Sporolide B: synthetic studies

Jeffery A. Gladdinga, James P. Baccia, Scott A. Shawa, Amos B. Smith, IIIa,b,c,*

aDepartment of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, United States
bLaboratory for Research on the Structure of Matter, University of Pennsylvania, Philadelphia, PA 19104, United States
cThe Monell Chemical Senses Center, Philadelphia, PA 19104, United States

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Studies directed toward the synthesis of the architecturally complex marine natural product sporolide B are described. Synthetic analysis suggested advanced hydroquinone and benzodiquinane fragments, which upon elaboration were successfully united via an ester linkage. Macrocyclization studies were then carried out, and although a novel macrocyclization product was obtained, subsequent studies revealed that the tertiary hydroxyls at C(6) and C(10) were too sterically encumbered to participate in a successful macrocyclization to furnish sporolide B.

1. Introduction

Sporolides A and B (1 and 2, Scheme 1), two secondary metabolites isolated by Fenical and co-workers1 from the fermentation broth of the marine actinomycete Salinispora tropica, differing only in the position of the chlorine, are among the most complex members of this class of natural products.2 Another significant metabolite emanating from S. tropica is salinosporamide A3, a 20S proteasome inhibitor structurally related to omuralide and lactacystin4, that was recently (2005) advanced to phase I clinical trials as a chemotherapeutic agent.5

Scheme 1.

Architecturally the sporolides are remarkable. Embedded within the macrocyclic framework are ten stereogenic centers, seven rings, and a high level of functionalization: 22 of the 24 carbon atoms are either oxygenated or sp² hybridized. Additional structural features include an epoxyquinone hemi-ketal fused to a 1,4-dioxane ring, a chlorinated cyclopent[a]indane (benzodiquinane) system, and a 13-membered macrolactone.

Intrigued by these unprecedented structures, we initiated a synthetic program to elaborate the sporolides. At the outset, little was known about their biosynthetic origin, other than they were likely of mixed origin. Recent detailed genetic studies of S. tropica, however, now reveal that the epoxyquinone moiety (cf., 3, Scheme 2)d erives from L-tyrosine, while the benzodiquinane most likely arises from a nine-membered cyclic enediyne (cf., 4), that in turn is produced from acetyl and malonyl subunits (Scheme 2).6

The final biosynthetic events leading to the sporolides, upon union of 3 and 4, are likely to include two distinct epoxide openings of enediyne 5 to form the fused 1,4-dioxane ring of macrocycle 6, thus permitting a spontaneous Bergman–Masamune cycloaromatization7 with concomitant non-regiospecific introduction of the chlorine and hydrogen atoms to the resultant p-benzene 7 (Scheme 2). Evidence demonstrating the feasibility of this process, including the non-regioselective introduction of chlorine, was provided by Perrin and co-workers, employing a 10-membered enediyne model system.8 Namely, nucleophilic attack of a chloride ion on the benzene, formed via cycloaromatization, followed by protonation of the resulting aryli on furnished the corresponding chloride isomers. Studies to exploit this reactivity pattern are ongoing in our laboratory.

Although the sporolides do not possess significant biological activity, the extraordinary architecture engendered considerable synthetic challenge. Not surprisingly, studies toward the total synthesis of sporolide B were initiated shortly after the isolation report, with several synthetic approaches disclosed,9,10 including
2. Results and discussion

2.1. Synthetic analysis

The unprecedented 1,4-dioxane ring/epoxy quinone is clearly the most significant challenge for any successful synthesis leading to the sporolides. Toward this end, we envisioned an endgame strategy wherein union of structures such as 8 and 9 (Scheme 3) would precede dioxane ring formation. Lacking detailed information on the biosynthesis at the outset of our synthetic program, we reasoned that the macrocycle might arise via formation of a hemi-ketal, followed by formation of the dioxane via condensation of the tertiary hydroxyl group at C(10) with a hydroxyquinone. We were of course cognizant of the 'high-risk' nature of this approach, given that the tertiary hydroxyl groups at C(6) and C(10) are adjacent and would likely experience severe steric interactions in any bond formation event. Nonetheless, we reasoned that the intramolecular nature of the proposed cyclization might overcome these steric issues. With this thesis in mind, we set out to construct hydroquinone 8 and benzdiquinane 9, the two key fragments of sporolide B.

