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Sporolide B: synthetic studies

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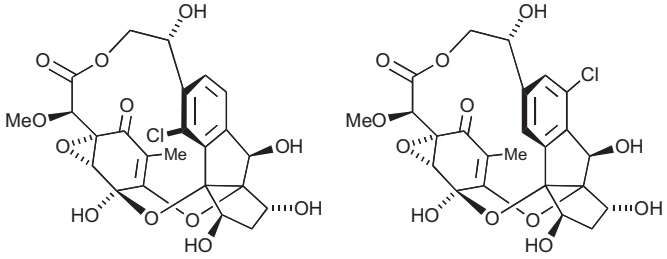
ABSTRACT

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-workers[1] 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 A[3], a 20S proteasome inhibitor structurally related to omuralide and lactacystin[4], 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 sp^2 hybridized. Additional structural features include an epoxyquinone hemi-ketal fused to a 1,4-dioxane ring, a chlorinated cyclopenta[*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) derives 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 cycloaromatization[7] with concomitant non-regiospecific introduction of the chlorine and hydrogen atoms to the resultant *p*-benzyne **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 benzyne, formed via cycloaromatization, followed by protonation of the resulting aryl anion 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

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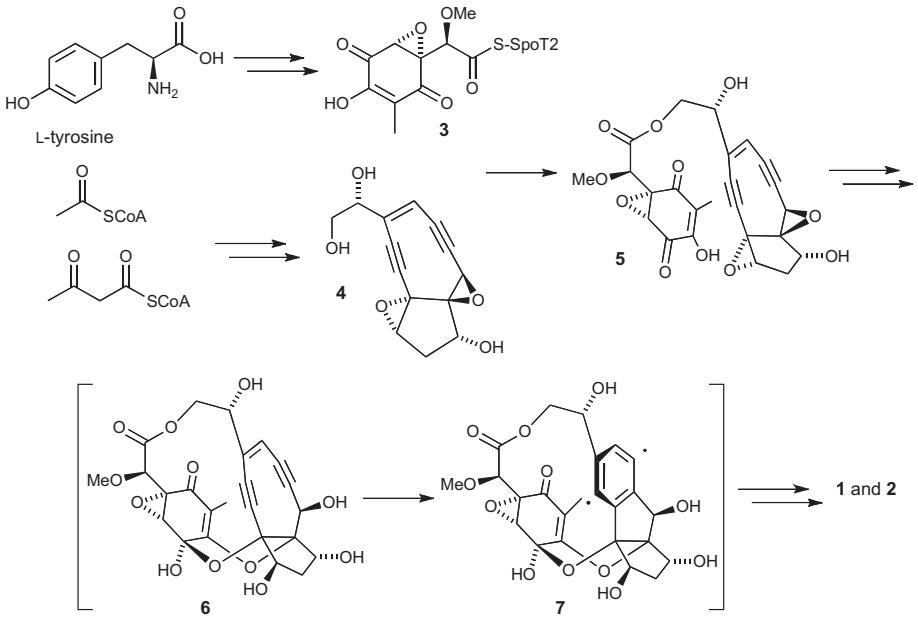


Scheme 2.

the first, and to date, only total synthesis of sporolide B by Nicolaou and co-workers in 2009.[9b]

