# Total Synthesis of Sporolide B and 9-*epi*-Sporolide B

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***Abstract:*** The total synthesis of the structurally unique secondary metabolite sporolide B (**1b**) is described. The total synthesis of **1b** was developed on the basis of preliminary studies that revealed the reactivity of an appropriate *o*-quinone as a diene system toward a number of indene derivatives as dienophiles, first in intermolecular and thence intramolecular settings. Thus, substrates were devised (**37** and **75**) that underwent exquisite intramolecular [4+2] cycloaddition reactions under thermal conditions to provide primitive sporolide-type structures that were subsequently elaborated to a sporolide model system, 9-*epi*-sporolide B, and **1b**. The requisite indene *o*-quinone precursor **75** was synthesized through a ruthenium-catalyzed [2+2+2] cycloaddition reaction between a propargylic alcohol and a chloroacetylenic cyclopentenyne, followed by elaboration and silver-promoted oxidation of the resulting chloroindene derivative. In addition to the total synthesis of **1b**, this work demonstrated, for the first time, the power of the intramolecular hetero [4+2] cycloaddition reaction in the total synthesis of complex molecules and the application of the ruthenium-catalyzed [2+2+2] cycloaddition reaction to highly substituted indene systems possessing a chlorine residue on the aromatic nucleus.

## Introduction

The marine actinomycete *Salinospora tropica* is the producer of salinosporamide A,[1] a potent inhibitor of the 20S proteasome that elicited considerable interest as a lead compound for cancer chemotherapy.[2] In addition to this natural product, the Fenical group has recently disclosed the isolation, from the same species, of sporolides A (**1a**) and B (**1b**) (Figure 1).[3] Despite their striking molecular architectures, the latter natural products exhibited no biological activities for which they were tested. Their conspicuous indanoid structural motif, however, gave rise to the intriguing hypothesis[4] that they are derived from the nine-membered enediyne **2** (Figure 1), which was named pre-sporolide,[5] through a Bergman cycloaromatization.[6] As shown

in Figure 1, the conversion of the initially generated benzenoid diradical **3** from the Bergman cycloaromatization of **2** required a hitherto unknown reaction, namely the sequential trapping of the diradical with a chloride anion ($Cl^{\ominus}$) and a proton ($H^{\oplus}$). This mode of reactivity was later demonstrated by Perrin and O'Connor through experimentation that included supporting kinetic studies.[7] Thus, it does appear that *S. tropica* produces, in addition to salinosporamide A, a second, structurally distinct cytotoxic agent, presporolide **2**, whose rapid rearrangement and subsequent reactions lead to the inactive, but revealing, sporolides A (**1a**) and B (**1b**).

Fascinated by the unprecedented molecular structures of the sporolides, and the interesting hypothesis regarding their origins, we contemplated their total synthesis, an endeavor that we felt could lead to new synthetic strategies and technologies and may also serve as a prelude to a possible approach toward the more challenging structure of presporolide (**2**) by virtue of its expected strain and lability. In previous communications, we disclosed preliminary results leading to the construction of a sporolide model system (**4**, Figure 1)[8] and sporolide B (**1b**).[9] In this article, we provide a full account of our investigation that led to the

(1) (a) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355–357. (b) Williams, P. G.; Buchanan, G. O.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2005**, *70*, 6196–6203.

(2) (a) Macherla, V. R.; Mitchell, S. S.; Manam, R. R.; Reed, K. A.; Chao, T.-H.; Nicholson, B.; Deyanat-Yazdi, G.; Mai, B.; Jensen, P. R.; Fenical, W.; Neuteboom, S. T. C.; Lam, K. S.; Palladino, M. A.; Potts, B. C. M. *J. Med. Chem.* **2005**, *48*, 3684–3687. (b) Palladino, M. A.; Neuteboom, S. T. C.; Theodora, C.; Macherla, V. R.; Potts, B. C. Patent WO 02005002572, 2005.

(3) (a) Buchanan, G. O.; Williams, P. G.; Feling, R. H.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2005**, *7*, 2731–2734. (b) Fenical, W.; Jensen, P. R. *Nature Chem. Biol.* **2006**, *2*, 666–673. (c) Jensen, P. R.; Williams, P. G.; Oh, D.-C.; Zeigler, L.; Fenical, W. *Appl. Environ. Microbiol.* **2007**, *73*, 1146–1152.

(4) (a) Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2006**, *8*, 1021–1024. (b) McGlinchey, R. P.; Nett, M.; Moore, B. S. *J. Am. Chem. Soc.* **2008**, *130*, 2406–2407. (c) Nett, M.; Moore, B. S. *Pure Appl. Chem.* **2009**, *81*, 1075–1084.

(5) Udwary, D. W.; Zeigler, L.; Asolkar, R. N.; Singan, V.; Lapidus, A.; Fenical, W.; Jensen, P. R.; Moore, B. S. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 10376–10381.

(6) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. For selected reviews on naturally occurring enediynes exhibiting Bergman cycloaromatization properties, see: (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387–1416. (c) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103–2117.

(7) Perrin, C. L.; Rodgers, B. L.; O'Connor, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4795–4799.

(8) Nicolaou, K. C.; Wang, J.; Tang, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1432–1435.

(9) (a) Nicolaou, K. C.; Tang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3449–3453. (b) Li, P.; Menche, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 5078–5080.
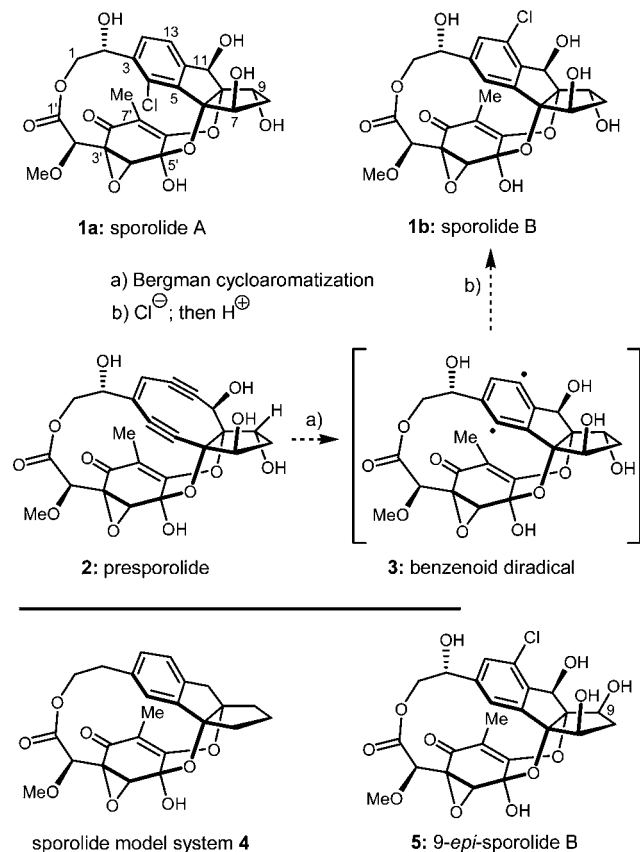
**Figure 1.** Molecular structures of sporolide A (**1a**), sporolide B (**1b**), presporolide (**2**), benzenoid diradical **3**, sporolide model system **4**, and 9-*epi*-sporolide B (**5**).



**Figure 2.** Plausible synthetic approaches to sporolide B: path a, biomimetic approach; path b, *o*-quinone [4+2] cycloaddition approach. P = protecting group.

total synthesis of sporolide B (**1b**) and its diastereoisomer, 9-*epi*-sporolide B (**5**, Figure 1).

## Results and Discussion

**Initial Retrosynthetic Considerations and Model Studies.**
Sporolides A (**1a**) and B (**1b**) share the same molecular structure except for the location of the chlorine atom on the benzenoid nucleus. Of their 24 carbons, 22 are either oxygenated or $sp^2$ hybridized, forming a web of unusual structural motifs, including a highly substituted indane system, a [1,4]-dioxane ring, an epoxy cyclohexenone hemiacetal, and a 13-membered macrolide moiety.[3a] Considering the unprecedented and complex molecular architectures of the sporolides, the discovery and development of new synthetic strategies and technologies were essential prerequisites for a serious attempt of their total synthesis. Figure 2 outlines, in retrosynthetic format, two plausible approaches to sporolide B (**1b**). Based on the postulated biosynthesis of the sporolides (**I + II → 1b**),[4b] the first approach (path a, Figure 2) was considered risky, despite the rather conventional steps required for its implementation, due to the expected lability of some of the obligatory intermediates. Therefore, the second approach, based on the rarely employed [4+2] cycloaddition reaction of *o*-quinones[10] (**III + IV → 1b**, path b, Figure 2), became our preferred choice for initial exploration.

In contemplating the *o*-quinone-based strategy toward sporolide B (**1b**), the two approaches shown retrosynthetically in Figure 3 (both relying on the same bond disconnections) came to mind. Path a requires an intermolecular *o*-quinone [4+2] cycloaddition with an indene partner, followed by a macrolactonization of seco acid **V** to forge the main ring skeleton of the target
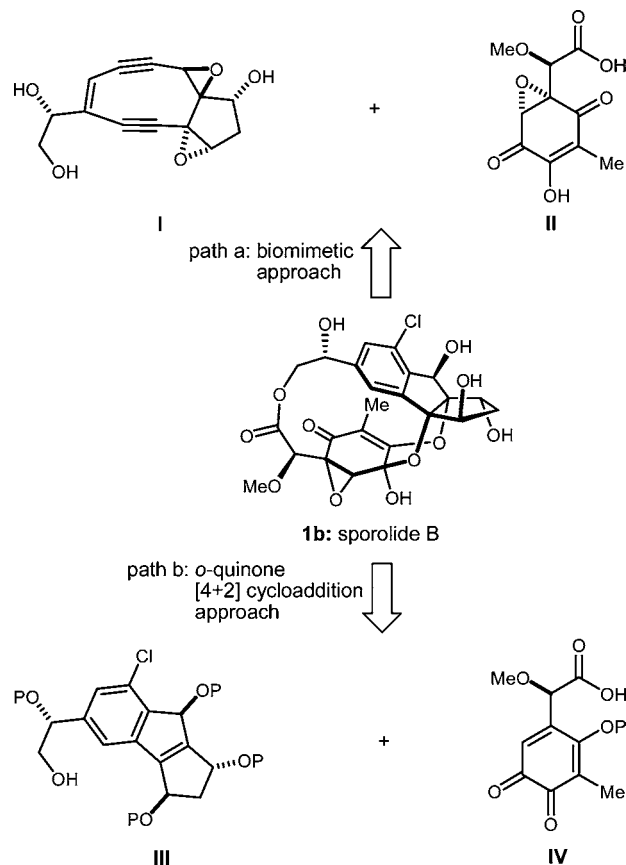
molecule. Path b reverses these two key steps and requires substrate **VI** as an intermediate postulated to undergo an intramolecular [4+2] cycloaddition[11] involving its *o*-quinone and indene structural motifs.

In order to test the viability of these two synthetic strategies (paths a and b, Figure 3a), we designed model systems **4** and **4′** and pursued their synthesis from an *o*-quinone derivative or surrogate (**6** or **8**, respectively, Figure 3b) and hydroxy indene fragments (**7** or **9**, respectively, Figure 3b). Our first task toward this goal was to prepare *o*-quinone **6** and study its reactivity toward suitable indene fragments. Scheme 1 summarizes the synthesis of this *o*-quinone starting with 3-methylsesamol (**10**).[12a] Thus, activation of phenol **10** with MeMgBr,[12b] followed by addition of glyoxalate **11**, led to phenolic hydroxy ester **12**

(10) (a) Horner, L.; Merz, H. *Justus Liebigs Ann. Chem.* **1950**, *570*, 89–120. (b) Finley, K. T. In *The Chemistry of Quinoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1988; Vol. II, pp 538−717. (c) Nair, V.; Kumar, S. *Synlett* **1996**, 1143–1147. (d) Kharisov, B. I.; Mendez-Rojas, M. A.; Garnovskii, A. D.; Ivakhnenko, E. P.; Ortiz-Mendez, U. *J. Coord. Chem.* **2002**, *55*, 745–770. (e) Aly, A. A.; Ehrhardt, S.; Hopf, H.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2006**, 335–350. (f) Varma, R. L.; Ganga, V. B.; Sureshc, E.; Suresh, C. H. *Tetrahedron Lett.* **2006**, *47*, 917–921.

(11) For recent examples of macrocyclization by standard cycloadditions, see: (a) Zapf, C. W.; Harrison, B. A.; Drahl, C.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6533–6537. (b) Johannes, J. W.; Wenglowsky, S.; Kishi, Y. *Org. Lett.* **2005**, *7*, 3997–4000. (c) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908–3909. (d) Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740–742.