2.2. Synthesis of hydroquinone acid 8a

The synthesis of hydroquinone acid 8a proceeded in much the same manner as that of Nicolaou and co-workers.9b Commercially available sesamol was protected as the MOM-ether and subjected to selective ortho-methylation, followed by acid-catalyzed hydrolysis to furnish methylsesamol (Scheme 4).11 Known aldehyde 1011 was then constructed by Duff ortho-formylation12 and etherification with benzyl bromide. After methylation, the resultant styrene was subjected to Sharpless asymmetric dihydroxylation13 with AD-mix β to provide known diol (–)-11 with high optical purity (97% ee). The secondary hydroxyl group was methylated in a three-step protocol to furnish known alcohol (–)-12. Transformation of (–)-12 to known hydroquinone acid (–)-8a was then achieved by successive Swern14 and Lindgren–Kraus oxidations.15 The sequence from sesamol proceeded in 12 steps and in 25% overall yield.
With the desired hydroquinone in hand, we thought it prudent to explore oxidation of the corresponding methyl ester of \((-\text{8a})\) to the quinone. Treatment of \((-\text{8a})\) with trimethylsilyldiazomethane furnished methyl ester \((-\text{13})\). After removal of the benzyl group, phenol \((-\text{14})\) was exposed to \(\text{FeCl}_3\) to afford known hydroxyquinone \((-\text{15})\) in 86% yield (Scheme 5). Oxidation to \((-\text{15})\) could also be accomplished directly by treatment of \((-\text{13})\) with ceric ammonium nitrate (CAN).

Although oxidation of the model hydroquinone was successful, we were concerned that the hydroxyl might not be an effective leaving group for the requisite addition/elimination sequence. Also of concern was the stability of the fully elaborated benzoquinine during oxidation of the hydroquinone to the quinone. To address these issues, additional hydroquinones \((-\text{8b})\) and \((-\text{8c})\) were designed and constructed (Scheme 3).

### 2.3. Synthesis of hydroquinone acid 8b

Elaboration of hydroquinone \((-\text{8b})\) began with commercially available 3,4-dimethoxyphenol (Scheme 6). A modified Parker procedure\(^{16}\) was employed to install the methyl group after protection of the phenolic hydroxyl group as the corresponding MOM ether. Removal of this directing substituent then led to the known compound 3,4-dimethoxy-2-methylphenol.\(^{16,17}\) Installation of the aldehyde was best accomplished by employing the Hofslokken modification of the Casiraghi procedure.\(^{18}\) After introduction of the benzyl group, known aldehyde \(\text{16}\) was isolated in 50% yield over the two steps. Next, methylation was followed by Sharpless asymmetric dihydroxylation to provide the requisite diol \((-\text{17})\) in high yield and optical purity (94% over two steps, 93% ee). The secondary hydroxyl group was then methylated via a three-step sequence, similar to that employed for hydroquinone fragment \((-\text{8a})\) to furnish alcohol \((-\text{18})\), which was then subjected to oxidation. Overall, hydroquinone \((-\text{8b})\) was produced in 12 steps and 16% yield.

### 2.4. Synthesis of hydroquinone acid 8c

The third hydroquinone fragment \((\text{8c}, \text{Scheme } 3)\) was prepared from commercially available 2,5-dihydroxybenzaldehyde (Scheme 7). Regioselective bromination and methylation provided known aldehyde \(\text{19}\). At this stage, reduction of the aldehyde to the corresponding methyl group was necessary. Most traditional methods (e.g., Wolff–Kishner, Clemmensen, etc.) did not provide the desired product in a clean fashion. Hydrogenation, on the other hand, proved rapid and clean, but unavoidably led to arene debromination. Ultimately, we chose an ionic hydrogenation protocol employing trifluoroacetic acid and triethylsilane. Although this method routinely furnished dimeric side products, the desired phenol was produced in useful yield (ca. 50%).

Casiraghi/Hoflokken ortho-formylation then provided aldehyde \(\text{20}\), which was converted to diol \((-\text{21})\) and subsequently to primary alcohol \((-\text{22})\) (97% ee) in a similar manner as described for the two previous hydroquinone acids. Overall, \((-\text{8c})\) was constructed in 11 steps and 7.8% yield.

