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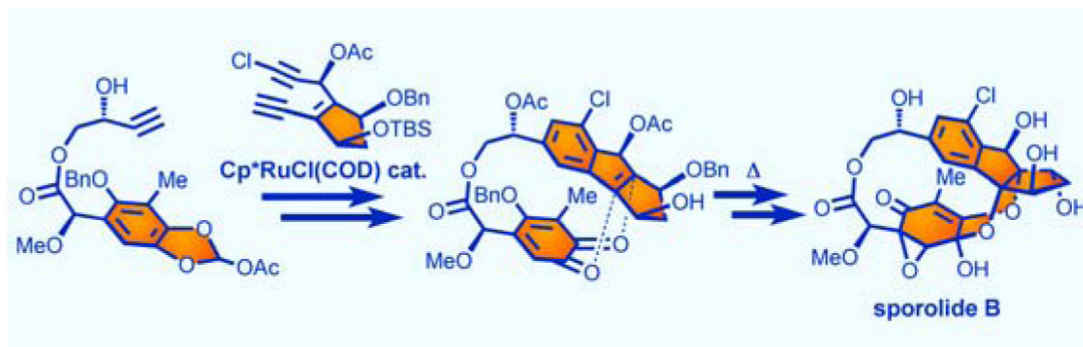
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Total Synthesis of Sporolide B**

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Abstract



The first total synthesis of the highly oxygenated, marine derived, natural product sporolide B was achieved through a convergent strategy involving a ruthenium-catalyzed [2+2+2] cycloaddition to assemble the indene structural motif and a thermally-induced Diels-Alder-type reaction to forge the macrocycle.

Keywords

 cycloaddition; Diels-Alder; natural product; *o*-quinone; sporolide

Sporolides A (**1a**) and B (**1b**) (Figure 1) are two highly unusual natural products reported by the Fenical group in 2005.[1] Isolated from the marine actinomycete *Salinospora tropica*, these molecules possess no obvious biological activity, yet their intriguing molecular architectures imply the existence of an as yet unidentified, secondary metabolite of the enediyne class,[2] whose fleeting nature may explain the incorporation of the chloro-substituted aryl rings within their structures[2,3] through a Bergman cycloaromatization reaction.[4] In view of the importance of the enediyne family of natural products[5] and in order to better understand the biosynthetic origins of the sporolides A and B and their postulated enediyne precursor, we embarked on the total synthesis of these molecules. In this communication we report the first total synthesis of sporolide B (**1b**) in its naturally occurring enantiomeric form through a highly stereoselective and convergent strategy that involves two important cycloaddition reactions.

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The unprecedented C24 polycyclic structure of sporolide B (**1b**) includes 12 oxygen atoms, 10 stereogenic centers, a 13-membered macrolide ring, a chlorobenzene nucleus embedded within an indane structural motif, and two oxygen bridges that, together with the ester bond, connect the two domains of the molecule into its cage-like structure.

These special structural elements and unique connectivities amounted to a formidable synthetic challenge that was eventually met by adopting the devised synthetic strategy outlined retrosynthetically in Scheme 1. This strategy was based on two key retrosynthetic disconnections, a thermally-induced, intramolecular [4+2] cycloaddition reaction involving an *o*-quinone and a tetrasubstituted olefin to form the macrocyclic structure of the molecule (**2** → **1b**),[6] and a ruthenium-catalyzed, intermolecular [2+2+2] cycloaddition reaction between two acetylenic units,[7] building blocks **3** and **4**, to forge its chlorobenzenoid indane structural motif. The complexity of the substrates involved in these planned reactions and the lack of any precedent for their application in complex natural product synthesis made them risky propositions with regards to both feasibility and topology (regio- and stereoselectivity). Nevertheless, model studies[6] and inspection of manual molecular models were encouraging.