(12) (a) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408. (b) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919–4922.
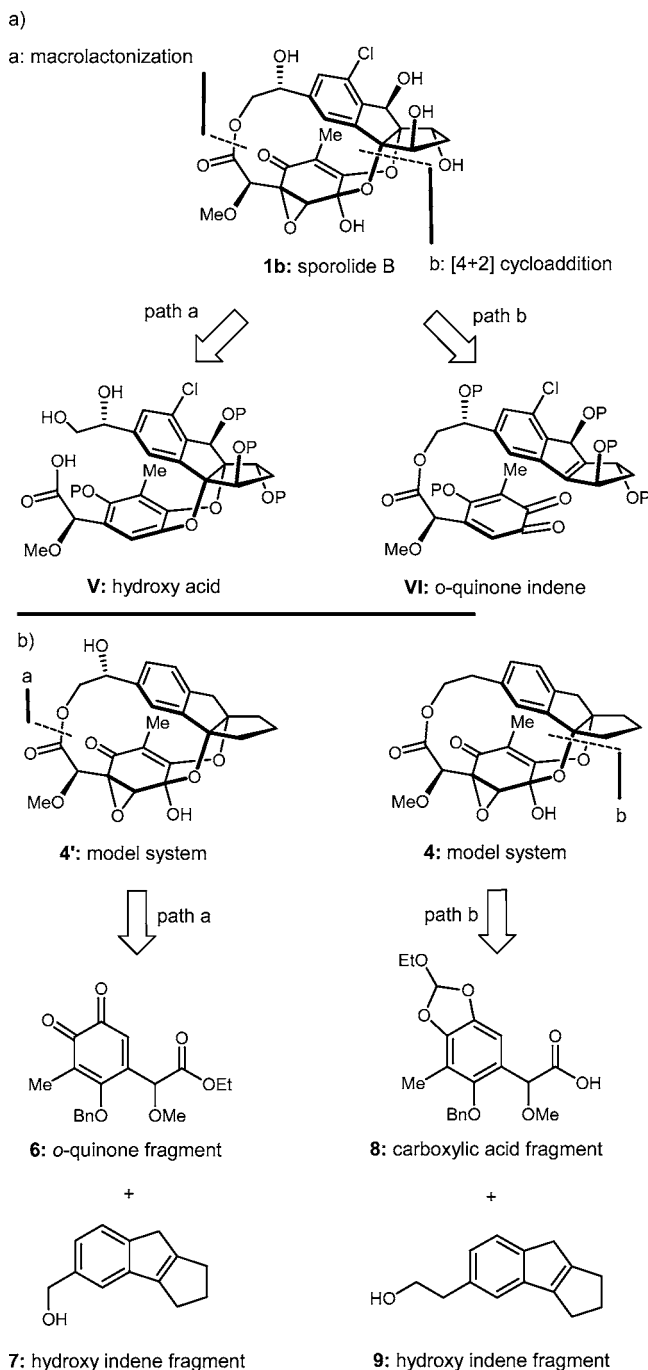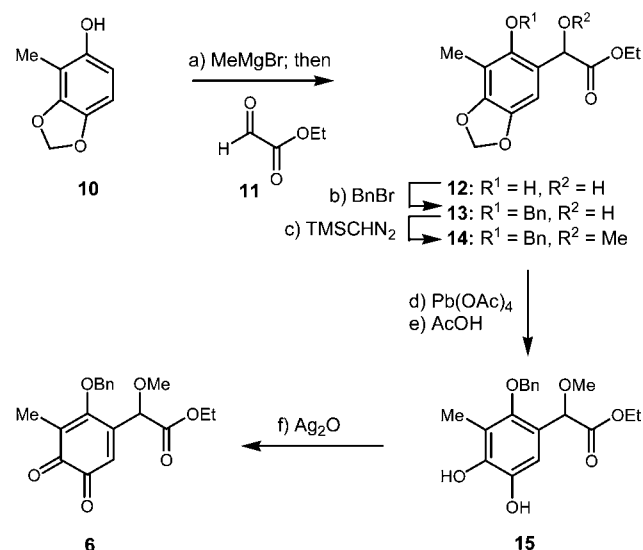
a)

a: macrolactonization



**1b**: sporolide B     b: [4+2] cycloaddition

path a          path b



**V**: hydroxy acid          **VI**: *o*-quinone indene

b)



**4'**: model system          **4**: model system

path a          path b



**6**: *o*-quinone fragment          **8**: carboxylic acid fragment

+          +



**7**: hydroxy indene fragment          **9**: hydroxy indene fragment

**Figure 3.** Retrosynthetic analysis of sporolide B (**1b**) and sporolide model systems **4'** and **4**.

in 98% yield. Reaction of the latter compound with BnBr in the presence of Cs$_2$CO$_3$ and NaI resulted in selective formation of hydroxy benzyl ether **13** (92% yield), which was methylated (TMSCHN$_2$, HBF$_4$)[13] to afford fully protected derivative **14**. Cleavage of the rather robust dioxolane ring within **14** was achieved through sequential treatment with Pb(OAc)$_4$ (benzene, with heating)[14] and AcOH, furnishing diphenol **15** in 95% overall yield. Interestingly, while **15** proved inert toward DDQ oxidation at ambient temperature and led to the corresponding

(13) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1990**, *31*, 5507–5508.
(14) Hussain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023–7032.

**Scheme 1.** Construction of *o*-Quinone **6**[a]



a) MeMgBr; then

**10**          **11**

b) BnBr      **12**: R$^1$ = H, R$^2$ = H
c) TMSCHN$_2$ **13**: R$^1$ = Bn, R$^2$ = H
              **14**: R$^1$ = Bn, R$^2$ = Me

d) Pb(OAc)$_4$
e) AcOH

f) Ag$_2$O

**6**          **15**

[a] Reagents and conditions: (a) **10**, MeMgBr (3.0 M in Et$_2$O, 1.2 equiv), THF, 0 °C, 0.5 h; then **11** (50% in toluene, 1.5 equiv), THF, 0 °C, 0.5 h, 98%; (b) BnBr (3.0 equiv), Cs$_2$CO$_3$ (2.0 equiv), NaI (1.0 equiv), DMF, 0 → 25 °C, 3 h, 92%; (c) TMSCHN$_2$ (2.0 M in hexanes, 2.0 equiv), HBF$_4$ (49% in H$_2$O, 1.0 equiv), CH$_2$Cl$_2$, 0 → 25 °C, 2 h, 81%; (d) Pb(OAc)$_4$ (1.5 equiv), benzene, 80 °C, 16 h; (e) AcOH:THF:H$_2$O (10:5:1), 25 °C, 6 h, 95% for the two steps; (f) Ag$_2$O (2.5 equiv), CH$_2$Cl$_2$, 25 °C, 15 min, 94%. Bn = benzyl, TMS = trimethylsilyl.

*p*-quinone in the presence of DMP or CAN, it reacted smoothly with Ag$_2$O to afford the desired *o*-quinone **6** in 94% yield.

Since the mode of [4+2] cycloaddition reactions of *o*-quinones with dienophiles depends on the nature of their substituents and is often unpredictable,[10] an initial investigation of the reactivity of *o*-quinone **6** toward indenes was deemed important. Scheme 2 summarizes a number of illuminating observations made in this model study. Thus, reaction of **6** with indene (**16**) in toluene at 110 °C proceeded smoothly but afforded 1,2-cyclohexadione system **17** as a mixture with its facial diastereoisomer **17'** (ca. 1.5:1 dr), products of the undesired reactivity mode for the *o*-quinone that involved its all-carbon diene system. The precise structure of this cycloadduct was evident from its NMR spectroscopic analysis, including the NOE correlation between the methyl group and its adjacent proton as indicated on its structure (see **17**, Scheme 2). The exquisite regioselectivity of this cycloaddition reaction may be explained by assuming polarization[10e] of the two reactants as indicated on transition state **6,16-TS** (see Scheme 2) and the relatively low steric demands associated with the olefinic bond of indene **16**. This leads to the engagement of the dienophile with the apparently more reactive, all-carbon diene system of *o*-quinone **6**. This reasoning led us to believe that by increasing the steric demands[10f] of the indene dienophile through fusion of the additional cyclopentane ring as required for our target molecule, we may be able to reverse the reactivity mode of the *o*-quinone component from the all-carbon diene to the 1,2-dicarbonyl moiety. Indeed, indene derivative **18**[15] reacted with *o*-quinone **6** under the same conditions as above to afford, presumably through transition state **6,18-TS** (see Scheme 2), 1,4-dioxane derivative **19** (ca. 1:1 mixture with its facial diastereoisomer **19'**) exclusively and in 57% yield. Needless to say, this was exciting news, but before we describe the next

(15) Halterman, R. L.; Zhu, C. *Tetrahedron Lett.* **1999**, *40*, 7445–7448.

**Scheme 2.** Intermolecular [4+2] Cycloaddition Reaction between Indene Derivatives and *o*-Quinone **6**[a]
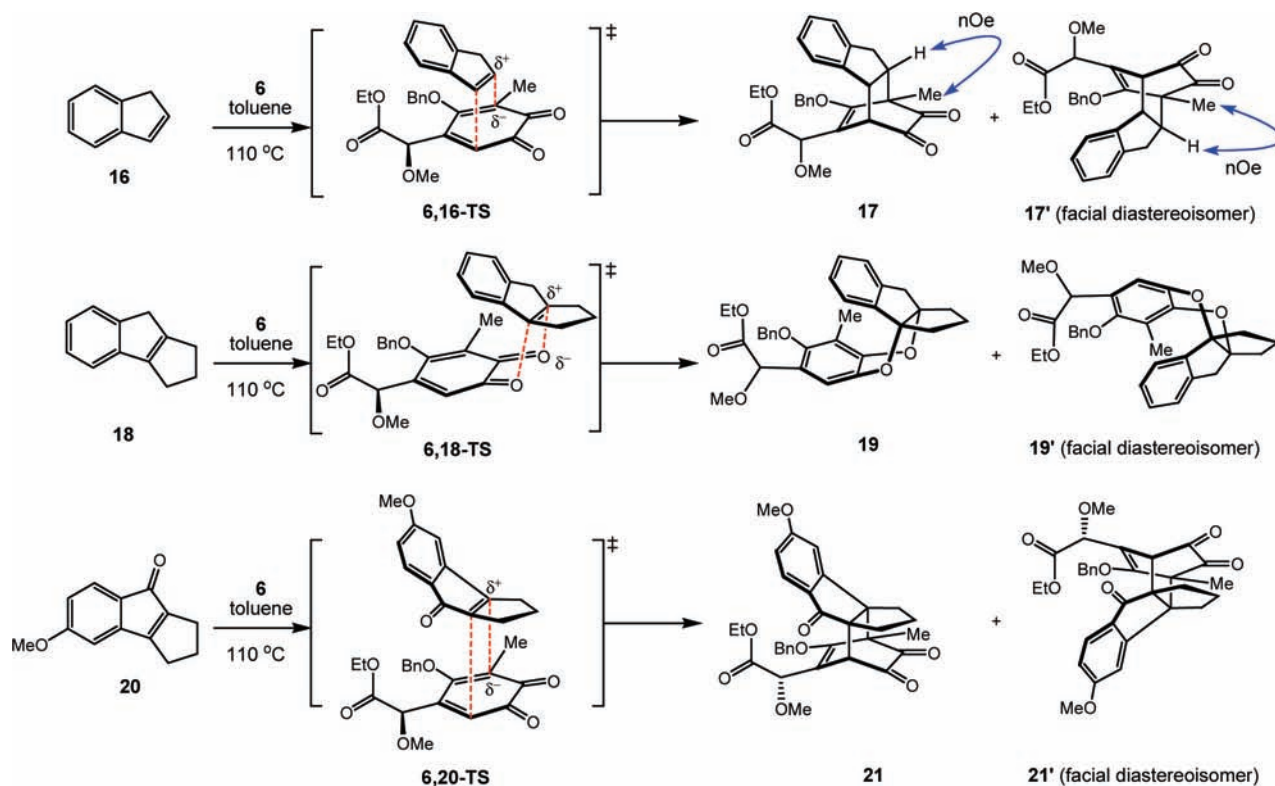


[a] Reagents and conditions: indene derivatives **16**, **18**, **20** (1.0 equiv), *o*-quinone **6** (1.2 equiv), toluene, 115 °C, 4 h **17,17′**, 82%, ca. 1.5:1 dr; **19,19′**, 57%, ca. 1:1 dr; and **21,21′**, 80%, ca. 10:1 dr.

phase of the campaign we should note that indene derivative **20** (Scheme 2) reacted with *o*-quinone **6** in yet another exquisite mode. Specifically, this [4+2] cycloaddition reaction led to carbocyclic system **21** as the major product in high yield (80%, ca. 10:1 mixture with its facial diastereoisomer **21′**), presumably through transition state **6,20-TS** as shown in Scheme 2. In this case, the regioselectivity exhibited by the *o*-quinone moiety of **6** toward indene (i.e., **16**) is preserved, whereas that of the dienophile is now reversed, apparently due to the presence of the polarizing carbonyl group within the indene partner. The higher reactivity of the latter component may explain its ability to overcome its steric demands and reach the more reactive, but more sterically shielded, all-carbon diene system of *o*-quinone **6**. The structure of the observed major product **21**, preferentially crystallized from EtOAc/hexanes (mp 210−212 °C, acetone/hexanes), was unambiguously proven through X-ray crystallographic analysis[16] (see ORTEP representation, Figure 4).