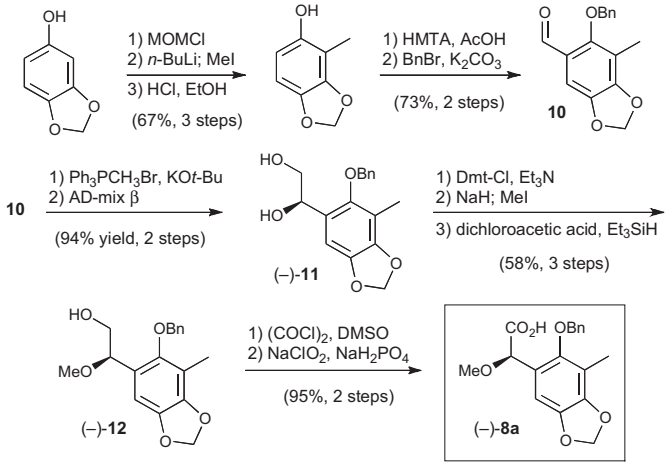
2. Results and discussion

2.1. Synthetic analysis

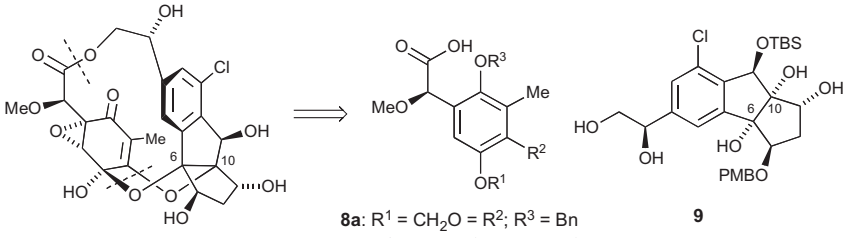
The unprecedented 1,4-dioxane ring/epoxy quinone is clearly the most significant challenge for any successful synthesis leading to the sporolides. Toward this end, we envisioned an endgame strategy wherein union of structures such as **8** and **9** (Scheme 3) would precede dioxane ring formation. Lacking 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 benzodiquinane **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 **10**[11] was then constructed by Duff *ortho*-formylation[12] and etherification with benzyl bromide. After methylenation, the resultant styrene was subjected to Sharpless asymmetric dihydroxylation[13] with AD-mix β to provide known diol (−)-**11**[1] with high optical purity (97% ee). The secondary hydroxyl group was methylated in a three-step protocol to furnish known alcohol (−)-**12**.[9b] Transformation of (−)-**12** to known hydroquinone acid (−)-**8a** was then achieved by successive Swern[14] and Lindgren–Kraus oxidations.[15] The sequence from sesamol proceeded in 12 steps and in 25% overall yield.

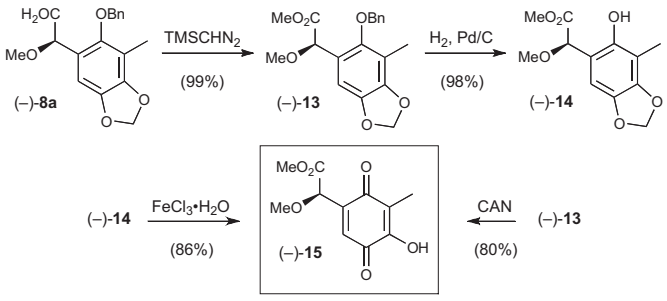


Scheme 4.



Scheme 3.

With the desired hydroquinone in hand, we thought it prudent to explore oxidation of the corresponding methyl ester of (−)-**8a** to the quinone. Treatment of (−)-**8a** with trimethylsilyldiazomethane furnished methyl ester (−)-**13**. After removal of the benzyl group, phenol (−)-**14** was exposed to $FeCl_3$ to afford known hydroxyquinone (−)-**15**[10a] in 86% yield (Scheme 5). Oxidation to (−)-**15** could also be accomplished directly by treatment of (−)-**13** with ceric ammonium nitrate (CAN).



Scheme 5.

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 benzodiquinane during oxidation of the hydroquinone to the quinone. To address these issues, additional hydroquinones (−)-**8b** and (−)-**8c** were designed and constructed (Scheme 3).

2.3. Synthesis of hydroquinone acid 8b

Elaboration of hydroquinone (−)-**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 **16**[19] was isolated in 50% yield over the two steps. Next, methylenation was followed by Sharpless asymmetric dihydroxylation to provide the requisite diol (−)-**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 (−)-**8a** to furnish alcohol (−)-**18**, which was then subjected to oxidation. Overall, hydroquinone (−)-**8b** was produced in 12 steps and 16% yield.

2.4. Synthesis of hydroquinone acid 8c

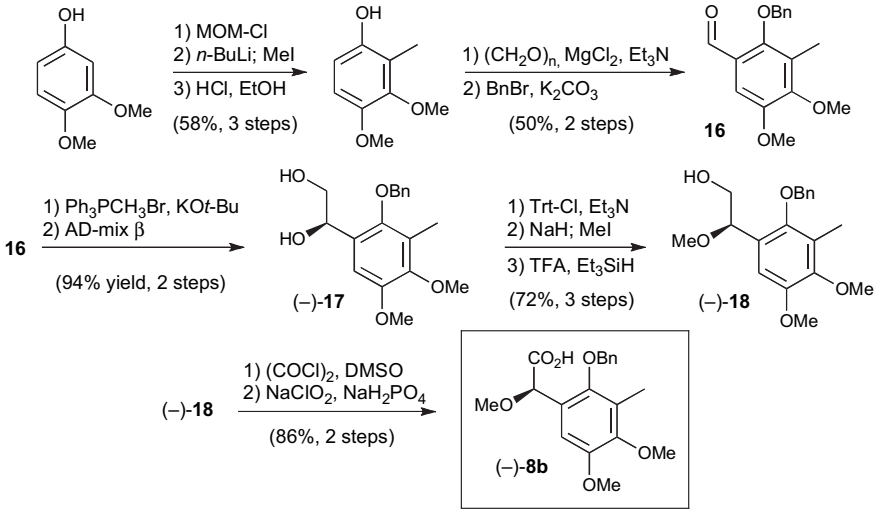
The third hydroquinone fragment (**8c**, Scheme 3) was prepared from commercially available 2,5-dihydroxybenzaldehyde (Scheme 7). Regioselective bromination and methylation provided known aldehyde **19**.[20] At this stage, reduction of the aldehyde to the corresponding methyl group was necessary. Most 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 **20**, which was converted to diol (−)-**21** and subsequently to primary alcohol (−)-**22** (>97% ee) in a similar manner as described for the two previous hydroquinone acids. Overall, (−)-**8c** was constructed in 11 steps and 7.8% yield.