Scheme 2 summarizes the construction of chloroacetylene building block **3**. Thus, enantiomerically pure iodoenone **5** (ee > 99 %)[8] was reduced under Luche conditions[9] (NaBH₄, CeCl₃·7H₂O, -78 °C) to afford, upon benzylation (NaH, BnBr, THF), vinyl iodide **6** (ca. 10:1 diastereomeric ratio, 95 % combined yield).[10] Carboxymethylation of the latter compound under palladium-catalyzed conditions [Pd(PPh₃)₂Cl₂ cat., CO, MeOH] led to methyl ester **7** (95 % yield), whose reduction (DIBAL-H, 95 % yield), protection as a THP ether (DHP, TsOH·H₂O), and desilylation (TBAF) furnished allylic alcohol **8**. Oxidation of **8** with Dess-Martin periodinane[11] (DMP) gave the corresponding enone (83 % overall yield for the last three steps), which was iodinated (I₂, CH₂Cl₂/pyridine) to afford iodoenone **9** in 80 % yield. Luche reduction of the latter (NaBH₄, CeCl₃·7H₂O, -78 °C) proceeded stereoselectively (ca. 5:1 diastereomeric ratio)[10] to afford, upon silylation (TBSCl, imidazole, 4-DMAP), vinyl iodide **10** in 94 % yield for the two steps. Sonogashira coupling of **10** with TMS-acetylene [Pd(PPh₃)₂Cl₂ cat., CuI cat., Et₂NH, 98 % yield] followed by removal of the THP protecting group (Et₂AlCl, -25 → 25 °C, 99 % yield) and oxidation of the resulting primary alcohol (DMP, 79 % yield) furnished aldehyde **11**. The required chloroacetylene structural motif was then installed within the growing molecule by reaction of aldehyde **11** with a preformed solution of lithiochloroacetylene (*cis*-1,2-dichloroethylene, MeLi, Et₂O, 0 °C) to furnish the expected secondary alcohol, which, however, possessed the undesired stereochemistry at C11.[12] This stereochemistry was inverted through an oxidation-reduction protocol. Thus, oxidation of this alcohol with DMP led to ketone **12** (93 % overall yield for the last two steps), which was reduced stereoselectively (chelation controlled, ca. 7:1 diastereomeric ratio) with DIBAL-H (toluene, -78 °C)[12] to afford the desired alcohol **13** with 81 % yield after silica gel chromatographic separation from its undesired diastereomer. Finally, removal of the TMS group from its acetylene host in **13** (K₂CO₃, MeOH, 99 % yield), followed by acetylation (Ac₂O, Et₃N, 4-DMAP, 98 % yield), led to the targeted acetoxy chloroacetylene **3** via hydroxy precursor **14**.

Scheme 3 depicts the construction of propargyl alcohol building block **4** starting from aldehyde **15**. [13] Thus, **15** was subjected to Wittig olefination (Ph₃P=CH₂, -78 → 0 °C, 98 % yield) to afford styrene derivative **16**, which entered a highly enantioselective Sharpless asymmetric dihydroxylation reaction[14] (AD-mix β, 96 % yield, 98 % ee) to afford, after sequential silylation (TBSCl, Et₃N, 4-DMAP, 99% yield) and methylation (*t*BuOK, MeI, 95 % yield), fully protected pentasubstituted aryl system **18**. The latter compound was converted to carboxylic acid **19** through a three-step sequence involving desilylation (TBAF, 99 % yield) and oxidation of the resulting primary alcohol, first with DMP (78 % yield), and then with NaClO₂ (96 % yield). Coupling of **19** with acetylenic alcohol **20**, [15] as facilitated by EDCI

and 4-DMAP, led to the selective formation of hydroxy ester **21** (73 % yield). Reaction of the latter intermediate with Pb(OAc)₄ in benzene at 75 °C led smoothly to the required hydroxy acetylenic building block **4** in 89 % yield (ca. 6:1 diastereoisomeric mixture).