These studies suggested that hydroxy indene derivative **7** (Scheme 3) might be an appropriate partner, indeed, for *o*-quinone **6** in our first strategy toward sporolide model system **4′**. Its construction from benzoic acid derivative **22**[17] is summarized in Scheme 3. Thus, reduction of the carboxylic acid moiety of **22** with borane (80% yield), followed by protection of the resulting alcohol (dihydropyran, TsOH·H₂O, 95% yield),
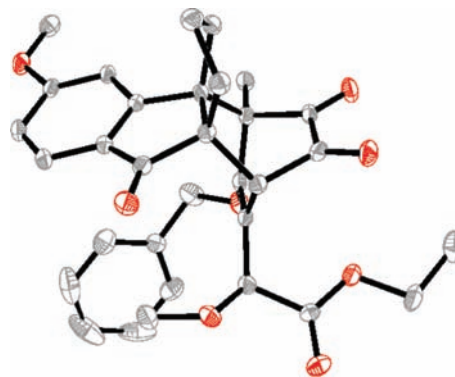
(16) CCDC-773715 contains the supplementary crystallographic data for compound **21**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc. cam.ac.uk/data_request/cif and are also available as Supporting Information.

(17) Shankar, S.; Vaidyanathan, G.; Affleck, D.; Welsh, P. C.; Zalutsky, M. R. *Bioconjugate Chem.* **2003**, *14*, 331–341.



**Figure 4.** ORTEP of **21** derived from X-ray crystallographic analysis (non-hydrogen atoms are shown as 30% ellipsoids).

furnished THP ether **23**. This benzyl bromide derivative (**23**) was then used to alkylate cyclopentanone (**24**, LDA) to afford aryl iodide **25** (65% yield), whose intramolecular Nozaki−Hiyama−Kishi reaction (CrCl₂, NiCl₂)[18] led to tricyclic tertiary alcohol **26** in 76% yield. Exposure of the latter compound to TsOH·OH caused both elimination of water and cleavage of the THP ether to afford the desired hydroxy indene **7** in 82% yield. The other required indene derivative **9** for model system **4** (path b, see Figure 3b) was formed from **7** by one-carbon homologation in 76% overall yield through the standard four-step sequence summarized in Scheme 3.

With both required fragments now available, we proceeded to explore the first approach to the designed sporolide model

(18) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, 1996; pp 711−730. (c) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991–1046.

**Scheme 3.** Construction of Indene Derivatives **7** and **9**[a]
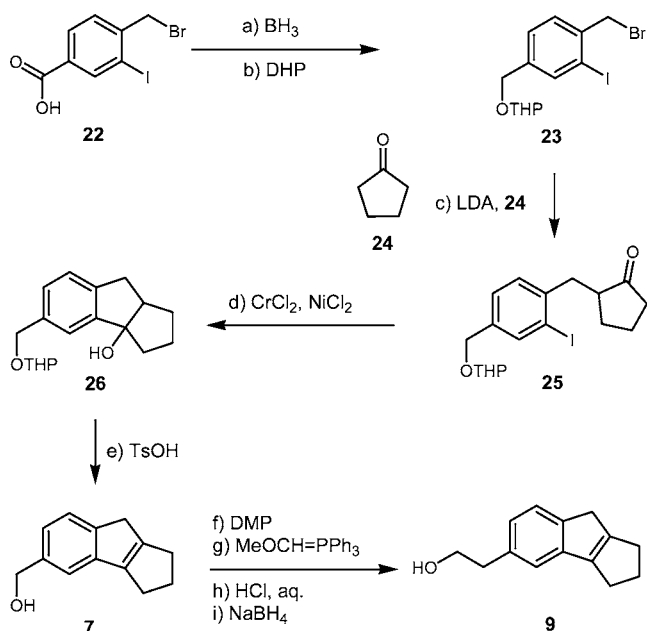


[a] Reagents and conditions: (a) BH$_3$·THF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 2 h, 80%; (b) DHP (1.2 equiv), TsOH·H$_2$O (0.1 equiv), CH$_2$Cl$_2$, 0 °C, 0.5 h, 95%; (c) **24** (1.3 equiv), LDA (1.3 equiv), THF:HMPA (5:1), −78 → 0 °C, 1 h; then **23** (1.0 equiv), −78 → 25 °C, 2 h, 65%; (d) CrCl$_2$ (4.0 equiv), NiCl$_2$ (0.02 equiv), DMF, 100 °C, 16 h, 76%; (e) TsOH·H$_2$O (0.1 equiv), benzene, 80 °C, 0.5 h; then MeOH, 25 °C, 0.5 h, 82%; (f) DMP (1.2 equiv), NaHCO$_3$ (3.0 equiv), CH$_2$Cl$_2$, 25 °C, 0.5 h, 95%; (g) MeOCH$_2$PPh$_3$Br (1.5 equiv), KHMDS (0.5 M in toluene, 1.5 equiv), THF, 0 → 25 °C, 2 h, 96%; (h) HCl (aq., 2.0 N, 4.0 equiv), THF, 60 °C, 3 h, 88%; (i) NaBH$_4$ (1.1 equiv), THF:MeOH (5:1), 0 °C, 0.5 h, 95%. DHP = 3,4-dihydro-2*H*-pyran, DMP = Dess−Martin periodinane, HMPA = hexamethylphosphoramide, KHMDS = potassium hexamethyldisilazane, LDA = lithium diisopropylamide, Ts = *p*-toluenesulfonyl.

system **4′** involving, in that order, the [4+2] cycloaddition and macrolactonization reactions, as outlined in Scheme 4. Thus, heating hydroxyl indene derivative **7** with *o*-quinone **6** in toluene at 115 °C led, as expected, and presumably through transition state **6,7-TS**, to 1,4-dioxa cycloadduct **27**, together with its facial diastereoisomer **27′**, in 62% combined yield (ca. 1:1 dr). This mixture was taken forward through the rest of the sequence in order to test the key macrolactonization step. Oxidation of **27+27′** (DMP, 88% yield), followed by olefination of the resulting aldehyde (**28+28′**, CH$_2$=PPh$_3$), furnished styrene derivative **29** (together with its facial diastereoisomer **29′**), whose asymmetric dihydroxylation (AD-mix β)[19] afforded diols **30+30′** (93% yield). Finally, saponification of the ethyl ester moiety within **30+30′** (LiOH) furnished seco acids **31+31′** (98% yield). All attempts to macrolactonize **31+31′** through either carboxyl[20] or hydroxyl activation[21] (see legend, Scheme 4) failed to produce any detectable amounts of the desired model system **32** (or its facial diastereoisomer **32′**), presumably due to overwhelming strain within the expected transition state for the macrolactonization reaction. These failures led us to the second, and more daring, appoach involving the risky intramolecular [4+2] cycloaddition as the means to forge the sporolide framework.

Scheme 5 summarizes the intramolecular *o*-quinone [4+2] cycloaddition approach to sporolide model system **4** from fragments **15** and **9**. Thus, catechol **15** was protected as orthoester **33** [CH(OEt)$_3$, TsOH·H$_2$O, 96% yield], which was saponified (LiOH, 99% yield) to afford carboxylic acid **34**.

**Scheme 4.** Synthesis of Dihydroxy Acid **31** and Failed Attempts To Form Macrocycle **32** through Macrolactonization[a]
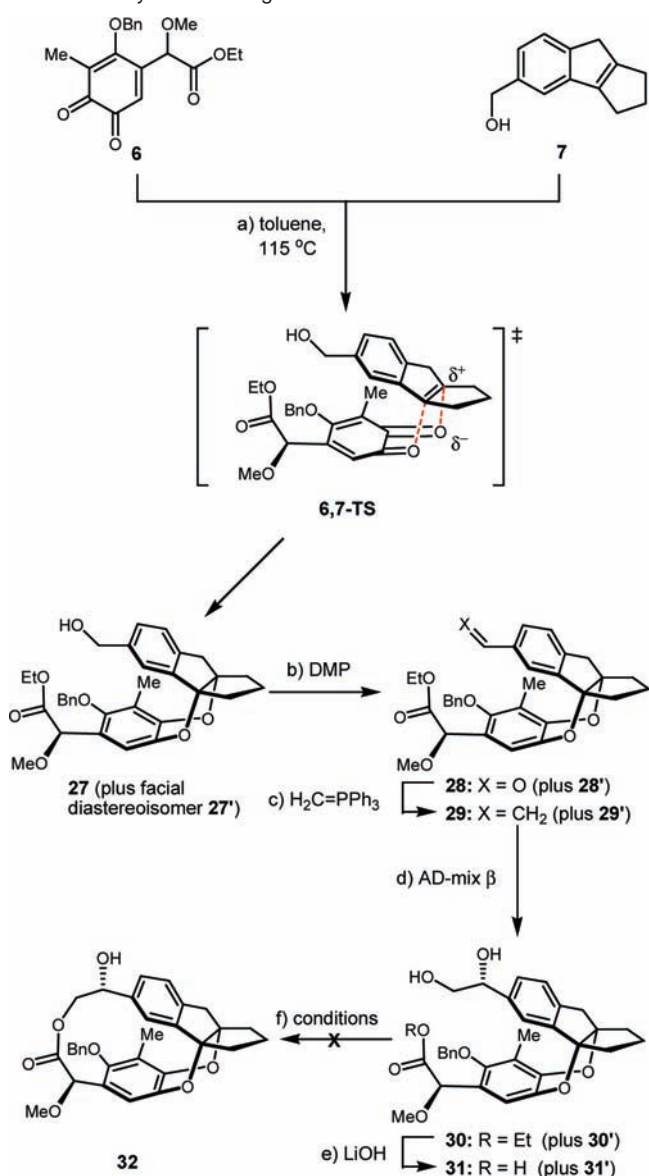


[a] Reagents and conditions: (a) **6** (1.0 equiv), **7** (1.2 equiv), toluene, 115 °C, 3 h, 62% [**27+27′** (not shown), ca. 1:1 dr]; (b) DMP (1.5 equiv), NaHCO$_3$ (5.0 equiv), CH$_2$Cl$_2$, 25 °C, 0.5 h, 88% [**28+28′** (not shown), ca. 1:1 dr]; (c) MePPh$_3$Br (4.5 equiv), KHMDS (0.5 M in toluene, 3.0 equiv), THF, −78 → 25 °C, 0.5 h; then **28+28′** (ca. 1:1 dr, 1.0 equiv), THF, −78 → 25 °C, 0.5 h, 91% [**29+29′** (not shown), ca. 1:1 dr]; (d) AD-mix β (1.4 g per 1.0 mmol of **29+29′**), *t*-BuOH:H$_2$O (1:1), 0 °C, 4 h, 93% [**30+30′** (not shown), ca. 1:1 dr]; (e) LiOH (30 equiv), dioxane:H$_2$O (5:1), 80 °C, 6 h, 98% [**31+31′** (not shown), ca. 1:1 dr]; (f) carboxylic acid activation methods (Corey−Nicolaou,[22] Yamaguchi,[23] cyanuric chloride,[24] Mukaiyama salt,[25] Shiina[26]); alcohol activation method (Mitsunobu[21]).

Coupling of the latter intermediate with hydroxy indene **9** (see Scheme 3 for preparation) through DCC/4-DMAP esterification

(19) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768–2771. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(20) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911–939.

(21) (a) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, *17*, 2455–2458. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656. (d) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164.