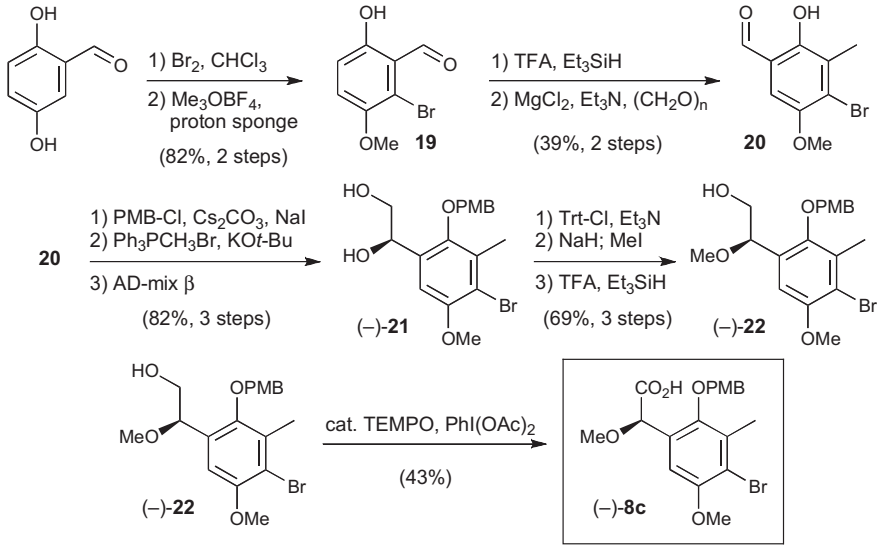
2.5. Synthesis of the benzodiquinane fragment 9

From the retrosynthetic perspective (Scheme 8), we anticipated that the *syn* 1,2-diol functionality at C(9–10) of benzodiquinane **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 **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 **24** in turn would be installed via dihydroxylation of alkene **25**, which would arise via Stille union of aryl bromide **26** with stannane **27**.

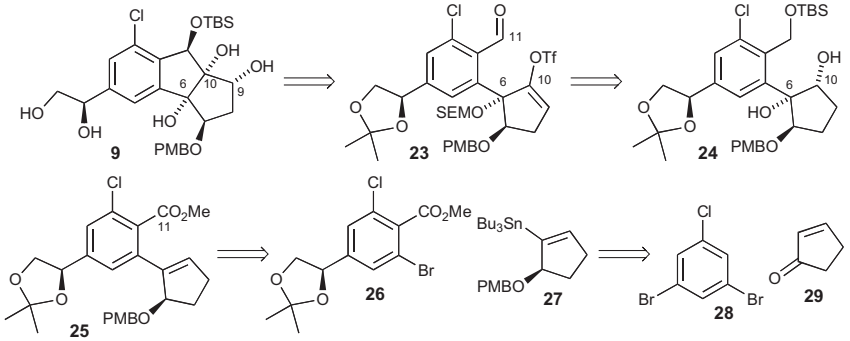
Construction of aryl bromide **26** began via deprotonation of 1-chloro-3,5-dibromobenzene with LDA, followed by addition of solid CO_2 (Scheme 9).[21] After treatment of the resultant carboxylic acids with diazomethane, a mixture of isomeric esters **30a** and **30b** (1:3) was obtained. Although the 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 **30b** and returning **30a**. Diol (−)-**31** was



Scheme 6.

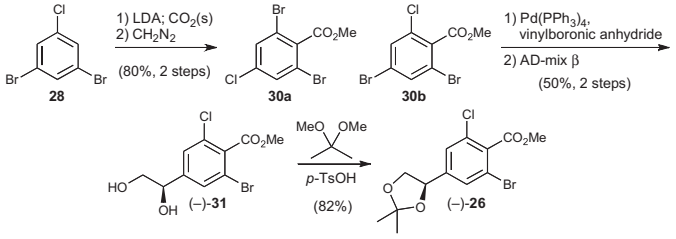


Scheme 7.



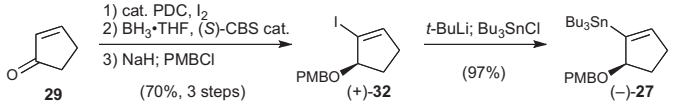
Scheme 8.