### 2.5. Synthesis of the benzoquinine fragment 9

From the retrosynthetic perspective (Scheme 8), we anticipated that the syn 1,2-diol functionality at C(9–10) of benzoquinine \(\text{9}\) could be installed via substrate-controlled dihydroxylation, to reveal a C(11) allylic alcohol, which in turn would be generated by intramolecular cyclization of a metalated olefin at C(10) with the C(11) carbonyl in aldehyde \(\text{23}\). Critical here would be protection of the free hydroxyl groups within intramolecular range of the carbonyl to avoid lactol or lactone formation. The C(6–10) syn diol of \(\text{24}\) in turn would be installed via dihydroxylation of alkene \(\text{25}\), which would arise via Stille union of aryl bromide \(\text{26}\) with stannane \(\text{27}\).

Construction of aryl bromide \(\text{26}\) began via deprotonation of 1-chloro-3,5-dibromobenzene with \(\text{LDA}\), followed by addition of solid \(\text{CO}_2\) (Scheme 9). After treatment of the resultant carboxylic acids with diazomethane, a mixture of isomeric esters \(\text{30a}\) and \(\text{30b}\) (1:3) was obtained. Although the mixture proved difficult to separate, the subsequent palladium-catalyzed Suzuki coupling\(^{22}\) with vinylboronic anhydride effectively resolved the isomers, furnishing only the styrene derived from \(\text{30b}\) and returning \(\text{30a}\). Diol \((-\text{31})\) was
then obtained upon Sharpless asymmetric dihydroxylation (93% ee). Subsequent protection of the diol as the acetonide furnished the first of the Stille coupling partners, aryl bromide (–)–26.

The second Stille partner, stannane (–)–27, was constructed via a four-step sequence, beginning with 2-cyclopentenone. After iodination and asymmetric reduction employing the Corey–Bakshi–Shibata catalyst,23a the resultant known alcohol23b was protected as the PMB ether to furnish vinyl iodide (–)–32 (Scheme 10). This iodide was then transformed to the corresponding stannane by metalation with t-BuLi and capture with Bu3SnCl to deliver (–)–27.

Union of aryl bromide (–)–26 with vinyl stannane (–)–27 via a palladium-catalyzed Stille reaction24 proved to be a significant challenge. The choice of catalyst system and solvent proved critical. Under our initial conditions, which involved the use of Pd(PPh3)4 in DMF at 125 °C, the reaction suffered both from poor catalyst turnover and formation of several uncharacterized byproducts (entry 1, Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/ligand a</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (–)–25 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)4</td>
<td>DMF</td>
<td>125</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Pd(t-Bu3P)2</td>
<td>Toluene</td>
<td>110</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>Pd(t-Bu3P)2</td>
<td>DMF</td>
<td>125</td>
<td>3</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>Pd2dba2/AdPh3</td>
<td>DMF</td>
<td>100</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Pd2dba2/AdPh3</td>
<td>NMP</td>
<td>100</td>
<td>20</td>
<td>79</td>
</tr>
</tbody>
</table>

* Catalyst loadings equivalent to 10 mol % Pd. Added 40 mol % AsPh3.

By employing a more active catalyst system,25 we were able to achieve better turnover employing either toluene and DMF (entries 2 and 3, Table 1), but ultimately the resultant reaction mixtures were
too complex to pursue. Less complex mixtures were obtained via use of triphenylarsine, a ligand, that is, known to accelerate the Stille reaction of vinyl stannanes.\textsuperscript{26} Although in DMF only a 27\% yield of desired product was obtained (entry 4, Table 1), the lack of byproduct formation suggested that further optimization would be worthwhile. Pleasingly, N-methyl-2-pyrrolidinone (NMP) proved to be a superior solvent, affording the desired product (-)-25 in 79\% yield.

The next challenge was installation of the oxygen atoms at C(6) and C(10). From previous work on this system, we knew that the presence of a carbonyl at C(11) would be problematic. For example, when ester (-)-25 was subjected to the Upjohn dihydroxylation protocol,\textsuperscript{27} the expected diol was not isolated (Scheme 11). Instead, we obtained only lactone (\textsuperscript{\textbullet}34, the stereochemistry of which was confirmed by NMR NOE studies. Clearly, adjustment of the oxidation state of C(11) was required prior to oxygenation.

