preparation of **3**, see Ref. [11a], and references therein.

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[12] Refs. [11a] and [11b] include the addition of nucleophiles derived from **3** to primary halides and acid chlorides.

[13] Several preparations of **6** exist; see, for example, Ref. [6b], and references therein.

[14] All new compounds display satisfactory spectroscopic and analytical data consistent with the assigned structures. Crystallographic data (excluding structure factors) for compound **9** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147018. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[15] Stereochemical assignments of compounds **11** and **12** were based upon similarity of spectroscopic data in comparison to compounds **9** and **10**, respectively. See the Supporting Information.

[16] We use the expression β-face migration as referring to establishment of the S–C(7) bond *syn* to position C(9) of the spiro diketopiperazine substructure.

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[18] A similar stabilizing interaction between a sulfur atom and a carbonyl group was invoked in Ref. [11b].

[19] The arguments advanced above focus on the migrating sulfur atom wherein the sense of rotation around the C(7)–C(8) bond accommodates the preferred modality of sulfur migration. Alternatively, it could be that a preferred sense to the C–C rotation itself serves to determine the face of the sulfur migration.

[20] We note that the observed rearrangement process is suggestive of a possible biosynthesis of aspirochlorine.

Ion-Specific Aggregation in Conjugated Polymers: Highly Sensitive and Selective Fluorescent Ion Chemosensors**

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Conjugated polymers are emerging as versatile elements for the design of chemical sensors.[1, 2] An expansive range of structures is known, and thus the facile tuning of properties by modification of the polymer backbone or the introduction of side groups is possible. A variety of transduction methods that modify the emission and conductivity of a conjugated polymer is available, these include photochemically induced electron transfer, doping, conformational changes, and metal ligation.[1–3] Interchain interactions play a decisive role in controlling the conductive and emissive properties of conjugated polymers in the bulk material.[4] Nevertheless, no sensory system which directly exploits interchain interactions in conjugated polymers has been reported. Herein, we report a new transduction mechanism based on the aggregation of

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