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**.



Scheme 9.

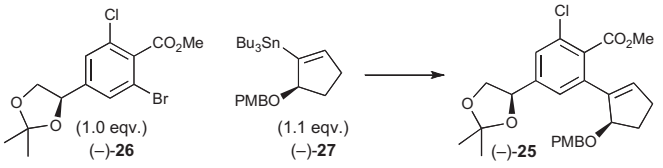
The second Stille partner, stannane (−)-**27**, was constructed via a four-step sequence, beginning with 2-cyclopentenone. After iodination and asymmetric reduction employing the Corey–Bakshi–Shibata catalyst,[23a] the resultant known alcohol[23b] was protected as the PMB ether to furnish vinyl iodide (+)-**32** (Scheme 10). This iodide was then transformed to the corresponding stannane by metalation with *t*-BuLi and capture with Bu_3SnCl to deliver (−)-**27**.



Scheme 10.

Union of aryl bromide (−)-**26** with vinyl stannane (−)-**27** via a palladium-catalyzed Stille reaction[24] proved to be a significant challenge. The choice of catalyst system and solvent proved critical. Under our initial conditions, which involved the use of $Pd(PPh_3)_4$ in DMF at 125 °C, the reaction suffered both from poor catalyst turnover and formation of several uncharacterized byproducts (entry 1, Table 1).

Table 1
Optimization of Stille reaction conditions



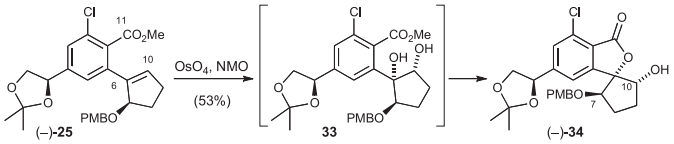
Entry	Catalyst/ligand[a]	Solvent	Temp. (°C)	Time (h)	Yield (−)-**25** %
1	$Pd(PPh_3)_4$	DMF	125	14	25
2	$Pd(t\text{-}Bu_3P)_2$	Toluene	110	14	38
3	$Pd(t\text{-}Bu_3)P_2$	DMF	125	3	45
4	$Pd_2dba_3/AsPh_3$	DMF	100	14	27
5	$Pd_2dba_3/AsPh_3$	NMP	100	20	79

[a] Catalyst loadings equivalent to 10 mol % Pd. Added 40 mol % $AsPh_3$.

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

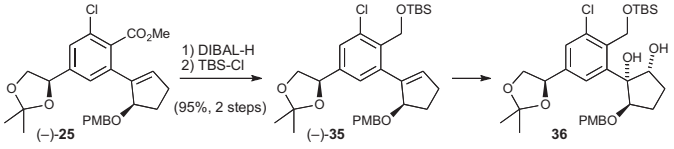
too complex to pursue. Less complex mixtures were obtained via use of triphenylarsine, a ligand, that is, known to accelerate the Stille reaction of vinyl stannanes.[26] Although in DMF only a 27% yield of desired product was obtained (entry 4, Table 1), the lack of byproduct formation suggested that 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,[27] the expected diol was not isolated (Scheme 11). Instead, we obtained only lactone (−)-**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.



Scheme 11.

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).

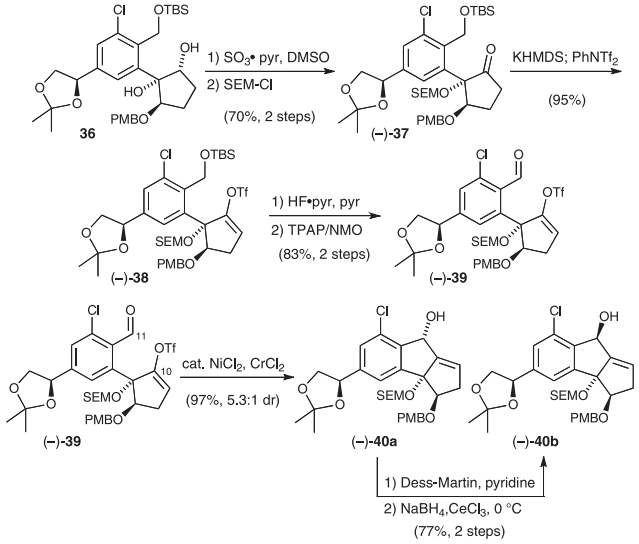


Scheme 12.

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 β 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 *anti* to the PMB ether. We had reasoned that AD-mix β might enhance this selectivity, but unfortunately, this catalyst system appears to represent the mismatched substrate/reagent case.