With this scenario in mind, ester (-)-25 was reduced to the corresponding benzylic alcohol, which was then protected as the TBS ether to furnish (-)-35 in high overall yield for the two steps (Scheme 12).

Dihydroxylation of olefin (-)-35 required some optimization. Initial attempts employing the Upjohn protocol gave good diastereoselectivity, albeit in modest yield (entry 1, Table 2). Moreover, an extended reaction period was required. Use of AD-mix \(\beta\) at room temperature led to a similar yield of diol 36, but with reduced diastereoselectivity (entry 2, Table 2). Improved yields were obtained when the temperature was lowered to 0 °C, but the diastereoselectivity did not improve (entry 3, Table 2). Olefin (-)-35 appeared to have an inherent preference for delivery of the oxygen atoms \textit{anti} to the PMB ether. We had reasoned that AD-mix \(\beta\) might enhance this selectivity, but unfortunately, this catalyst system appears to represent the mismatched substrate/reagent case.

By employing AD-mix \(\alpha\), we were able to restore the diastereoselectivity (entry 4, Table 2), but these conditions proved even more sluggish than the original OsO\(_4\)/NMO conditions. By increasing the catalyst loading and pre-mixing the ligand with osmium, we were able to effect an increase in both reaction rate and diastereoselectivity (entries 5 and 6, Table 2). Ultimately, the reaction was optimized to give a 91\% yield of an inseparable mixture (15:1) of diastereomers, the with desired diol 36 predominating.

Having successfully installed the C(6) and C(10) oxygens, we turned to elaboration of the requisite benzoquinuine 6-5-5 ring system. To this end, the secondary hydroxyx group of 36 was oxidized to the corresponding ketone with SO\(_3\)-pyridine/DMSO.\textsuperscript{28} After separation of the minor diastereomer, that was left over from the dihydroxylation, the tertiary hydroxy group of diol 36 was protected as the SEM ether to furnish ketone (-)-37 in 70\% yield over the two steps (Scheme 13). Ketone (-)-37 was next converted to the corresponding vinyl triflate by treatment with KHMD and trapping with N-phenyltrifluoromethanesulfonimide to afford (-)-38 in 95\% yield.

![Scheme 11.](image1)

![Scheme 12.](image2)

![Scheme 13.](image3)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst system</th>
<th>Os loading</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (-)-33</th>
<th>dr</th>
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<tr>
<td>1</td>
<td>OsO(_4), NMO</td>
<td>1 mol %</td>
<td>25</td>
<td>3</td>
<td>59</td>
<td>10:1</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix (\beta)</td>
<td>1 mol %</td>
<td>25</td>
<td>3</td>
<td>58</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix (\beta)</td>
<td>1 mol %</td>
<td>0</td>
<td>6</td>
<td>76</td>
<td>6:5:1</td>
</tr>
<tr>
<td>4</td>
<td>AD-mix (\alpha)</td>
<td>1 mol %</td>
<td>25</td>
<td>5</td>
<td>46</td>
<td>10:1</td>
</tr>
<tr>
<td>5</td>
<td>AD-mix (\alpha)</td>
<td>2 mol %</td>
<td>25</td>
<td>3</td>
<td>91</td>
<td>15:1</td>
</tr>
</tbody>
</table>

\(\alpha\) AD-mix provided 0.7 mol % osmium, the remainder was added as K\(_2\)OsO\(_4\).

\(\beta\) Amount of AD-mix and K\(_2\)OsO\(_4\) doubled from previous entries.

Further elaboration of the cyclization precursor began with removal of the TBS group of (-)-38, an operation that required use of buffered HF-phosphine, as more nucleophilic fluoride sources effected cleavage of the triflate. The liberated hydroxyl group was then subjected to the Ley oxidation\textsuperscript{29} to furnish aldehyde (-)-39 in 83\% for the two steps.