With the two fragments **3** and **4** in hand, we set out to investigate their fusion into the desired polycyclic precursor for the final casting of the sporolide B macrocyclic structure. Although known to proceed well, the intermolecular, ruthenium-catalyzed [2+2+2] cycloaddition reaction of diynes with alkyl substrates to form benzenoid systems[7] was complicated in this instance by the presence of the chlorine atom and the complexity of the substrates involved. However, we were counting on the steric bulk of the chlorine residue on **3** (as compared to a hydrogen atom) and the coordinating ability of the free hydroxyl group in **4** to provide favorable conditions for the desired outcome of the reaction, including its regiochemistry with regards to the position of the chlorine atom on the aryl ring. In the event, combining **3** and **4** in 1,2-dichloroethane in the presence of Cp*RuCl(COD) catalyst[16] resulted, within 30 min, in the formation of compound **22** in 87 % yield and as a single regioisomer (Scheme 4). That this highly productive process led rapidly and exclusively to the desired *meta*-chloro isomer may be explained by inspection of transition states **3-TS_a**, **3-TS_b** and **3-TS_c**, through which this reaction is presumed to proceed.

In preparation for the next challenging task, the forging of the cyclic framework of the sporolide molecule through the proposed [4+2] cycloaddition reaction,[6] compound **22** was converted to *o*-quinone **2** via catechol derivative **23** through sequential treatment with Ac₂O-Et₃N-4-DMAP (92 % yield) and aq.HF-MeOH (74 % yield), followed by Ag₂O oxidation (94 % yield) as shown in Scheme 4.

Scheme 5 presents the final stages and the completion of the total synthesis of sporolide B (**1b**). Thus, upon heating in toluene at 110 °C, *o*-quinone **2** underwent the much anticipated Diels-Alder reaction to afford desired product **24** (40 % yield based on ca. 50 % conversion), [17] apparently through transition state **2-TS**. Although the remarkable diastereoselectivity (facial orientation of *o*-quinone) of this reaction can be rationalized by the steric bias of the dienophile (top face blocked by the substituents on the 5-membered rings), an explanation for its regioselectivity (*o*-quinone rotation around C2'-C3' bond) remains elusive. It should be noted that the C-9 oxygen substituent within **24** and all its precursors resides (by design) in the opposite configuration from that required for sporolide B (**1b**), and therefore requires inversion. This task was to be achieved at some point downstream through an oxidation-reduction sequence, with the C-7 hydroxy group playing a directing role in the reduction. Therefore, subsequent steps had to accommodate, in addition to the obligatory dearomatization of the trioxxygenated benzenoid ring, the two steps required for this inversion. To this end, a TES group was placed on the well positioned C-7 oxygen (TESOTf, Et₃N, 95 % yield) before the two benzyl groups were removed [H₂, Pd(OH)₂ cat., 92 % yield] to afford hydroxy phenol **26** via intermediate **25**. Exposure of **26** to PhI(OCOCF₃)₂ in the presence of PMBOH in acetonitrile furnished *p*-ketal quinone **27** in 75 % yield, providing the opening for the oxidation-reduction protocol to invert the C-9 stereochemistry. Indeed, oxidation of **27** (DMP, 90 % yield) followed by removal of the TES protecting group (aq.HF, MeCN, 85 % yield) gave, through the corresponding carbonyl compound, β-hydroxy ketone **28**, whose reduction with Me₄NBH(OAc)₃ [MeCN:AcOH (10:1)] led to 1,3-diol **29** as a single stereoisomer, and in 85 % yield. This compound was treated sequentially with DDQ [CH₂Cl₂:H₂O (10:1), 70 % yield] and DBU [CH₂Cl₂:MeOH (3:1), 78 % yield] to remove the PMB and acetate protecting groups, furnishing deoxysporolide B **30**. The final step of the total synthesis of sporolide B (**1b**) involved regio- and stereoselective introduction of the missing oxygen atom from precursor **30** in the required epoxide form by reaction with *t*BuOOH in the presence of DBU in CH₂Cl₂ at 40 °C (3 h, 63 % yield). Synthetic sporolide B (**1b**) exhibited identical

chromatographic data, spectroscopic data, and optical rotation sign to those of the authentic sample.[18]