By employing AD-mix α, 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 benzodiquinane 6-5-5 ring system. To this end, the secondary hydroxyl group of **36** was oxidized to the corresponding ketone with SO_3·pyridine/DMSO.[28] After separation of the minor diastereomer, that was left over from the dihydroxylation, the tertiary hydroxyl 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 KHMDS and trapping with *N*-phenyltrifluoromethanesulfonimide to afford (−)-**38** in 95% yield.



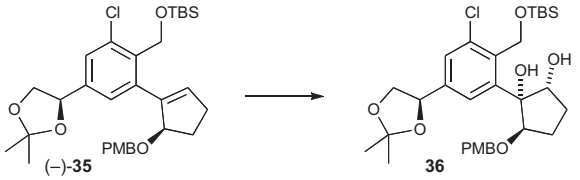
Scheme 13.

Further elaboration of the cyclization precursor began with removal of the TBS group of (−)-**38**, an operation that required use of buffered HF·pyridine, as more nucleophilic fluoride sources effected cleavage of the triflate. The liberated hydroxyl group was then subjected to the Ley oxidation[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.[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 α-alcohol to the desired β-alcohol (−)-**40b** in two steps. The stereogenicities of both alcohols were determined by NMR NOE correlations as illustrated in Fig. 1.

With the benzodiquinane 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

Table 2
Optimization of dihydroxylation of (−)-**35**



Entry	Catalyst system[a]	Os loading	Temp. (°C)	Time (h)	Yield (−)-**33** %	dr
1	OsO_4, NMO	1 mol %	25	3	59	10:1
2	AD-mix β	1 mol %	25	3	58	6:1
3	AD-mix β	1 mol %	0	6	76	6.5:1
4	AD-mix α	1 mol %	25	5	46	10:1
5	AD-mix α[b]	2 mol %	25	3	91	15:1

[a] AD-mix provided 0.7 mol % osmium, the remainder was added as K_2OsO_4.
[b] Amount of AD-mix and K_2OsO_4 doubled from previous entries.

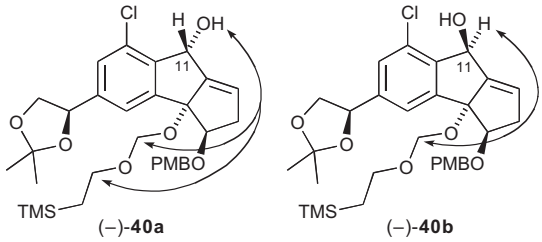
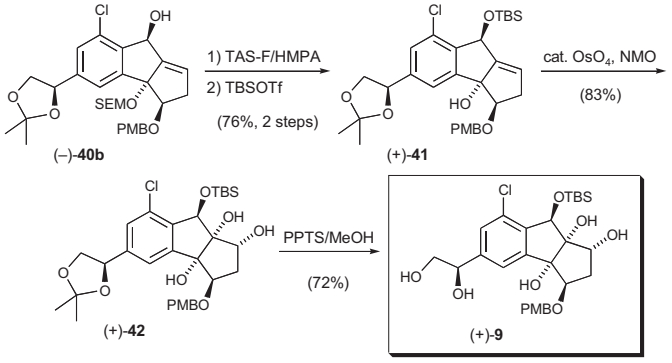


Fig. 1. Key NMR N.E. correlations of alcohols (−)-**40a** and (−)-**40b**.

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.



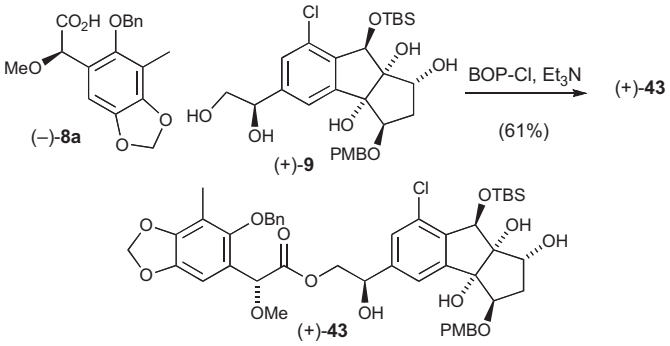
Scheme 14.

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, Yamaguchi[31]), 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).

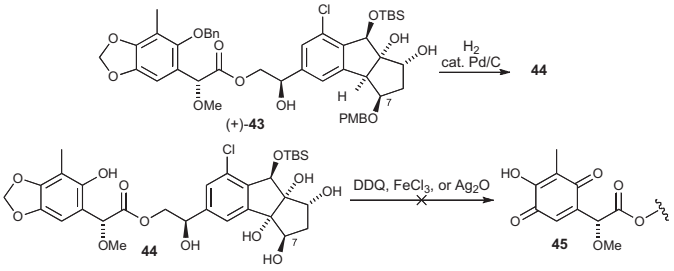
2.7. Macrocyclization: a challenging 'high-risk' event

To test the hypothesis that the sporolide 1,4-dioxane can be formed via a ketalization/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



Scheme 15.