For the ring-closing tactic, we chose to employ the Nozaki–Hiyama–Kishi (NHK) reaction.\textsuperscript{30} Toward this end, aldehyde (-)-39 was treated with catalytic NiCl\(_2\) and super stoichiometric CrCl\(_2\) in freshly degassed anhydrous DMF at 0.1 M. A mixture of cyclized alcohols (-)-40a and (-)-40b (ca. 5:3:1) was obtained in high yield (Scheme 13). While the diastereoselectivity was far from ideal, we were able, after separation, to convert the undesired \(\alpha\)-alcohol to the desired \(\beta\)-alcohol (\textsuperscript{\textbullet}40b) in two steps. The stereoeconomicity of both alcohols were determined by NMR NOE correlations as illustrated in Fig. 1.

With the benzoquinuine framework firmly established, we set out both to install the remaining stereogenic centers and prepare the fragment for union with hydroquinone acid (-)-8a. First, the SEM protecting group was removed by treatment of (-)-40b with TAS-F in HMPA at 70 °C, and then the free secondary hydroxyl group was protected as the TBS ether to furnish (-)-41 (two steps, 76\%; Scheme 14). Dihydroxylation was next performed via the
Upjohn protocol to furnish triol (−)-42 as a single diastereomer in 83% yield. As we had anticipated from the outset, only the cis-fused product was obtained. The high energy of the competing trans-fused transition state and steric encumbrance of the protected hydroxyls effectively prohibits formation of the undesired diastereomer. Completion of the benzodiquinane fragment of sporolide B entailed removal of the acetonide with PPTS in methanol, to furnish penta-ol (−)-9 in 72% yield. Overall, (−)-9 was produced via a longest linear sequence of 21 steps and in 4.4% yield.

[Diagram of molecular structures]

**Scheme 14.**

**Scheme 15.**

**Scheme 16.**

**2.6. Fragment union**

Having successfully prepared the requisite coupling partners for the construction of sporolide B, we turned to their union via ester bond formation. While we had some confidence that the primary hydroxyl group of (−)-9 would out compete the four other hydroxyls for reaction with an activated acid fragment, we had at the ready a strategy whereby we could protect the primary and secondary hydroxyls, and then selectively remove the primary protecting group. In fact, this strategy was called upon later in the study (Scheme 16). After examining several methods (DCC, EDCI, Yamaguchi31), the optimal coupling conditions in terms of yield and selectivity proved to be treatment of a slight excess of acid (−)-8a with BOP-Cl and triethylamine at room temperature, followed by addition of alcohol (−)-9 after the mixture had been cooled to 0 °C. Ester (−)-43 was isolated in 61% yield after 17 h at 0 °C (Scheme 15).

**2.7. Macrocyclization: a challenging ‘high-risk’ event**

To test the hypothesis that the sporolide 1,4-dioxane can be formed via a ketolization/Michael addition/elimination sequence, oxidation of the hydroquinone moiety in (−)-43 was required. Although the CAN-mediated oxidation of methyl ester (−)-13 (Scheme 5) proceeded with concurrent removal of the benzyl and methylene acetal protecting groups, we found that ester (−)-43 was not stable to this oxidant, as the benzodiquinane portion of the molecule decomposed. The use of DDQ, a milder oxidant, resulted only in the removal of the PMB ether at C(7). This result was somewhat surprising, as DDQ had led to decomposition of methyl ester (−)-13 in a model study. In analogy to our model oxidations (Scheme 5), we chose to unmask the phenol. Toward this end, (−)-43 was subjected to hydrogenolysis, affording phenol 44, the product of both benzyl and PMB ether removal (Scheme 16). This compound proved to be unstable to silica gel chromatography and was used in subsequent experiments directly after filtration through Celite. Phenol 44 was treated with DDQ, FeCl₃, and Ag₂O; these reagents, however, gave numerous unidentified products, with no trace of quinone 45, presumably due to instability of the benzodiquinane portion of the molecule.

We reasoned that the difficulties encountered in the oxidation of hydroquinone 44 were due to the slow oxidative cleavage of the methylene acetal relative to deleterious benzodiquinane oxidation. We therefore attempted to remove this group prior to union of (−)-8a with the benzodiquinane. Conditions that successfully removed this group however led to partial racemization of the stereogenic center at C(2'). We therefore turned to hydroquinone fragment (−)-8b (vide supra), which features two methyl ethers rather than the methylene acetal.

Union of acid (−)-8b with alcohol (−)-9 was carried out by employing the optimal conditions defined for construction of (−)-43 (Scheme 15); ester (−)-46 was obtained in 63% yield (Scheme 17). Hydrogenolysis of the benzyl and PMB ethers then produced phenol 47, a compound that also proved unstable to silica gel chromatography, and was thus used immediately after filtration through Celite.