The described regio- and stereocontrolled total synthesis of sporelone B (**1b**) demonstrates the power of the ruthenium-catalyzed intermolecular [2+2+2] cycloaddition reaction of acetylenic substrates and provides further insight into possible biosynthetic pathways to this novel secondary metabolite and its regioisomeric sibling sporelone A (**1a**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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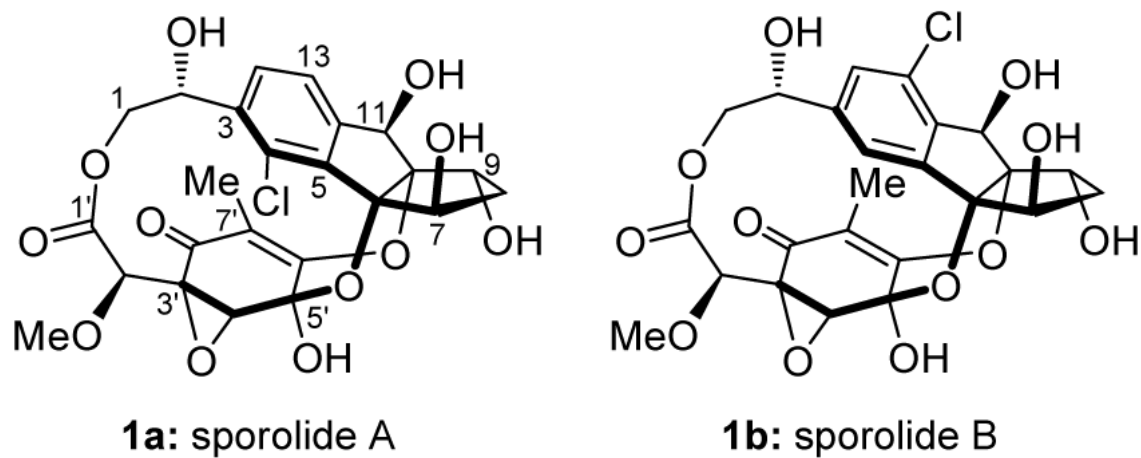
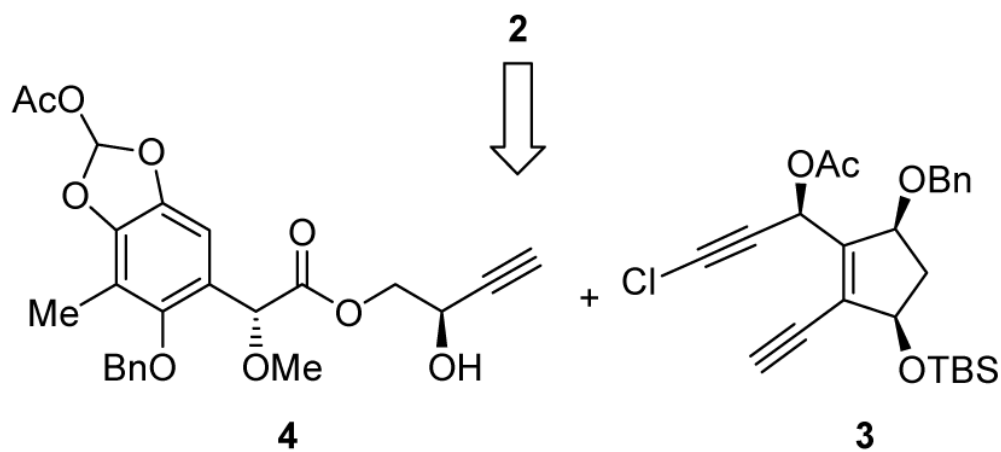
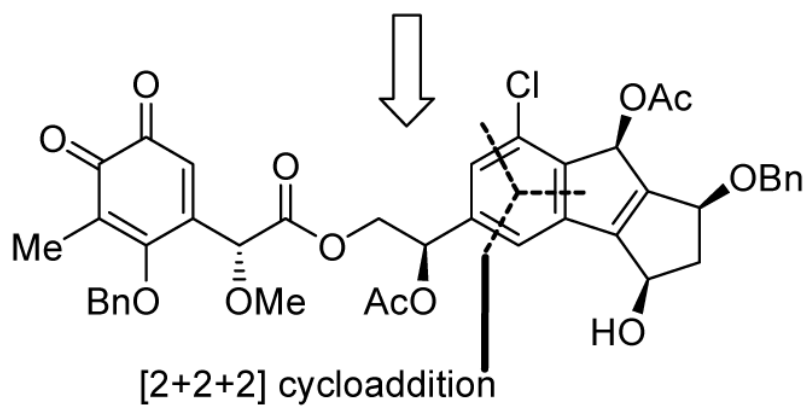
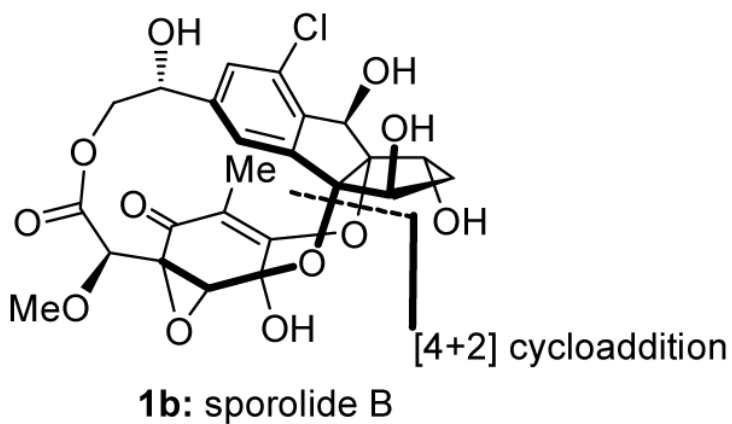
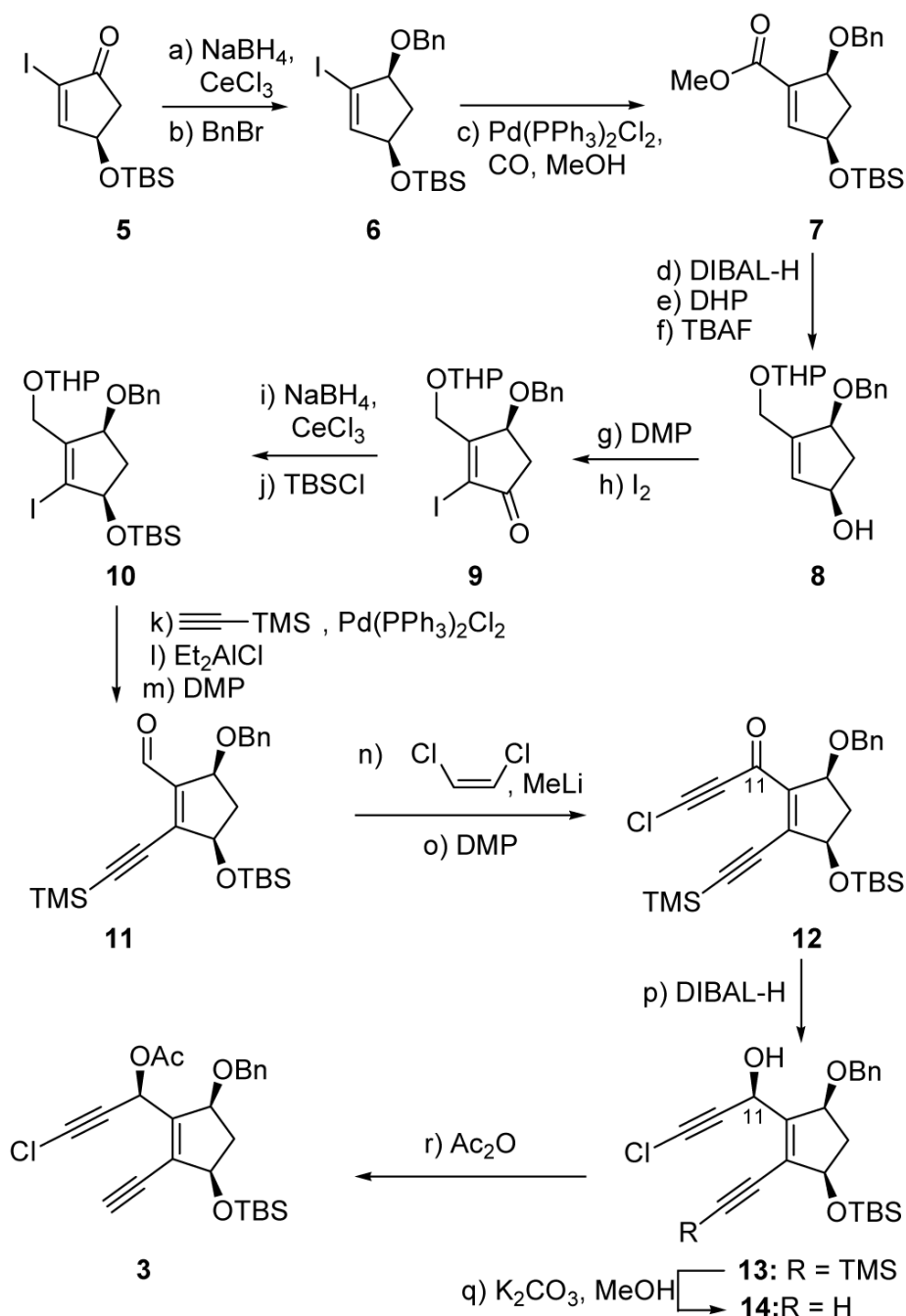