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, $FeCl_3$, and Ag_2O; these reagents, however, gave numerous unidentified products, with no trace of quinone **45**, presumably due to instability of the benzodiquinane portion of the molecule.

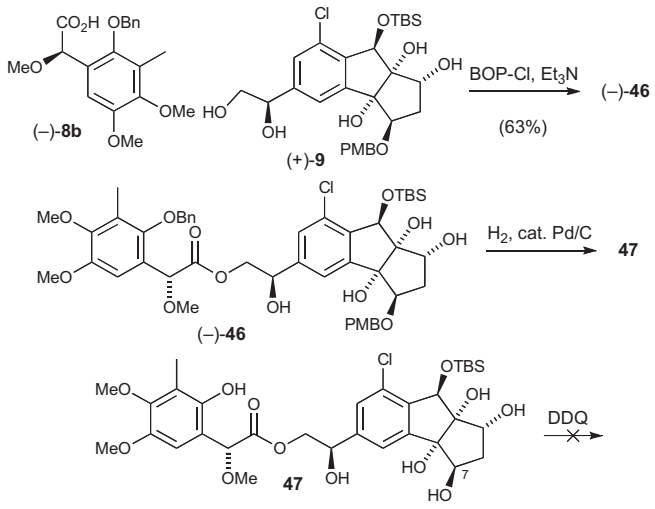


Scheme 16.

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 $PhI(OAc)_2$, 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

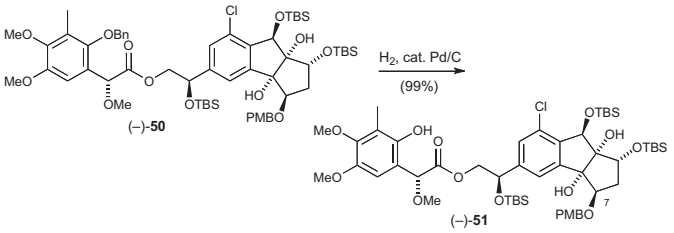


Scheme 17.

reasoned that the rate of cleavage at this sterically encumbered site would be slow relative to hydroquinone oxidation.

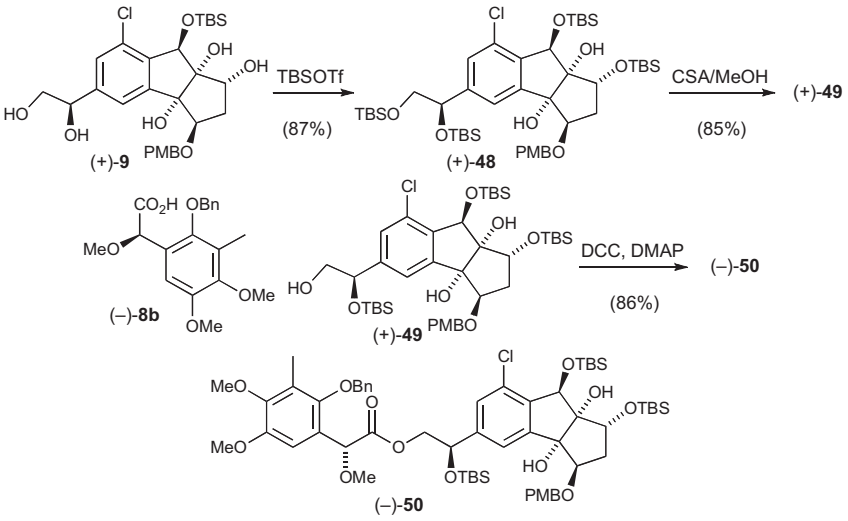
Execution of this strategy began with treatment of (+)-**9** with excess TBSOTf to protect the primary and secondary hydroxyl groups to furnish (+)-**48** in 87% yield (Scheme 18). The primary TBS ether was then removed with a catalytic amount of CSA in methanol to provide alcohol (+)-**49** in 85% yield.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

To prepare ester (–)-**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 (–)-**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 (–)-**51** was faster than hydroquinone oxidation.