When phenol 47 was exposed to DDQ in the presence of water, rapid decomposition occurred (Scheme 17). Careful analysis of the reaction mixture indicated that hydroquinone oxidation was accompanied by a host of unidentified side reactions. As was the case with CAN, the oxidant was presumably reacting with both the hydroquinone and the benzodiquinane portion of the molecule, which features five unprotected hydroxyls. If this were indeed the case, protecting at least the more accessible secondary hydroxyls should lead to a more selective oxidation. A second advantage of hydroxyl protection would entail possible use of hypervalent iodine oxidants, such as Ph[I(OAc)₂], which are known to proceed under mild conditions.32 We had previously avoided the use of such oxidants given their propensity to cleave 1,2-diols.33 Although the tertiary hydroxyls at C(6) and C(10) constitute a 1,2-diol, we
reasoned that the rate of cleavage at this sterically encumbered site would be slow relative to hydroquinone oxidation.

Execution of this strategy began with treatment of \((+\text{-})-9\) with excess TBSOTf to protect the primary and secondary hydroxyl groups to furnish \((+\text{-})-48\) in 87% yield (Scheme 18). The primary TBS ether was then removed with a catalytic amount of CSA in methanol to provide alcohol \((+\text{-})-49\) in 85% yield. Union of \((+\text{-})-49\) with acid \((-\text{-})-8b\) proceeded smoothly in the presence of DCC to generate ester \((-\text{-})-50\) in 86% yield, an improvement over previous unions due presumably to hydroxyl group protection.

Scheme 17.

To prepare ester \((-\text{-})-50\) for oxidation, we removed the benzyl group via hydrogenolysis (Scheme 19). In previous substrates, this reaction led to concomitant removal of the PMB ether, but with the hydroxyl groups protected, the rate of PMB removal was sufficiently slow that \((-\text{-})-51\) could be isolated. With the free phenol in hand, we attempted the oxidation with PhI(OAc)₂. Surprisingly, cleavage of the hindered 1,2-diol in \((-\text{-})-51\) was faster than hydroquinone oxidation.

Scheme 18.

At this stage, we turned to DDQ for the oxidation of \((-\text{-})-51\). We were however concerned that the C(7) PMB ether might prove problematic. To circumvent this issue, we removed the PMB ether at an earlier stage. Thus, \((-\text{-})-50\) was treated with DDQ in the presence of water and the resultant hydroxyl protected as the TBS ether to furnish \((\text{-})-52\) (76%, two steps; Scheme 20). Removal of the benzyl group via hydrogenation then proceeded in high yield to furnish phenol \((-\text{-})-53\). In turn we were able to access the desired quinone 54 via oxidation with DDQ in the presence of water. This quinone also proved to be unstable to silica gel and thus was again used in subsequent reactions, after NMR verification, without purification beyond an aqueous workup.

Scheme 19.

Scheme 20.
Turning to the critical ‘high-risk’ macrocyclization, we were cognizant of the fact that two distinct sequences could operate with quinone. One possibility was that ketalization would first occur to yield compound, thus bringing the second oxygen into proximity with the quinone and perhaps accelerating the addition/elimination reaction (Scheme 21). The second possibility would entail the reverse: addition/elimination to furnish, followed by ketalization. To the best of our knowledge, there is only a single example such a reaction in the literature, involving addition/elimination followed by oxidative dearomatization of ethers (e.g., reaction of sesamol with an oxidant in methanol to produce the corresponding ketal). In general such systems are produced via oxidative dearomatization of ethers (e.g., reaction of sesamol with an oxidant in methanol to produce the corresponding ketal).

Although this phenol contained a PMB ether, we reasoned that oxidation of the sodium alkoxide of cyclopentanol with an oxidant in methanol to produce the corresponding ketal.

To this end, treatment of known bromo dimethyl ketal with DDQ in anhydrous CH₂Cl₂ at room temperature led mostly to removal of the PMB ether. We were nonetheless able to isolate a small amount of a product wherein the newly revealed secondary hydroxyl group appeared to have participated in a macrocyclization. To explore this possibility, we intentionally removed the PMB ether in a separate step, and subjected the resultant alcohol to oxidation with DDQ (Scheme 22). Mass spectrometric and NMR analysis (¹H and ¹³C) indicated that macrocycle (+)-59 was indeed the product, isolated from phenol (-)-58 in 66% yield as a single diastereomer of unknown stereogenicity at C(7’).