**Scheme 5.** Synthesis of Sporolide Model System 4[a]
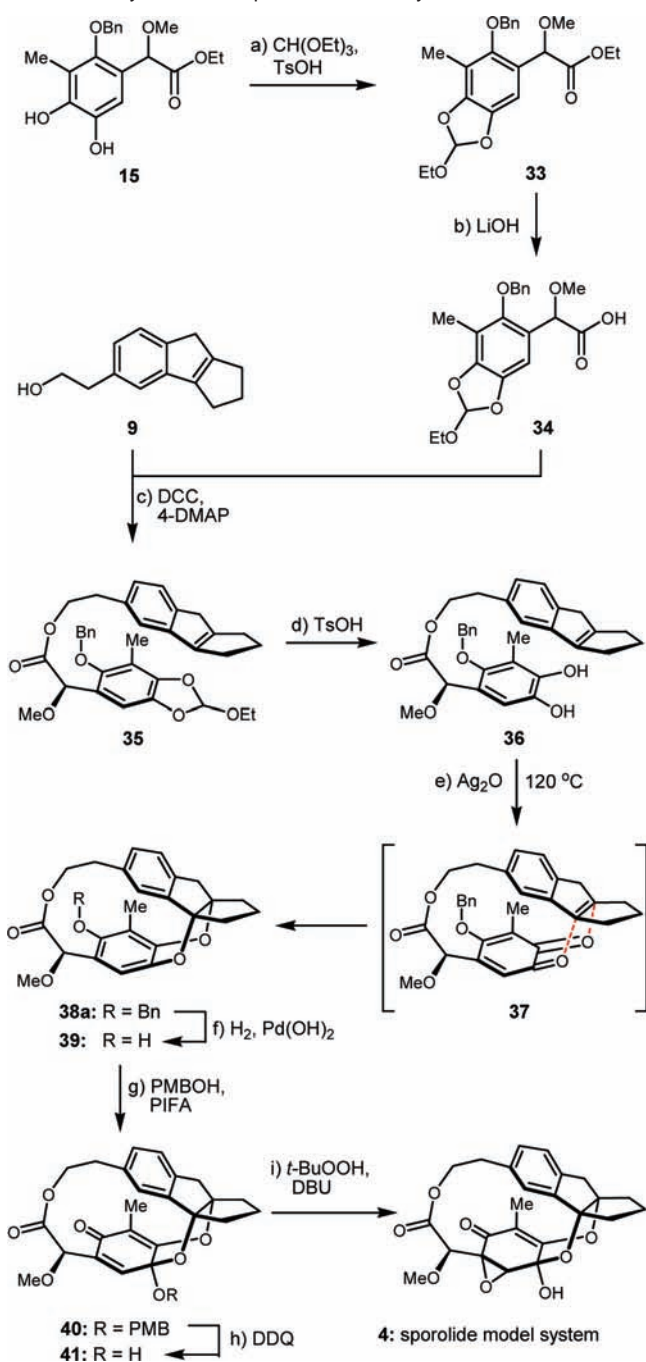


[a] Reagents and conditions: (a) CH(OEt)$_3$ (2.0 equiv), TsOH·H$_2$O (0.2 equiv), 4 Å MS (80 mg per mmol of 15), benzene, 80 °C, 16 h, 96%; (b) LiOH (20 equiv), dioxane:H$_2$O (5:1), 80 °C, 3 h, 99%; (c) 34 (1.25 equiv), 9 (1.0 equiv), DCC (1.3 equiv), 4-DMAP (0.2 equiv), CH$_2$Cl$_2$, 25 °C, 3 h, 84%; (d) TsOH·H$_2$O (0.05 equiv), MeOH, 25 °C, 24 h, 98%; (e) one-step procedure: Ag$_2$O (2.0 equiv), toluene (c = 0.005 M solution), 120 °C, 1 h, 60%; two-step procedure: (i) Ag$_2$O (2.0 equiv), CH$_2$Cl$_2$, 25 °C, 5 min, 99%; (ii) toluene (c = 0.005 M solution), 120 °C, 3 h, 50%; (f) H$_2$ (balloon), Pd(OH)$_2$/C (20 wt %), EtOH, 25 °C, 14 h, 85%; (g) PIFA (1.05 equiv), PMBOH (10.0 equiv), K$_2$CO$_3$ (5.0 equiv), MeCN, 0 → 25 °C, 5 min, 87%; (h) DDQ (1.5 equiv), CH$_2$Cl$_2$:H$_2$O (10:1), 25 °C, 15 h, 96%; (i) t-BuOOH (5.0 equiv), DBU (0.2 equiv), CH$_2$Cl$_2$, 40 °C, 24 h, 60%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCC = N,N'-dicyclohexylcarbodiimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 4-DMAP = 4-dimethylaminopyridine, PIFA = phenyliodine bis(trifluoroacetate), PMB = p-methoxybenzyl.

led to ester 35 (84% yield), whose exposure to TsOH·H$_2$O afforded catechol ester 36 in 98% yield. Pleasantly, the latter



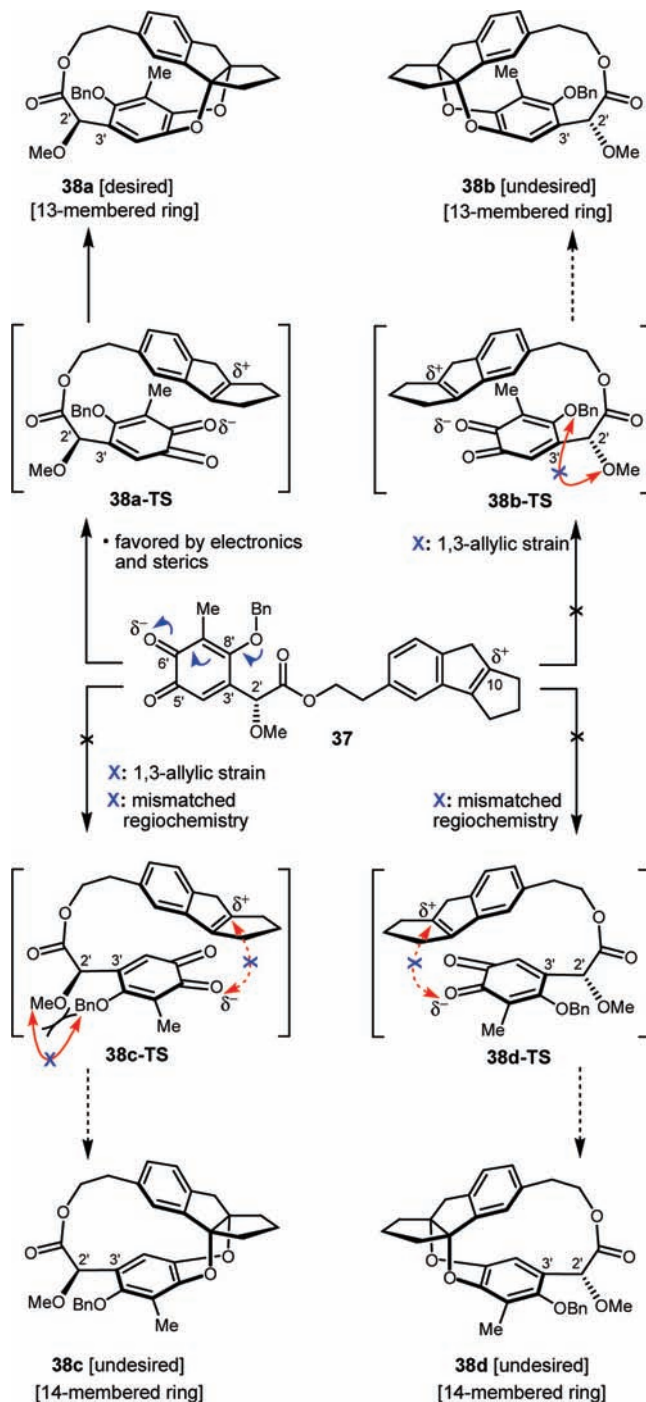**Figure 5.** Four possible diastereoisomers of macrolide 38 (a−d) and rationale for the exclusive formation of the only isomer (i.e., 38a).

compound served as a precursor, first to o-quinone 37 and then to the desired, doubly cyclized cycloadduct 38a. Thus, heating the deep-red solution of 36 in toluene at 120 °C (oil bath) in the presence of Ag$_2$O afforded compound 38a, presumably through o-quinone 37, in 60% isolated yield. Indeed, the latter intermediate was prepared from 36 by oxidation with Ag$_2$O at room temperature (99% yield) and, when heated in toluene at 120 °C, furnished compound 38a in 50% yield. This product was obtained as a single diastereoisomer (out of the four possible diastereoisomers, 38a−d, shown in Figure 5). Its structure was consistent with its NMR spectral data, including the ^{13}C NMR chemical shifts for the two newly formed tertiary dioxane
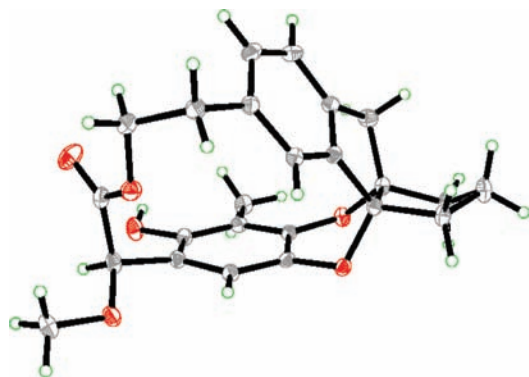
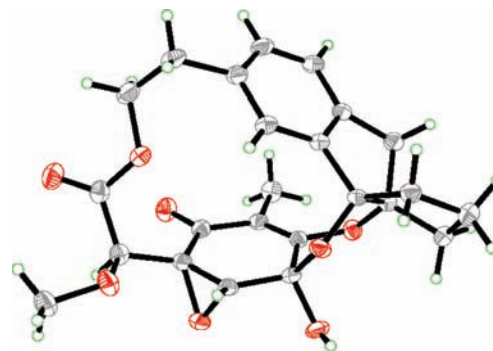**Figure 6.** ORTEP of compound **39** derived from X-ray crystallographic analysis (atoms are shown as 30% ellipsoids).



**Figure 7.** ORTEP of sporolide model system **4** derived from X-ray crystallographic analysis (atoms are shown as 30% ellipsoids).

carbons ($\delta = 101.5$ and 98.3 ppm, 150 MHz, CDCl$_3$). An X-ray crystallographic analysis[27] of the debenzylated derivative (**39**, mp 233−234 °C, acetone/hexanes) of **38a** provided unambiguous proof of its structure as shown (see ORTEP representation, Figure 6). This stereochemical outcome can be attributed to a combination of electronic and steric effects, as shown in Figure 5. Electron donation from the benzyl ether oxygen toward the C6′ carbonyl oxygen results in polarization of the *o*-quinone system of substrate **37**. The partial negative charge ($\delta^-$) on this oxygen atom matches the partial positive charge ($\delta^+$) on the C10 indene olefinic carbon, thereby providing guidance for the regiochemical outcome of the ensuing [4+2] cycloaddition. The other factors controlling the outcome of this reaction include steric effects (1,3-allylic strain) and feasibility of bond formation (ability of the two polarized ends to reach each other to form a bond). As depicted in Figure 5, from the four possible transition states (**38a−d-TS**), only **38a-TS**, leading to the desired product **38a**, is favored by both electronic matching and sterics. Indeed, in this case the OMe group (front) resides opposite the OBn (back), and the O$^{\delta-}$ is well positioned beneath the C$^{\delta+}$ for bonding interaction and ring formation. Transition state **38b-TS** suffers from 1,3-allylic strain (OBn group resides on the same side as the OMe group, both in back). Transition state **38c-TS** suffers from both 1,3-allylic strain (both OBn and OMe in front) and a mismatch of the positions of the partial charges ($\delta^-$ front, $\delta^+$ back). Transition state **38d-TS** suffers from a mismatch of the positions of the partial charges ($\delta^+$ front, $\delta^-$ back). In view of these considerations, the fact that only product **38a** is formed in this intramolecular [4+2] cycloaddition is no surprise.

Having secured key intermediate **38a**, its further elaboration, requiring dearomatization and appropriate functionalization, was undertaken (Scheme. 5). Thus, hydrogenolysis of the benzyl ether within **38a** [H$_2$, Pd(OH)$_2$/C] furnished phenol **39** (85%

yield), whose exposure to PIFA[28] in the presence of PMBOH and K$_2$CO$_3$ led to *p*-hemiquinone **40** in 87% yield. Treatment of the latter intermediate with DDQ gave *p*-hydroxy hemiquinol **41** (96% yield), which underwent selective epoxidation (*t*-BuOOH, DBU, 40 °C)[29] under controlled conditions to afford the targeted sporolide model system **4** in 60% yield. The regio- and stereocontrol observed in the latter reaction was ensured not only by the directing effect of the hemiacetal moiety but also by the shielding effects imposed upon the top face of the olefinic bond by the macrocyclic structural motif of the substrate (**41**). That all structural motifs were present within **4** (mp 218−219 °C, acetone/hexanes) in their proper stereochemical arrangements was proven through an X-ray crystallographic analysis[30] (see ORTEP representation, Figure 7)

**Unsuccessful Forays toward Sporolide B.** The successful model study culminating in the synthesis of sporolide model system **4** set the foundation for the next phase of the program toward the total synthesis of **1b**, the sporolide chosen as our synthetic target molecule. The two approaches considered toward sporolide B (**1b**) are shown retrosynthetically in Figure 8. Path a was based on the obvious disconnection of the ester bond within advanced precursor **VII** obtained through disassembly of the 1,4-dioxane ring of sporolide B (**1b**), as depicted. This analysis led to key building blocks carboxylic acid **VIII** and hydroxy chloroindene **IX** as the requisite fragments for the projected synthetic strategy.

Although a synthesis of enantiopure carboxylic acid **VIII** (P = Bn) could be secured (see below), repeated attempts to construct hydroxy chloroindene **IX** through conventional methods were met with difficulties, presumably due to the sensitive and crowded nature of this molecule. These failures let us to consider the alternative strategy (path b) shown in Figure 8 as a possible avenue to reach the desired precursor **VII**. In this scenario, the chlorobenzenoid nucleus in **VII** was disassembled through a metal-catalyzed [2+2+2] cycloaddition[31] that led to propargylic alcohol **42** and chloroacetylene enyne **43** as the desired building blocks for sporolide B (**1b**). These building blocks were then traced back to even simpler starting materials through the disconnections indicated on their structures (see Figure 8).

(22) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–5616.

(23) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(24) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893–1896.

(25) Mikaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50.

(26) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535–7539.

(27) CCDC-667552 contains the supplementary crystallographic data for compound **39**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif and are also available as Supporting Information.

(28) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927–3930.

(29) Zilbeyyaz, K.; Sahin, E.; Kilic, H. *Tetrahedron: Asymmetry* **2007**, *18*, 791–796.