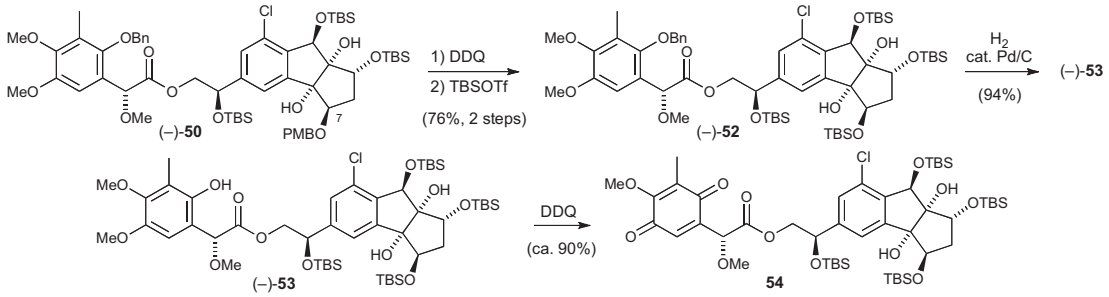


Scheme 19.

At this stage, we turned to DDQ for the oxidation of (–)-**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, (–)-**50** was treated with DDQ in the presence of water and the resultant hydroxyl protected as the TBS ether to furnish (–)-**52** (76%, two steps; Scheme 20). Removal of the benzyl group via hydrogenation then proceeded in high yield to furnish phenol (–)-**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.

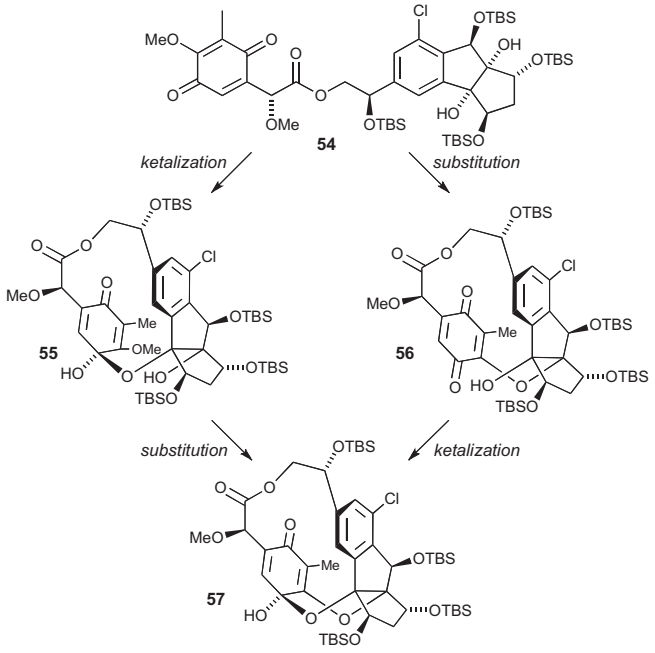


Scheme 18.



Scheme 20.

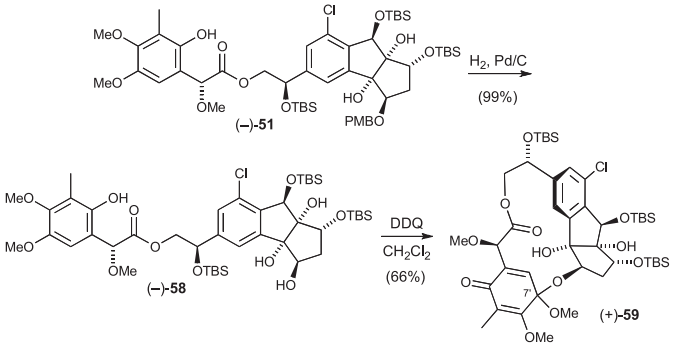
Turning to the critical 'high-risk' macrocyclization, we were cognizant of the fact that two distinct sequences could operate with quinone **54**. One possibility was that ketalization would first occur to yield compound **55**, thus bringing the second oxygen into proximity with the quinone and perhaps accelerating the addition/elimination reaction (Scheme 21). The second possibility would entail the reverse: addition/elimination to furnish **56**, 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 ketalization sequence.[34] 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).[35]



Scheme 21.

We quickly discovered however that quinone **54** was unstable in the presence of alkoxides (e.g., KO*t*-Bu). Equally disappointing, all attempts to affect an acid-promoted ring closure also proved unrewarding.

Undaunted, we turned to the possibility of an oxidative dearomatization. To this end, we returned to adduct (−)-**51** (Scheme 22). Although this phenol contained a PMB ether, we reasoned that reaction of the PMB ether with an oxidant would be slower than phenol oxidation. In the event, however, treatment of (−)-**51** with DDQ in anhydrous CH_2Cl_2 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



Scheme 22.

in a separate step, and subjected the resultant alcohol to oxidation with DDQ (Scheme 22). Mass spectrometric and NMR analysis (^1H and ^{13}C) 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).