Detailed 2-D NMR studies were performed to confirm the structure of (+)-59. Correlations involving NMR NOE’s were observed between what would be remote portions of the molecule if acyclic, including the C(7’) methyl ketal with the C(7) hydrogen, the C(7’) methyl ketal with one of the C(8) hydrogens, the C(8’) hydrogen with one of the C(8) hydrogens, and the C(6’) methoxy group with the C(7) hydrogen (see Fig. 2).

A subsequent HMBC correlation revealed that the C(7) hydrogen and the C(7’) ketal carbon were separated by at most four bonds, confirming the macrocyclic linkage. The stereogenicity of the C(7’) ketal center, however, was not evident from the 2-D NMR studies.

Despite the unsurprising fact that the tertiary hydroxyls were out-competed by the secondary, we were encouraged that oxidative dearomatization appeared to be a viable macrocyclization tactic. We therefore turned to a series of model reactions to better understand how to exploit an oxidative dearomatization protocol to access the 1,4-dioxane/ketal moiety.

To this end, treatment of known bromo dimethyl ketal with the sodium alkoxide of cyclopentanol resulted in a slow, but clean reaction to furnish ketal (+)-62 (Scheme 23). Hydrogenation then gave phenol (+)-63, which was subjected to intramolecular dearomatization at high dilution (1 μM). Pleasingly, cyclic ketal (+/-)-64 was produced as a mixture of diastereomers. To the best of our knowledge, (+/-)-64 comprises the first example of the preparation of this scaffold via intramolecular oxidative cyclization.

With (+/-)-64 as our only example of dioxane construction, we turned to bromohydroquinone acid (-/-)8c (Scheme 24). However, before esterification could be achieved, replacement of the PMB ether of benzodiquinane (+/-)48 with a TBS ether was required to avoid complications with the PMB ether of acid (-/-)8c. Toward this end,
(+)-48 was subjected to DDQ in the presence of water and the result-
ant secondary hydroxyl protected as the TBS ether to afford (+)-65
(Scheme 24). Selective removal of the primary TBS ether was then
accomplished with CSA in CH₂Cl₂/EtOH to furnish alcohol (+)-66.

Union of (+)–8c with benzodiquinane (–)–66 was performed with
DCC to provide ester 67 as an inseparable mixture (10:1) of dias-
tereomers (Scheme 24). Presumably, the oxidation of (–)–22 to
(+)-8c (Scheme 7) had caused partial racemization of the benzylic
stereocenter. Nonetheless, we chose to test the macrocyclization,
with the understanding that if successful, we could re-visit the ox-
idation and subsequent racemization issues. Removal of the phenolic
PMB group of 67 was accomplished with TFA and the resultant pheno-
lol subjected to oxidative ketalization with DDQ in MeOH to
provide cyclization precursor 68 in 54% over the two steps.

Macrocyclization studies began with the use of sodium hydride
as base (Scheme 25). No reaction was observed at 0°C, but as the
reaction was warmed to room temperature, we observed hydrolysis
of the ester. Changing the base to KHMsD gave the same result,
even when molecular sieves were added to remove adventitious
water. A number of other bases and additives were examined at
room and elevated temperatures, including cesium carbonate, DBU,
BTPP, silver oxide, and triethylphosphine. Only epimerization (with
DBU) and formal ester hydrolysis were observed. In the latter re-
actions, we were able to re-isolate the alcohol fragment, but the fate
of the corresponding acid fragment was unclear. It is possible that
when moisture was rigorously excluded hydrolysis occurred
through ketene formation, although we did not isolate any species
that would confirm this possibility.

3. Conclusion

Having attempted a variety of different macrocyclization strat-
egies in our sporolide synthetic studies, we have reluctantly come
to the conclusion that the tertiary hydroxyl groups at C(6) and C(10)
are simply sterically too encumbered to participate in a successful
macrocyclization.

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Supplementary data

Spectroscopic and analytical data as well as experimental pro-
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