(30) CCDC-669253 contains the supplementary crystallographic data for compound **4**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif and are also available as Supporting Information.
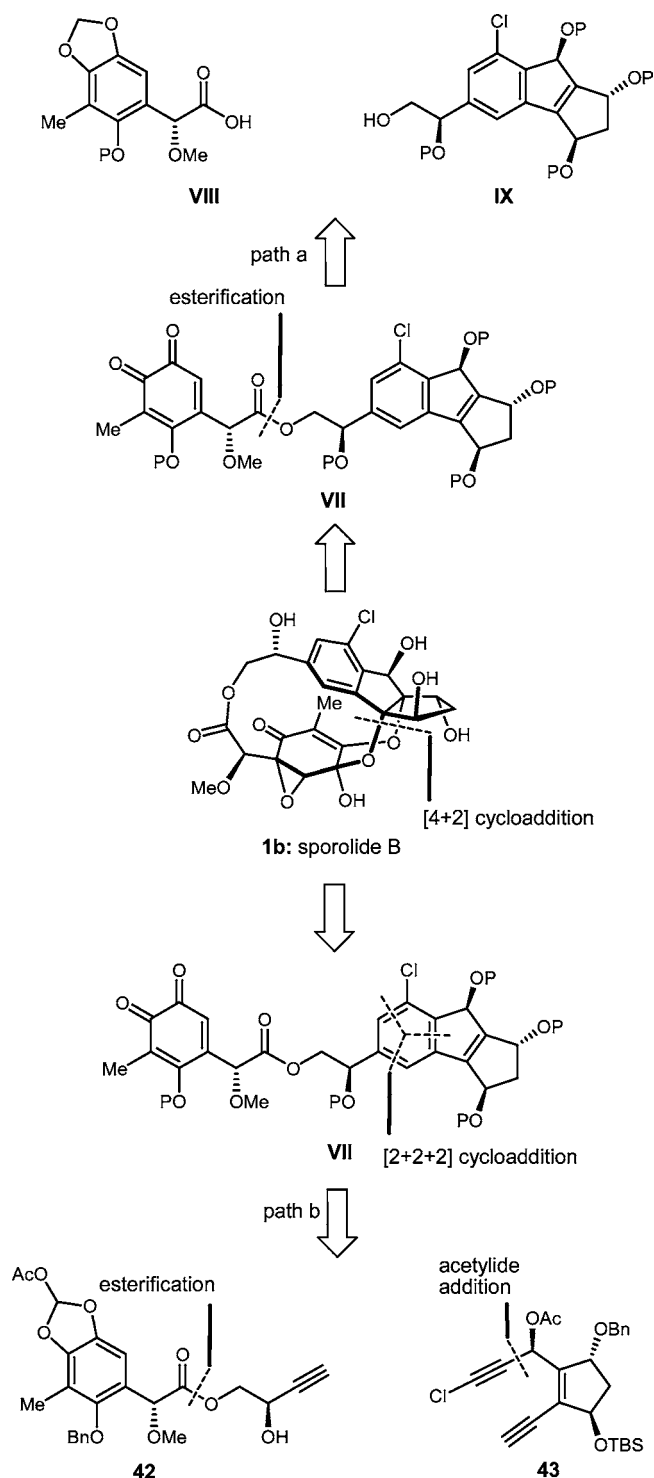
**Figure 8.** Retrosynthetic analysis (path a, top; path b, bottom) of sporolide B (**1b**).

The hydroxy ester fragment **42** was synthesized through coupling and elaboration of carboxylic acid **48** and acetylenic diol **49**, starting with benzaldehyde derivative **44**,[32] as summarized in Scheme 6. Thus, methylenation of aldehyde **44** (Ph$_3$P=CH$_2$, 98% yield) followed by asymmetric dihydroxylation (AD-mix $\beta$)[19] of the resulting styrene **45** furnished 1,2-diol **46** in 96% yield and 98% ee (chiral HPLC). Conversion of the latter compound to methoxy primary alcohol **47** required temporary silylation of the primary alcohol (TBSCl, 99% yield), methylation of the secondary alcohol (t-BuOK, MeI, 95% yield),

**Scheme 6.** Construction of Propargylic Alcohol **42**[a]
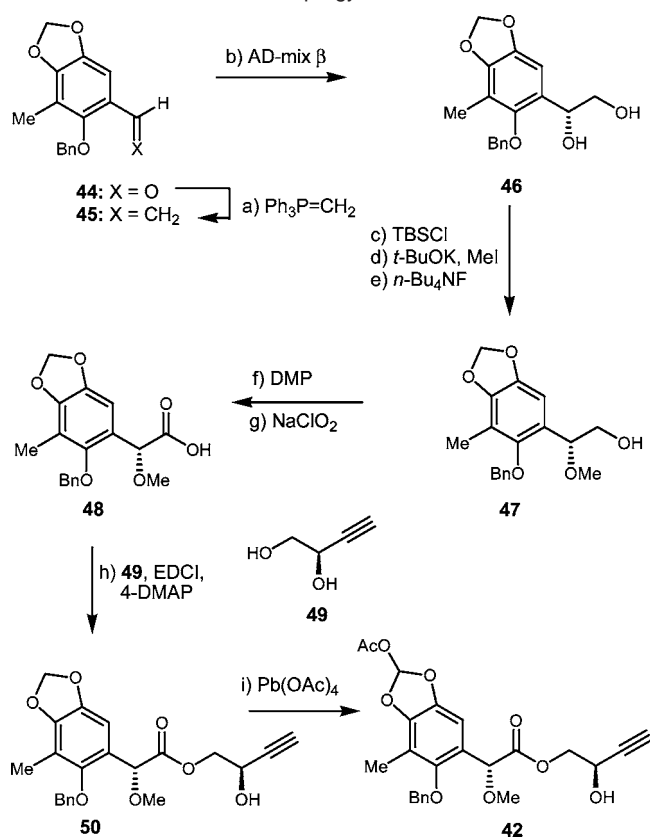


[a] Reagents and conditions: (a) MePPh$_3$Br (1.5 equiv), KHMDS (1.0 M in toluene, 1.2 equiv), THF, −78 → 0 °C, 0.5 h; then **44**, THF, −78 → 0 °C, 0.5 h, 98%; (b) AD-mix $\beta$ (1.4 g per mmol of **45**), t-BuOH:H$_2$O (1:1), 25 °C, 8 h, 96%, 98% ee by chiral HPLC; (c) TBSCl (1.5 equiv), Et$_3$N (1.5 equiv), 4-DMAP (0.1 equiv), CH$_2$Cl$_2$, 25 °C, 8 h, 99%; (d) t-BuOK (3.0 equiv), MeI (4.0 equiv), MeCN, 0 → 25 °C, 16 h, 95%; (e) n-Bu$_4$NF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 16 h, 99%; (f) DMP (1.5 equiv), NaHCO$_3$ (5.0 equiv), CH$_2$Cl$_2$, 25 °C, 1 h, 78%; (g) NaClO$_2$ (4.5 equiv), NaH$_2$PO$_4$·2H$_2$O (3.0 equiv), 2-methyl-2-butene (2.5 equiv), t-BuOH:H$_2$O (1:1), 25 °C, 0.5 h, 96%; (h) **49** (1.3 equiv), EDCI (1.2 equiv), 4-DMAP (0.2 equiv), CH$_2$Cl$_2$, 25 °C, 3 h, 73%; (i) Pb(OAc)$_4$ (1.5 equiv), benzene, 75 °C, 1 h, 89%. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

and removal of the TBS group (TBAF, 99% yield). Generation of the corresponding aldehyde from primary alcohol **47** (DMP, 78% yield) followed by Pinnick oxidation (96% yield, 98% ee, chiral HPLC) then led to carboxylic acid **48**. This intermediate proved rather sensitive to racemization even on standing, and, therefore, was freshly prepared and coupled with acetylenic diol **49**[33] in the presence of EDCI and 4-DMAP to afford hydroxy ester **50** in 73% yield. At this point, it was necessary to partially
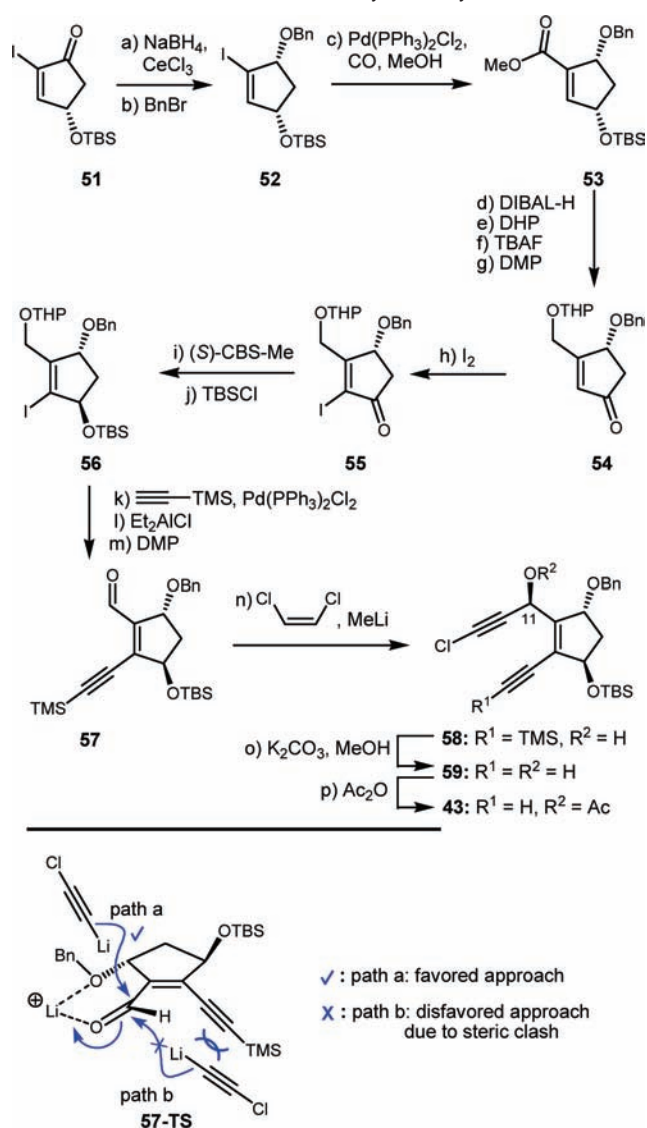
(31) (a) Shore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2916. (c) Varela, J. A.; Sa, C. *Chem. Rev.* **2003**, *103*, 3787–3802. (d) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043–6061. (e) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503–509. (f) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, *70*, 4741–4761. (g) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307–2327. (h) Tanaka, K. *Synlett* **2007**, 1977–1993. (i) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085–1094. (j) Agenet, N.; Busine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Org. React.* **2007**, *68*, 1–302. (k) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, *6*, 1317–1323. (l) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830–2834.
(32) Saito, N.; Tashiro, K.; Maru, Y.; Yamaguchi, K.; Kubo, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 53–69.
(33) Yadav, J. S.; Chander, M. C.; Joshi, B. V. *Tetrahedron Lett.* **1988**, *29*, 2737–2740.

oxidize the methylene protecting moiety within **50** in order to facilitate its pending rupture under mild conditions at a later stage. This was accomplished through the action of Pb(OAc)$_4$ in benzene[14] at 75 °C, which afforded acetoxy derivative **42** in 89% yield.

The readily available iodocyclopentenone **51**[34] served as an excellent precursor to the desired chloroacetylenic enyne fragment **43**, as shown in Scheme 7. Thus, Luche reduction (NaBH$_4$, CeCl$_3$·7H$_2$O)[35] of **51** followed by benzylation (BnBr, NaH, *n*-Bu$_4$NI) of the resulting secondary alcohol furnished vinyl iodide **52** in 95% overall yield. Carboxymethylation[36] of the latter compound [CO, Pd(PPh$_3$)$_2$Cl$_2$, MeOH] afforded methyl ester **53** in 95% yield. A sequence of four steps was then employed to convert ester **53** to enone **54** [(i) DIBAL-H, 95% yield; (ii) DHP, TsOH·H$_2$O; (iii) TBAF, (iv) DMP, 83% overall yield for the three steps]. Iodination (I$_2$, 80% yield) of this enone (**54**) afforded iodoenone **55**, whose CBS reduction [(S)-CBS-Me][37] and TBS protection of the so-obtained alcohol (ca. 10:1 dr) led to the intended TBS ether **56** in 97% overall yield for the two steps. Incidently, reduction of iodoenone **55** under standard Luche reduction conditions[35] led, as expected on steric grounds, to the corresponding 1,4-*syn* diol. Sonogashira coupling[38] of vinyl iodide **56** with TMS acetylene (79% yield) then furnished, after THP cleavage (Et$_2$AlCl) and DMP oxidation (73% yield for the two steps), aldehyde **57**. This aldehyde was added to lithio chloroacetylene, generated in situ from *cis*-1,2-dichloroethylene and MeLi,[39] to give propargylic alcohol **58** (ca. 7:1 dr, chelation-controlled, see path a in **57-TS**, Scheme 7) in 79% yield. Pure **58** was obtained at this stage by chromatographic removal of all other minor diastereoisomers obtained in the CBS reduction (**55** → **56**) and the lithio chloroacetylene addition (**57** → **58**). Finally, the TMS group was removed from intermediate **58** with K$_2$CO$_3$ in MeOH to afford compound **59**, whose hydroxy group was acetylated, leading to the targeted fragment chloroacetylenic enyne **43** in 93% yield for the two steps.