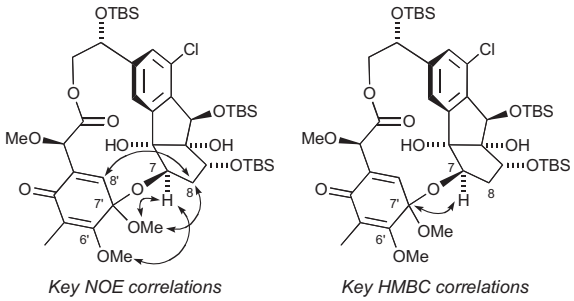


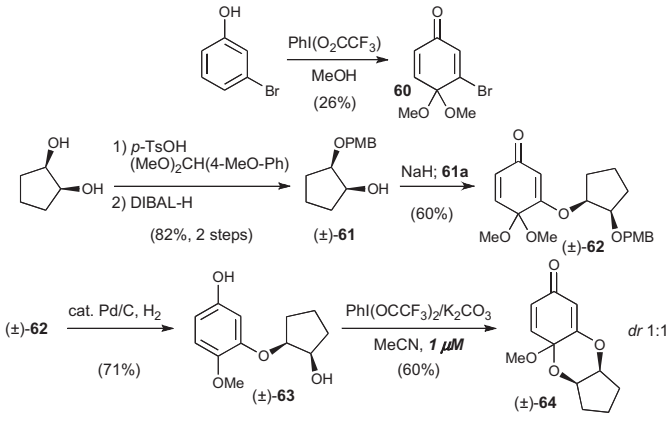
Fig. 2. Key 2-D NMR correlations of macrocycle (+)-**59**.

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.

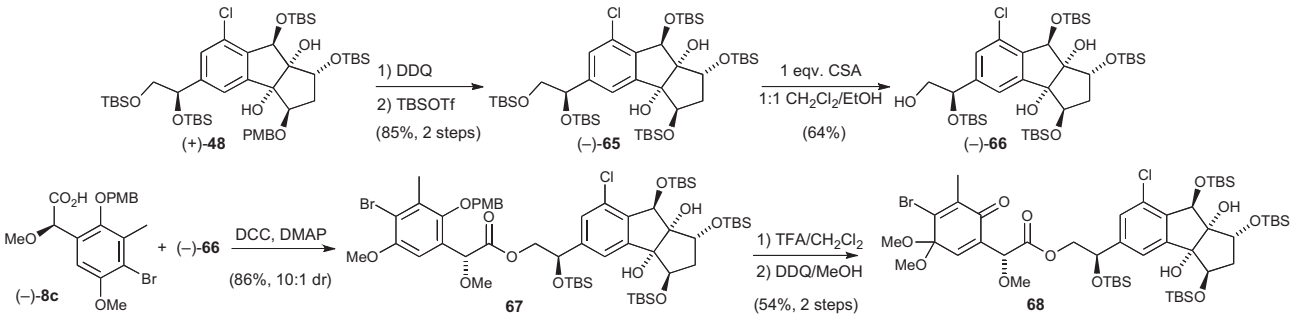
Despite the unsurprising fact that the tertiary hydroxyls were out-competed by the secondary, we were encouraged that oxidative dearomatization appeared to be a viable macrocyclization tactic. We therefore turned to a series of model reactions to better understand how to exploit an oxidative dearomatization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

To this end, treatment of known bromo dimethyl ketal **60**[36] with the sodium alkoxide of cyclopentanol (±)-**61** 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,



Scheme 23.

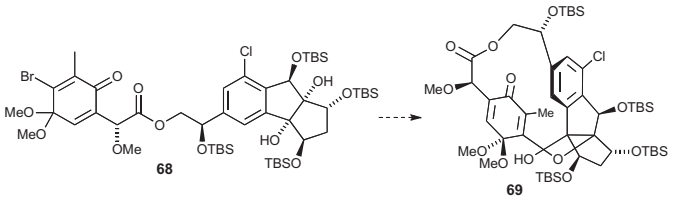


Scheme 24.

(+)-**48** was subjected to DDQ in the presence of water and the resultant 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 CH_2Cl_2/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 diastereomers (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 oxidation and subsequent racemization issues. Removal of the phenolic PMB group of **67** was accomplished with TFA and the resultant phenol 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 KHMDS 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 reactions, we were able to re-isolate the alcohol fragment, but the fate of the corresponding acid fragment was unclear. It is possible that even when moisture was rigorously excluded hydrolysis occurred through ketene formation, although we did not isolate any species that would confirm this possibility.



Scheme 25.

3. Conclusion

Having attempted a variety of different macrocyclization strategies 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.

Acknowledgements

This paper is dedicated to Professor Satoshi Omura, outstanding scientist, scholar and friend, who has enhanced the human existence with his interest in and contributions to the art world, on the occasion of receipt of the 2011 Tetrahedron Prize.

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Supplementary data

Spectroscopic and analytical data as well as experimental procedures associated with this article. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.094.

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