With both fragments acetylenic ester **42** and chloroacetylenic enyne **43** in hand, their [2+2+2] cycloaddition to form the desired indene structural motif became the next task. As shown in Scheme 8, it was found that reaction of these compounds in the presence of catalytic amounts of Cp*RuCl(COD)[40] at ambient temperature furnished a single regioisomer (77% yield) whose structure was determined to be that depicted as **60** (for a mechanistic rationale for this outcome, see below). Acetylation of the lone hydroxyl group within the latter intermediate (Ac$_2$O, 4-DMAP, Et$_3$N, 81% yield), followed by treatment with aqueous HF, caused desilylation and liberation of the catechol moiety (50% yield, unoptimized) to afford diphenolic hydroxy diacetate **61**, in which the C-11 stereocenter had apparently epimerized

(34) (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015. (b) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983–2004.

(35) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(36) Pichlmaira, S.; de Lera Ruiza, M.; Basua, K.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5178–5194.

(37) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(38) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470. (b) Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582–1583.

(39) Phillips, D.; Wickham, P.; Potts, G.; Arnold, A. *J. Med. Chem.* **1968**, *11*, 924–928.

(40) (a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549–550. (b) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143–12160. (c) Oshima, N.; Suzuki, H.; Moro-oka, Y. *Chem. Lett.* **1984**, *13*, 1161–1164.

**Scheme 7.** Construction of Chloroacetylenic Enyne **43**[a]



[a] Reagents and conditions: (a) NaBH$_4$ (1.2 equiv), CeCl$_3$·7H$_2$O (1.2 equiv), MeOH, −78 °C, 1 h; (b) NaH (60% in mineral oil, 1.5 equiv), THF, 0 °C, 0.5 h; then BnBr (1.5 equiv), *n*-Bu$_4$NI (0.2 equiv), THF, 0 → 25 °C, 16 h, 95% for the two steps (ca. 10:1 dr); (c) Pd(PPh$_3$)$_2$Cl$_2$ (0.05 equiv), Et$_3$N (5.0 equiv), CO (balloon), MeOH, 70 °C, 3 h, 95%; (d) DIBAL-H (1.0 M in toluene, 2.5 equiv), toluene, −78 → −10 °C, 1 h, 95%; (e) DHP (1.5 equiv), TsOH·H$_2$O (0.1 equiv), CH$_2$Cl$_2$, 0 °C, 0.5 h; (f) *n*-Bu$_4$NF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 3 h; (g) DMP (1.2 equiv), NaHCO$_3$ (5.0 equiv), CH$_2$Cl$_2$, 25 °C, 0.5 h, 83% for the three steps; (h) I$_2$ (3.0 equiv), CH$_2$Cl$_2$:pyridine (1:1), 25 °C, 15 h, 80%; (i) (S)-CBS-Me (1.0 M in toluene, 0.1 equiv), BH$_3$·THF (1.0 M in THF, 1.3 equiv), THF, −30 °C, 2 h, 99%; (j) TBSCl (2.0 equiv), imidazole (2.0 equiv), 4-DMAP (0.1 equiv), CH$_2$Cl$_2$, 25 °C, 16 h, 97%; (k) TMS acetylene (1.5 equiv), Pd(PPh$_3$)$_2$Cl$_2$ (0.02 equiv), CuI (0.04 equiv), Et$_2$NH, 25 °C, 16 h, 79%; (l) Et$_2$AlCl (1.8 M in toluene, 2.0 equiv), CH$_2$Cl$_2$, −25 → 25 °C, 3 h; (m) DMP (1.5 equiv), NaHCO$_3$ (5.0 equiv), CH$_2$Cl$_2$, 25 °C, 0.5 h, 73% for the two steps; (n) *cis*-1,2-dichloroethylene (4.5 equiv), MeLi (1.6 M in Et$_2$O, 3.0 equiv), Et$_2$O, 0 °C, 0.5 h; then **57**, Et$_2$O, 0 °C, 15 min, 79% of pure **58** (ca. 7:1 dr, all the undesired diastereoisomers were chromatographically removed at this stage); (o) K$_2$CO$_3$ (1.5 equiv), MeOH, 25 °C, 1 h, 99%; (p) Ac$_2$O (1.5 equiv), Et$_3$N (2.0 equiv), 4-DMAP (0.1 equiv), CH$_2$Cl$_2$, 0 °C, 0.5 h, 93%. (S)-CBS-Me = (S)-(−)-2-methyl-CBS-oxazaborolidine.

(ca. 1:1 dr). This mixture was oxidized with Ag$_2$O to furnish *o*-quinone **62** in 89% yield (mixture of C-11 diastereoisomers, ca. 1:1 dr). Attempts to induce the desired intramolecular [4+2] cycloaddition of substrate **62** (heating in toluene up to 120 °C), however, failed, leading to either no reaction or decomposition,
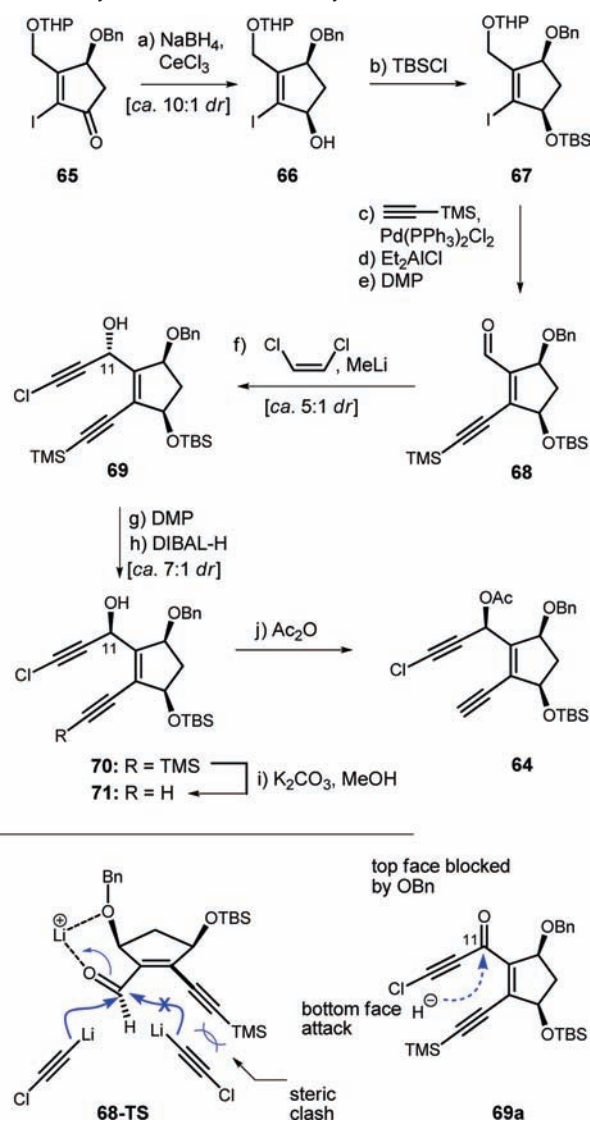
**Scheme 8.** Synthesis of *o*-Quinone **62** and Failed Attempt To Induce Its Intramolecular [4+2] Cycloaddition Reaction[a]



**Scheme 9.** Synthesis of Chloro Enediyne **64**[a]
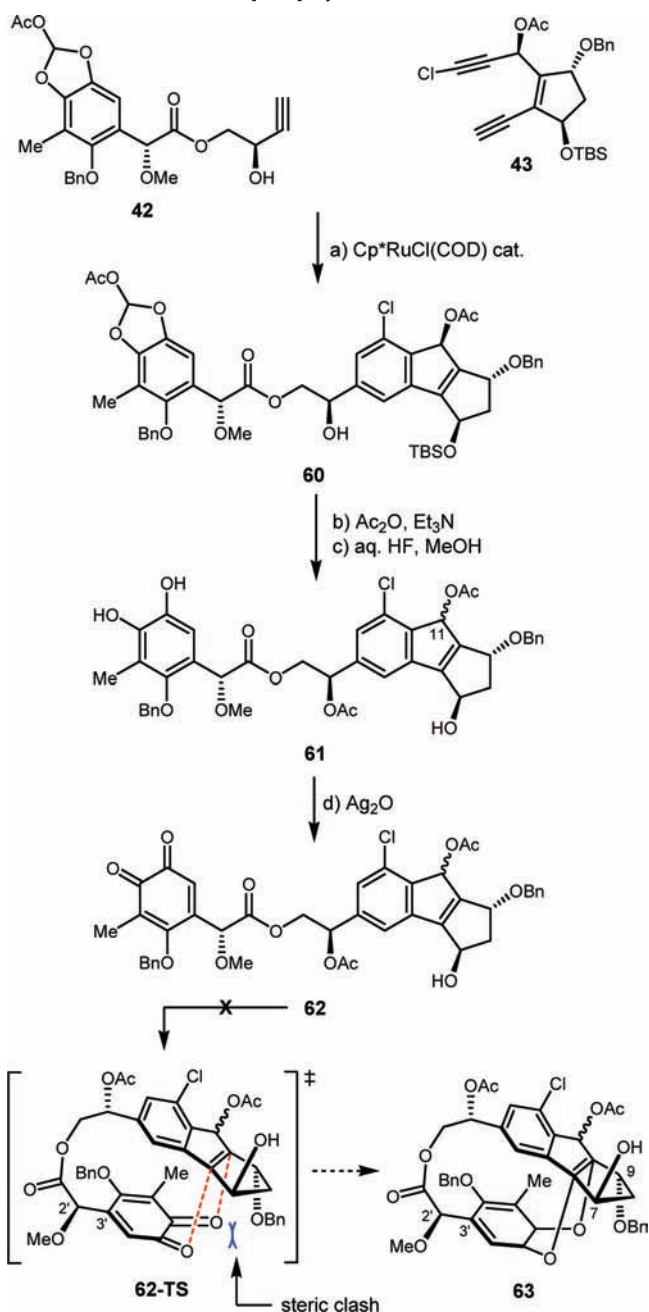


[a] Reagents and conditions: (a) **42** (1.0 equiv), **43** (1.0 equiv), Cp*RuCl(COD) (0.10 equiv), DCE, 25 °C, 0.5 h, 77%; (b) Ac₂O (2.0 equiv), Et₃N (2.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 0 °C, 0.5 h, 81%; (c) HF (48% aqueous solution, excess), MeCN, 25 °C, 0.5 h; then MeOH (excess), 25 °C, 3 h, 50%; (d) Ag₂O (2.5 equiv), CH₂Cl₂, 25 °C, 0.5 h, 89%. COD = 1,5-cyclooctadiene, Cp* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane.

with no detectable amounts of the expected cycloadduct **63**. The steric clash encountered by the approaching *o*-quinone moiety with the OBn group (see transition state **62-TS**, Scheme 8) is apparently prohibitive.

**Total Synthesis of 9-*epi*-Sporolide B.** Having failed to induce the intramolecular [4+2] cycloaddition reaction with the *o*-quinone–indene substrate possessing the desired C-9 configuration for sporolide B, we resorted to a modified strategy involving a substrate with the C-9 inverted stereochemistry in order to remove the steric barrier to the intended [4+2]

[a] Reagents and conditions: (a) NaBH₄ (1.2 equiv), CeCl₃·7H₂O (1.2 equiv), MeOH, −78 °C, 1 h, 99%, ca. 10:1 dr; (b) TBSCl (2.0 equiv), imidazole (2.0 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 25 °C, 3 h, 95%; (c) TMS acetylene (1.2 equiv), Pd(PPh₃)₂Cl₂ (0.02 equiv), CuI (0.04 equiv), Et₂NH, 25 °C, 16 h, 98%; (d) Et₂AlCl (1.8 M in toluene, 2.0 equiv), CH₂Cl₂, −25 → 25 °C, 2 h, 99%; (e) DMP (1.2 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 1 h, 79%; (f) *cis*-1,2-dichloroethylene (4.5 equiv), MeLi (1.6 M in Et₂O, 3.0 equiv), Et₂O, 0 °C, 0.5 h; then **68**, Et₂O, 0 °C, 10 min, ca. 5:1 dr; (g) DMP (1.5 equiv), NaHCO₃ (5.0 equiv), 25 °C, 0.5 h, 93% for the two steps; (h) DIBAL-H (1.0 M in toluene, 1.5 equiv), toluene, −78 °C, 0.5 h, 81% of pure **70** (ca. 7:1 dr, all the undesired diastereoisomers were chromatographically removed at this stage); (i) K₂CO₃ (1.5 equiv), MeOH, 25 °C, 1 h, 99%; (j) Ac₂O (1.5 equiv), Et₃N (1.5 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 0 °C, 0.5 h, 98%.

cycloaddition imposed by this substituent. The new strategy required chloroacetylene **64** (Scheme 9) as a key building block. Its synthesis from the readily available iodoenone **65**[41] is summarized in Scheme 9.

Thus, Luche reduction[35] of iodoenone **65** furnished hydroxy compound **66** (ca. 10:1 dr), which was converted to its TBS ether **67** (TBSCl) in 94% overall yield. Sonogashira coupling of **67** with TMS acetylene (Pd(PPh₃)₂Cl₂ catalyst, CuCl catalyst,

(41) Iodoenone **65** was prepared following the same chemical transformation steps as depicted in Scheme 7 (**51** → **56**), starting from the opposite enantioisomer of **51**.

Et$_2$NH, 98% yield), followed by THP removal (Et$_2$AlCl, 99% yield) and DMP oxidation (79% yield), led to aldehyde **68**. Addition of the latter substrate to the lithio derivative of chloroacetylene, generated from 1,2-*cis*-dichloroethylene, resulted in the formation of propargylic alcohol **69** as the major product (ca. 5:1 dr, chelation-controlled, see transition state **68-TS**, Scheme 9), possessing the undesired 11(*R*) configuration. Attempts to invert the C-11 stereocenter through the Mitsunobu reaction failed, prompting us to adopt an oxidation (DMP)−reduction (DIBAL-H) protocol, which led to the 11(*S*) propargylic alcohol **70** in a ca. 7:1 dr (steric effect, see depiction **69a**, Scheme 9) and 95% combined yield. Chromatographic purification at this stage led to pure isomer **70** (81% yield), from which the TMS group was removed (K$_2$CO$_3$, MeOH, 99% yield) to afford hydroxy acetylene **71**, whose acetylation under standard conditions furnished the coveted chloroacetylenic enyne fragment **64** (98% yield).

As previously (see Scheme 8 above), the [2+2+2] fusion of acetylenic fragments **42** and **64** under the influence of Cp*RuCl(COD) catalyst[40] was expected to proceed regioselectively toward the desired *meta*-substituted chlorobenzyl alcohol system **72** (see Scheme 10). This expectation was based on the established mechanism of the reaction (see Figure 9),[40] which dictated a preference, due to steric control, for only one orientation (out of the four possible) for the approach of the propargylic component (i.e., **42**) to the initially formed metallocycle (see transition state **XI**, Figure 9). As seen from inspection of the alternative transition state **XI**′ (Figure 9), this orientation of the two reacting species suffers from severe steric clash between the bulky R group and the ruthenium and its ligand entourage, and, therefore, does not provide a productive pathway. Similarly, the other two orientations (not shown) of the propargylic component on the side of the metallocycle chlorine residue are disfavored due to steric repulsion, from either the ruthenium moiety or the chlorine residue, and are, therefore, nonproductive. Indeed, exposure of a mixture of chloroacetylenic enyne **64** (1.1 equiv) and propargylic alcohol ester **42** (1.0 equiv) to Cp*RuCl(COD) catalyst in 1,2-dichloroethane at room temperature for 0.5 h led to chloroindene **72** in 87% yield. The *ortho*-substituted product **72**′ that would have been formed through transition states **XI**′ and **XII**′ (Figure 9) was not observed. The impressively short reaction time of this process was attributed to a possible coordination of the free hydroxyl group onto the ruthenium nucleus that may help in the initial anchoring of the hydroxy acetylene onto the metal (see **XI**, Figure 9). Supporting this notion was the observation that the corresponding acetyl-protected propargylic substrate (not shown) reacted with chloroacetylenic enyne **64** in the presence of Cp*RuCl(COD) catalyst under the same conditions significantly slower (ca. 10-fold) and with eroded regioselectivity (ca. 10:1). Erosion of regioselectivity (*meta:ortho* regioisomers, ca. 20:1 → 10:1) was also observed in the rhodium-catalyzed reaction (Wilkinson's catalyst) of **42** and **64**, which, however, proceeded equally well to afford the desired chloroindene **71** (85% combined yield). Proceeding toward the targeted *o*-quinone **75** (Scheme 10), the exclusively obtained hydroxy chloroindene product **72** was acetylated (Ac$_2$O, 4-DMAP, Et$_3$N, 92% yield), and the resulting product **73** was treated initially with aqueous HF in MeCN and then with MeOH to cleave both the silyl ether and the acetoxy acetal moiety, furnishing hydroxy catechol **74** in 74% yield. The latter compound was then smoothly oxidized with Ag$_2$O to afford the desired *o*-quinone **75** in 94% yield.

**Scheme 10.** Synthesis of *o*-Quinone 75[a]
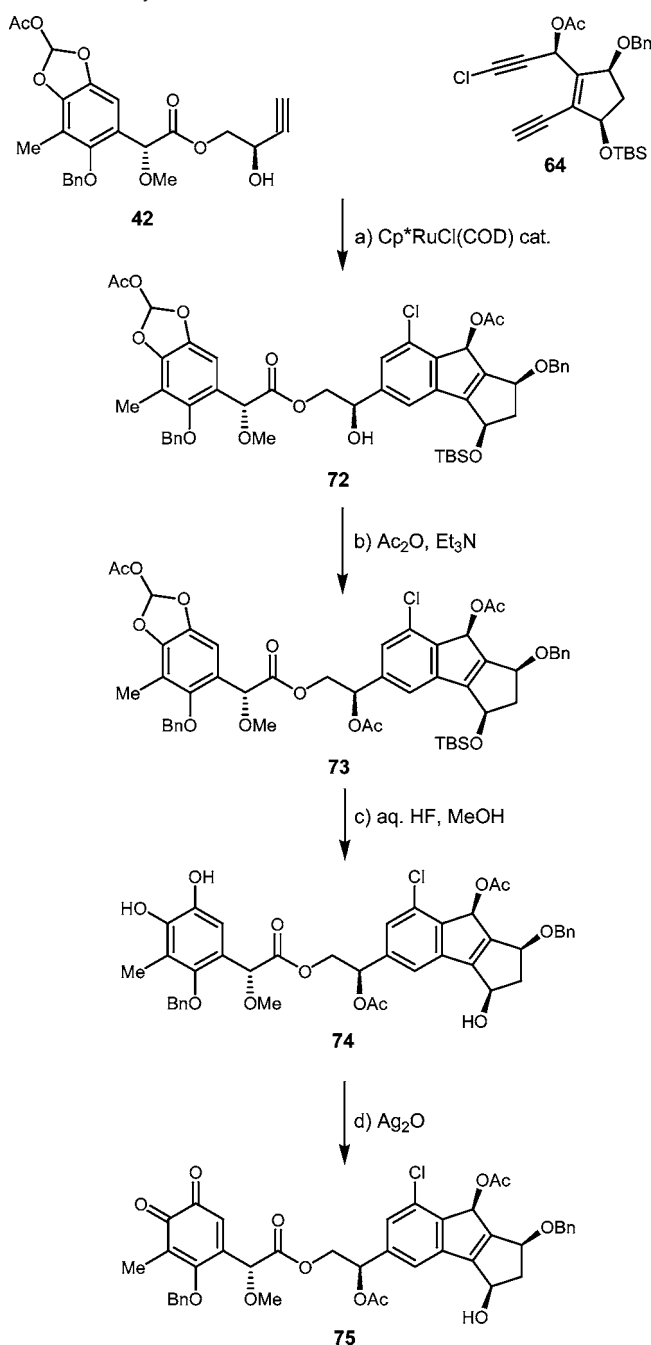


[a] Reagents and conditions: (a) **42** (1.0 equiv), **64** (1.1 equiv), Cp*RuCl(COD) (0.07 equiv), DCE, 25 °C, 0.5 h, 87%; (b) Ac$_2$O (2.0 equiv), Et$_3$N (2.0 equiv), 4-DMAP (0.1 equiv), CH$_2$Cl$_2$, 0 °C, 0.5 h, 92%; (c) HF (48% aqueous solution, excess), MeCN, 25 °C, 0.5 h; then MeOH (excess), 25 °C, 3 h, 74%; (d) Ag$_2$O (2.5 equiv), CH$_2$Cl$_2$, 25 °C, 0.5 h, 94%.

With *o*-quinone **75** in hand, we were now ready to attempt the much anticipated intramolecular [4+2] cycloaddition reaction (which had failed previously with the correct C-9 sporolide stereochemistry as discussed above, see Scheme 8). This time, and much to our delight, heating **75** at 110 °C in toluene for 1.5 h resulted in the formation of the desired cycloadduct **76** as a single isomer and in 40% yield (based on 50% consumed starting material, Scheme 11). Repeated attempts to improve the yield of this reaction (e.g., prolonged or shortened reaction times, lower or higher temperatures, Lewis acid catalysts, microwaves) proved fruitless, apparently due to the sensitivity
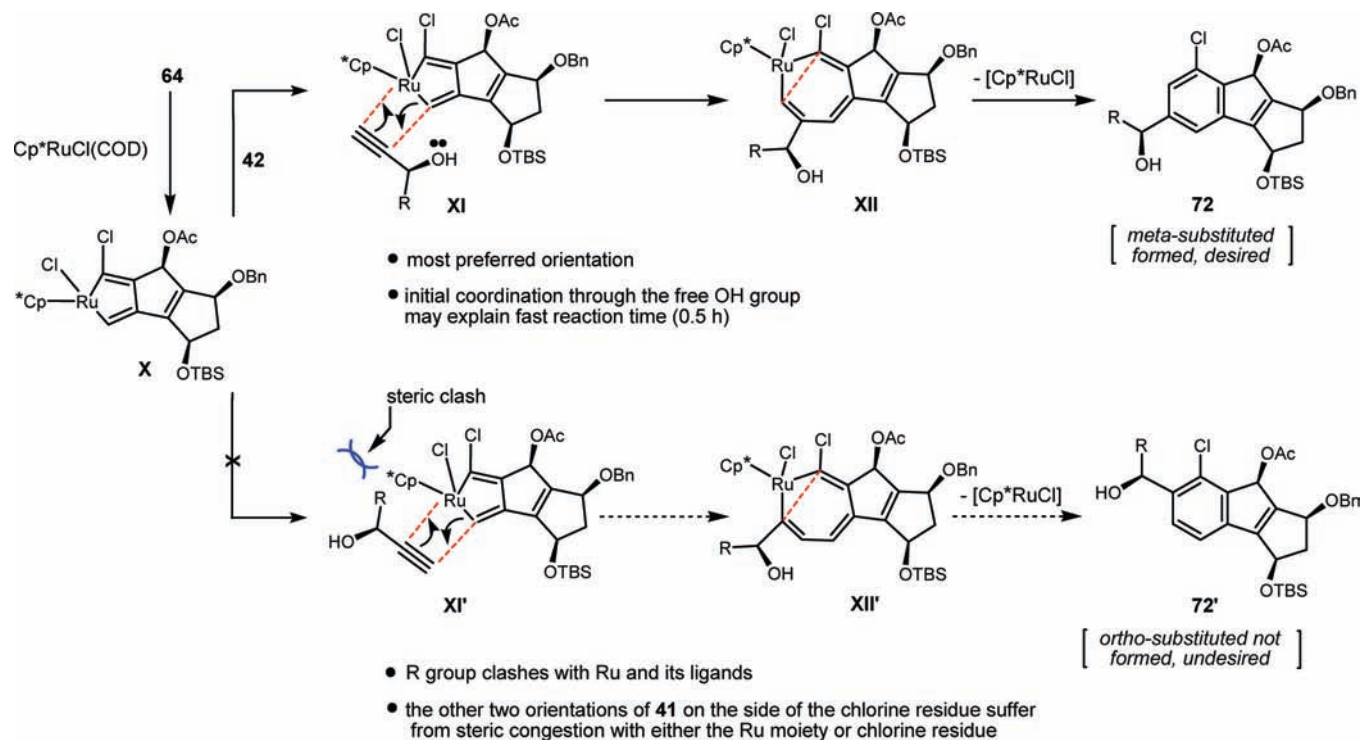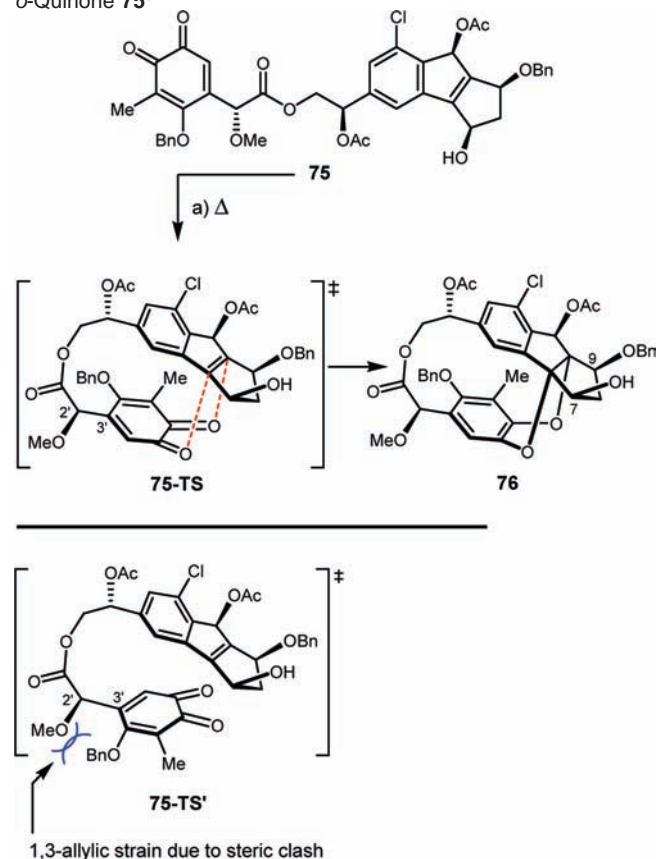
**Figure 9.** Mechanistic rationale for the exclusive regioselectivity of the ruthenium-catalyzed [2+2+2] cycloaddition reaction of acetylenic components **42** and **64** to afford indene **72**.
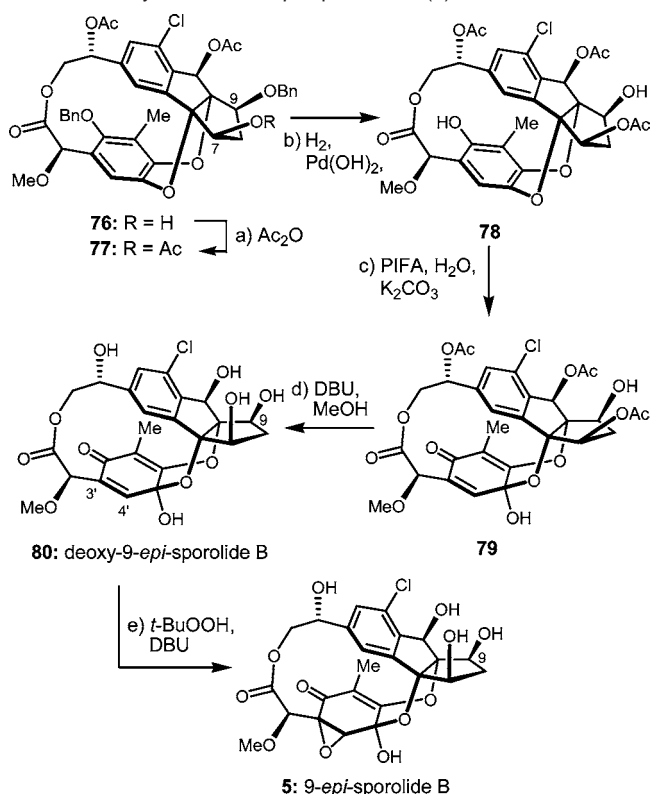
**Scheme 11.** Intramolecular Hetero [4+2] Cycloaddition Reaction of *o*-Quinone **75**[a]



[a] Conditions: (a) toluene, 110 °C, 1.5 h, 40% (based on 50% recovered starting material).
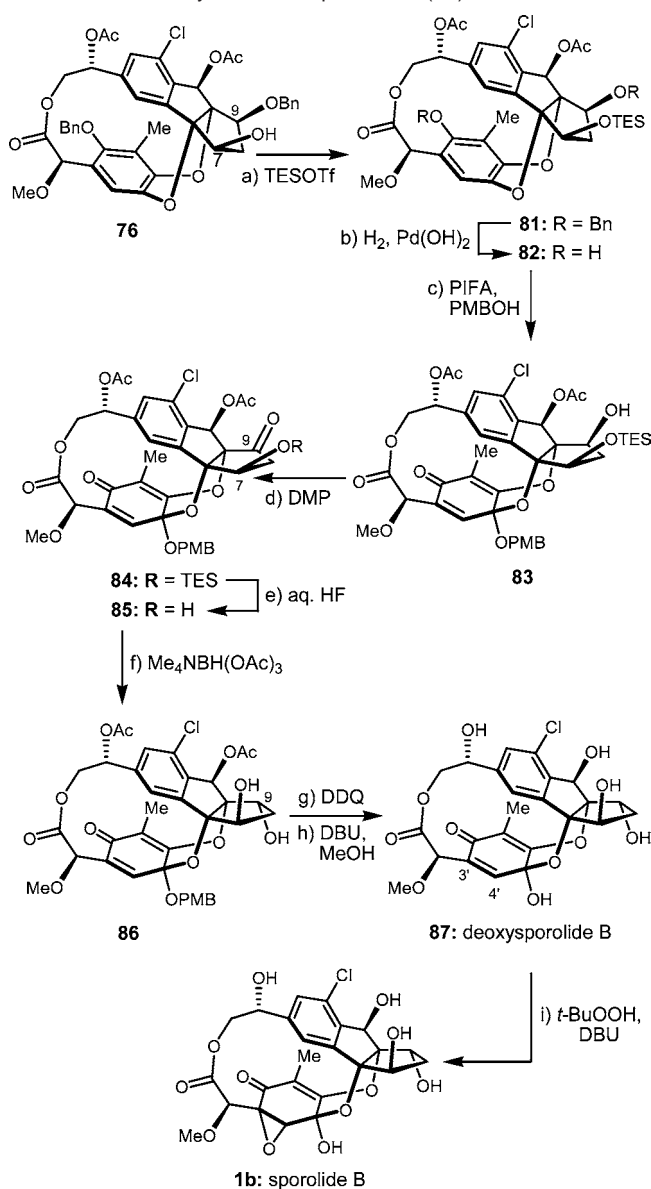
of both the substrate **75** and the product **76**. Due to the robustness of the sequence leading up to *o*-quinone **75**, however, sufficient quantities of sporolide scaffold **76** could be secured for further elaboration. The impressive exclusivity by which cycloadduct **76** is formed from **75** can be explained, as in the case of model system **4** (see above, Scheme 5 and Figure 5), upon inspection (manual molecular models) of postulated transition states [**75-TS** and **75-TS′** (generated by 180° rotation around the $C_{2'}-C_{3'}$ bond), see Scheme 11] that reveals the difficulties with **75-TS′** (inhibitive 1,3-allylic strain) and the impossibility of the other two diastereofacial arrangements (not shown).

At this stage and with sporolide B scaffold **76** in hand, we opted to explore the pending sequence to 9-*epi*-sporolide B (**5**, see Scheme 12) not only to obtain a new sporolide entity, but also as a means to scout the chemistry ahead in preparation for the final drive toward our ultimate target, sporolide B (**1b**) (which required inversion of configuration at C-9). Only five steps were needed to reach 9-*epi*-sporolide B (**5**) from intermediate **76**. Thus, and as shown in Scheme 12, hydroxy compound **76** was acetylated (Ac₂O, 4-DMAP, Et₃N) to afford triacetate **77** (92% yield), from which both benzyl groups were removed through hydrogenolysis [H₂, Pd(OH)₂/C, 92% yield], leading to hydroxy phenol **78**. The phenol moiety of the latter compound was dearomatized by reaction with PIFA in MeCN in the presence of H₂O and K₂CO₃ at 0 °C to afford *p*-hemiquinol **79** in a regio- and stereoselective manner (66% yield). All three acetates were then removed from **79** through the action of DBU in CH₂Cl₂:MeOH (3:1) at 40 °C, leading to 3′,4′-deoxy-9-*epi*-sporolide B (**80**) in 77% yield. Finally, the remaining oxygen atom was successfully installed onto the latter intermediate regio- and stereoselectively, as expected on steric grounds, through the use of *t*-BuOOH and DBU in CH₂Cl₂ at 40 °C, furnishing 9-*epi*-sporolide B (**5**) in 72% yield.

**Scheme 12.** Synthesis of 9-*epi*-Sporolide B (**5**)[a]



**76:** R = H
**77:** R = Ac

a) Ac₂O

**78**

b) H₂, Pd(OH)₂

c) PIFA, H₂O, K₂CO₃

**80:** deoxy-9-*epi*-sporolide B

d) DBU, MeOH

**79**

e) *t*-BuOOH, DBU

**5:** 9-*epi*-sporolide B

*a* Reagents and conditions: (a) Ac₂O (2.0 equiv), Et₃N (2.0 equiv), 4-DMAP (0.10 equiv), CH₂Cl₂, 0 °C, 0.5 h, 92%; (b) H₂ (balloon), Pd(OH)₂ (10% on carbon, 2.0 equiv), EtOAc, 25 °C, 4 h, 92%; (c) PIFA (2.0 equiv), H₂O (2.0 equiv), K₂CO₃ (5.0 equiv), MeCN, 0 °C, 0.5 h, 66%; (d) DBU (10.0 equiv), CH₂Cl₂:MeOH (3:1), 40 °C, 4 h, 77%; (e) *t*-BuOOH (10.0 equiv), DBU (5.0 equiv), CH₂Cl₂, 40 °C, 3 h, 72%.

**Total Synthesis of Sporolide B.** Armed with the confidence gained through the successful synthesis of 9-*epi*-sporolide B (**5**), we turned our attention toward the final stage of the total synthesis of sporolide B itself (**1b**, Scheme 13). This task required inversion of the C-9(*S*) configuration within **76**, which was intentionally and temporarily introduced as such for the sole purpose of facilitating the otherwise unattainable intramolecular *o*-quinone [4+2] cycloaddition reaction. To this end, the hydroxyl group of **76** was ephemerally protected with a TES group (TESOTf, 95% yield), and the benzyl groups were cleaved by hydrogenolysis [H₂, Pd(OH)₂/C, 92% yield] to afford hydroxy phenol **82** through bis-benzyl ether TES derivative **81** (see Scheme 13). Oxidative dearomatization of phenolic substrate **82** with PIFA in the presence of PMBOH furnished *p*-hemiquinone **83** (75% yield). Attempts to employ S_N2 displacement reactions (e.g., Mitsunobu reaction[21] or mesylate displacement[42]) as a means to achieve the desired inversion at C-9 failed, forcing us to adopt an oxidation–reduction protocol with the thought to exploit the 1,3-directing power of the C-7 β-hydroxyl group within a hydroxy carbonyl substrate. Thus, oxidation of **83** with DMP produced ketone **84** in 90% yield. Desilylation of the latter compound (aqueous HF, 85% yield) yielded β-hydroxy ketone **85**, whose reduction with Me₄NBH(OAc)₃[43] provided inverted [9(*R*)] diol **86** in 85% yield as a single diastereoisomer, apparently through the expected intramolecularly assisted hydride delivery from the β-face of the molecule. Cleavage of the PMB group from **86** with DDQ (70% yield), followed by methanolysis of the acetate groups from the resulting hemiacetal diacetate (DBU, MeOH, 40 °C), afforded

**Scheme 13.** Total Synthesis of Sporolide B (**1b**)[a]



**76**

a) TESOTf

b) H₂, Pd(OH)₂

**81:** R = Bn
**82:** R = H

c) PIFA, PMBOH

**84:** R = TES
**85:** R = H

d) DMP

**83**

e) aq. HF

f) Me₄NBH(OAc)₃

**86**

g) DDQ
h) DBU, MeOH

**87:** deoxysporolide B

i) *t*-BuOOH, DBU

**1b:** sporolide B

*a* Reagents and conditions: (a) TESOTf (1.5 equiv), Et₃N (2.0 equiv), CH₂Cl₂, 0 °C, 0.5 h, 95%; (b) H₂ (balloon), Pd(OH)₂ (10% on carbon, 2.0 equiv), EtOAc, 25 °C, 4 h, 92%; (c) PIFA (1.5 equiv), PMBOH (10.0 equiv), K₂CO₃ (5.0 equiv), MeCN, 0 °C, 0.5 h, 75%; (d) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 1 h, 90%; (e) HF (48% aqueous solution, excess), MeCN, 25 °C, 2 h, 85%; (f) Me₄NBH(OAc)₃ (10.0 equiv), MeCN:AcOH (10:1), 25 °C, 2 h, 85%; (g) DDQ (5.0 equiv), CH₂Cl₂:H₂O (10:1), 25 °C, 5 h, 70%; (h) DBU (10.0 equiv), CH₂Cl₂:MeOH (3:1), 40 °C, 4 h, 78%; (i) *t*-BuOOH (10.0 equiv), DBU (5.0 equiv), CH₂Cl₂, 40 °C, 3 h, 63%. Tf = trifluoromethanesulfonyl.

3′,4′-deoxysporolide B (**87**, 78% yield), whose intended regio- and stereoselective epoxidation was achieved through the use of *t*-BuOOH-DBU to afford sporolide B (**1b**) in 63% yield. The spectral data of synthetic **1b** were in accord with those reported for the natural product.[44]

## Conclusion

A stereocontrolled total synthesis of sporolide B (**1b**) has been achieved through a designed strategy that also delivered 9-*epi*-sporolide B (**5**) and sporolide model system **4**. In addition to delivering the latter compound, the undertaken model studies revealed the sensitivity of the intermolecular [4+2] cycloaddi-

tion reaction of *o*-quinones and indene-type dienophiles and its dependence on the substituents on both partners with regard to regioselectivity and diastereofacial selectivity. The intelligence gathered from these studies proved decisive in guiding the design of the eventually adopted synthetic strategy toward sporolide B (**1b**) and may prove useful in future explorations of the chemistry of *o*-quinones. The ultimately evolved synthetic strategy toward sporolide B involved a thermally induced intramolecular hetero [4+2] cycloaddition reaction with an appropriately designed substrate that proceeded with exquisite regio- and stereoselectivity. As a result of these investigations, this unprecedented intramolecular *o*-quinone [4+2] cycloaddition process may now be added to the repertoire of synthetic tools for future employment in complex molecule construction. In addition, the described chemistry demonstrated the power

of the ruthenium-catalyzed [2+2+2] cycloaddition of acetylenic substrates for the construction of highly substituted indenes, including chlorinated systems, that may prove useful in chemical and medicinal synthetic endeavors.

**Supporting Information Available:** Experimental procedures, list of abbreviations, and compound characterization (PDF); crystallographic information files (CIF) This material is available free of charge via the Internet at http://pubs.acs.org.

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(42) Torisawa, Y.; Okabe, H.; Ikegami, S. *Chem. Lett.* **1984**, *13*, 1555–1556.
(43) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
(44) We thank Prof. William Fenical for a sample of natural sporolide B.