Figure 1.
Molecular structures of sporolides A (**1a**) and B (**1b**).

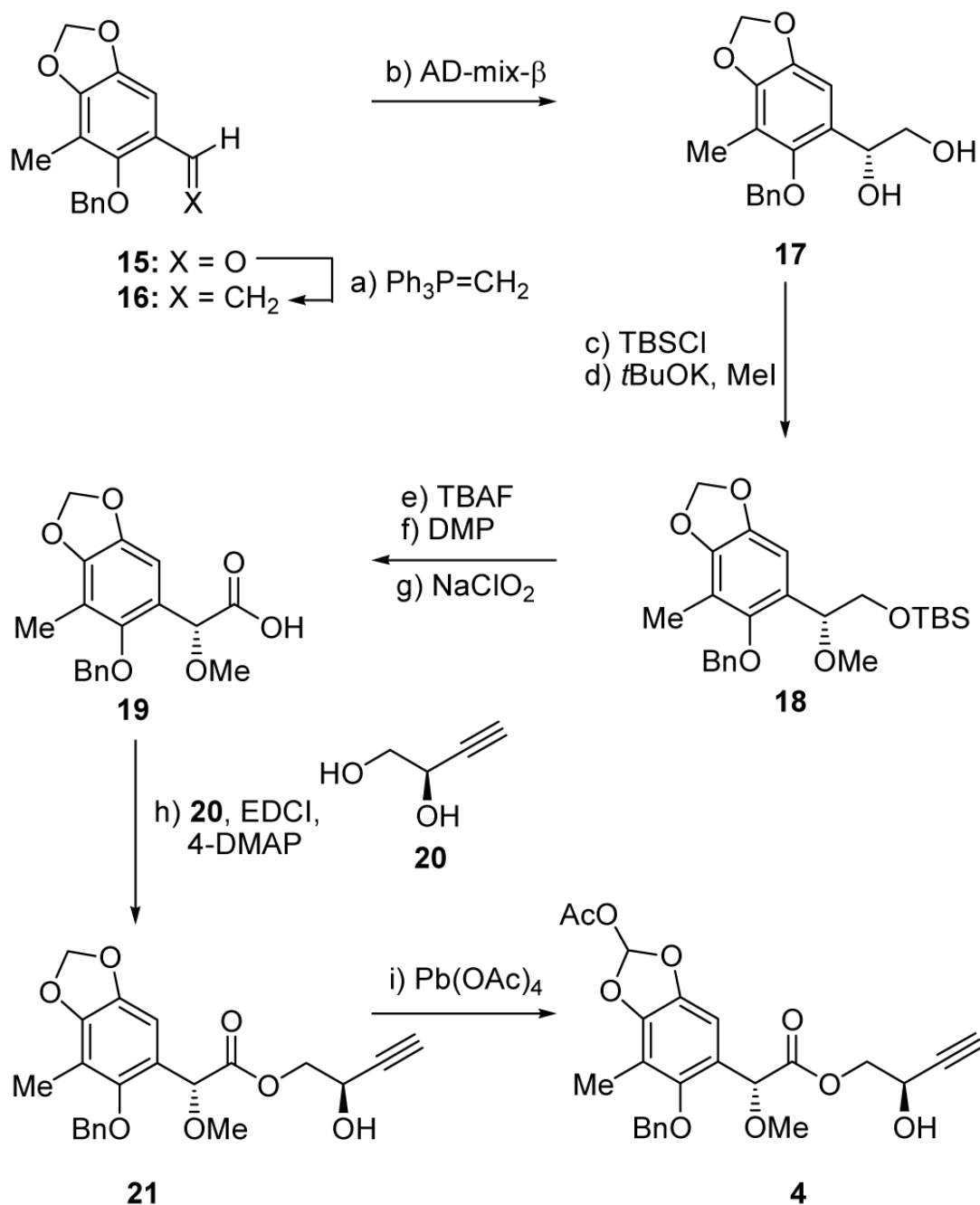


Scheme 1.
Retrosynthetic analysis of sporolide B (**1b**). Ac = acetyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

**Scheme 2.**

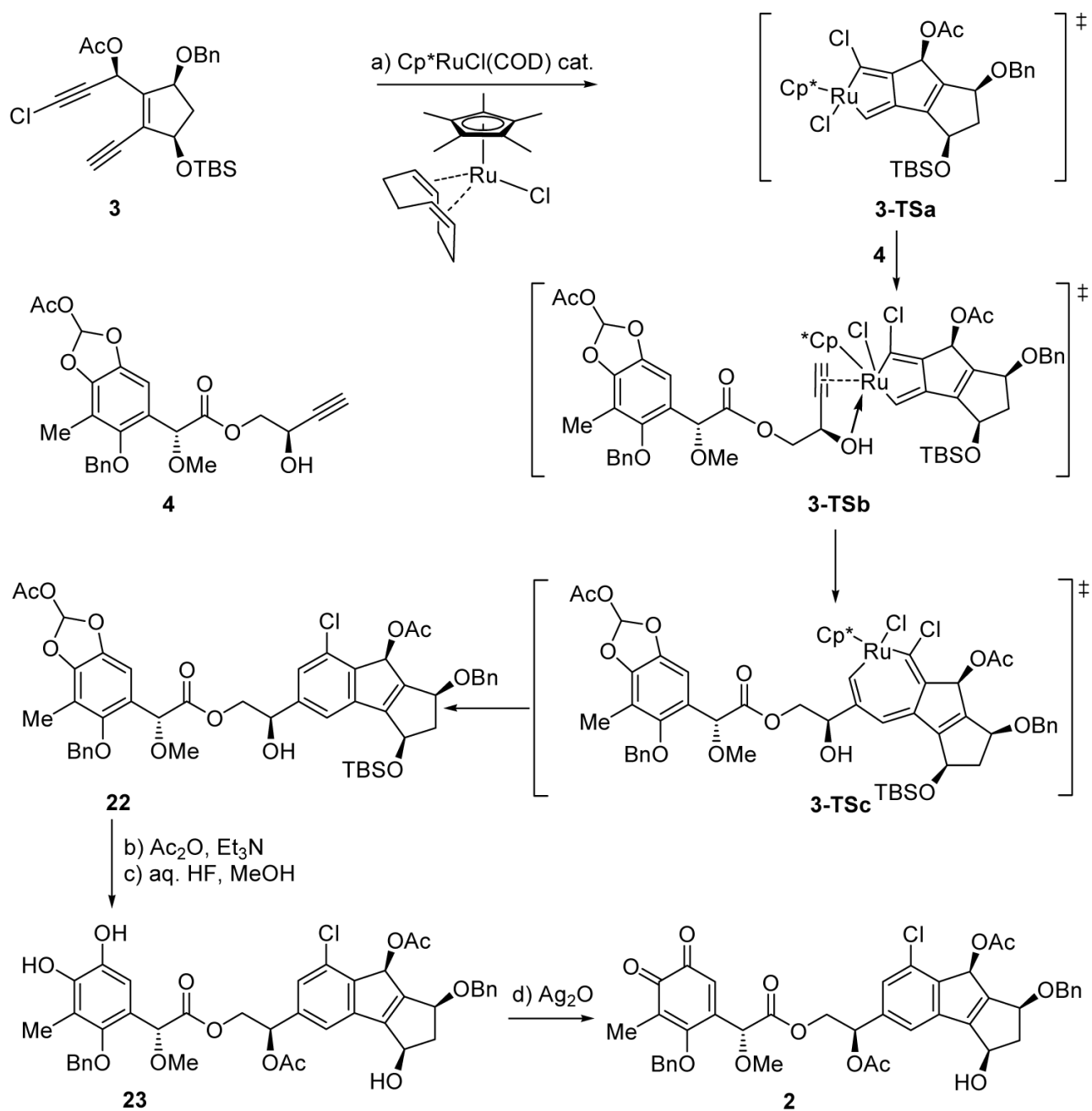
Construction of building block **3**. Reagents and conditions: a) NaBH_4 (1.2 equiv), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.2 equiv), MeOH , -78°C , 1 h; b) NaH (60 % in mineral oil, 1.5 equiv), THF , 0°C , 30 min; then BnBr (1.5 equiv), TBAI (0.2 equiv), THF , $0 \rightarrow 25^\circ\text{C}$, 16 h, 95 % for two steps; c) $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.05 equiv), Et_3N (5.0 equiv), CO (balloon pressure), MeOH , 70°C , 3 h, 95 %; d) DIBAL-H (1.0 M in toluene, 2.5 equiv), toluene, $-78 \rightarrow -10^\circ\text{C}$, 1 h, 95 %; e) DHP (1.5 equiv), $\text{TsOH} \cdot \text{H}_2\text{O}$ (0.1 equiv), CH_2Cl_2 , 0°C , 30 min; f) TBAF (1.0 M in THF , 1.5 equiv), THF , 25°C , 3 h; g) DMP (1.2 equiv), NaHCO_3 (5.0 equiv), CH_2Cl_2 , 25°C , 30 min, 83 % for three steps; h) I_2 (3.0 equiv), $\text{CH}_2\text{Cl}_2/\text{pyridine}$ (1:1), 25°C , 15 h, 80 %; i) NaBH_4 (1.2 equiv), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.2 equiv), MeOH , -78°C , 1 h; j) TBSCl (2.0 equiv), imidazole (2.0

equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 25 °C, 3 h, 94 % for two steps; k) TMS-acetylene (1.2 equiv), Pd(PPh₃)₂Cl₂ (0.02 equiv), CuI (0.04 equiv), Et₂NH, 25 °C, 16 h, 98 %; l) Et₂AlCl (1.8 M in toluene, 2.0 equiv), CH₂Cl₂, -25 → 25 °C, 2 h, 99 %; m) DMP (1.2 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 1 h, 79 %; n) *cis*-1,2-dichloroethylene (4.5 equiv), MeLi (1.6 M in Et₂O, 3.0 equiv), Et₂O, 0 °C, 30 min; then **11**, Et₂O, 0 °C, 10 min; o) DMP (1.5 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 1 h, 93 % for two steps; p) DIBAL-H (1.0 M in toluene, 1.5 equiv), toluene, -78 °C, 30 min, 81 %; q) K₂CO₃ (1.5 equiv), MeOH, 25 °C, 1 h, 99 %; r) Ac₂O (1.5 equiv), Et₃N (1.5 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 0 °C, 30 min, 98 %. DHP = 3,4-dihydro-2*H*-pyran, DIBAL-H = diisobutylaluminum hydride, 4-DMAP = 4-dimethylaminopyridine, DMP = Dess-Martin periodinane, TBAF = tetra-*n*-butylammonium fluoride, TBAI = tetra-*n*-butylammonium iodide, THF = tetrahydrofuran, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

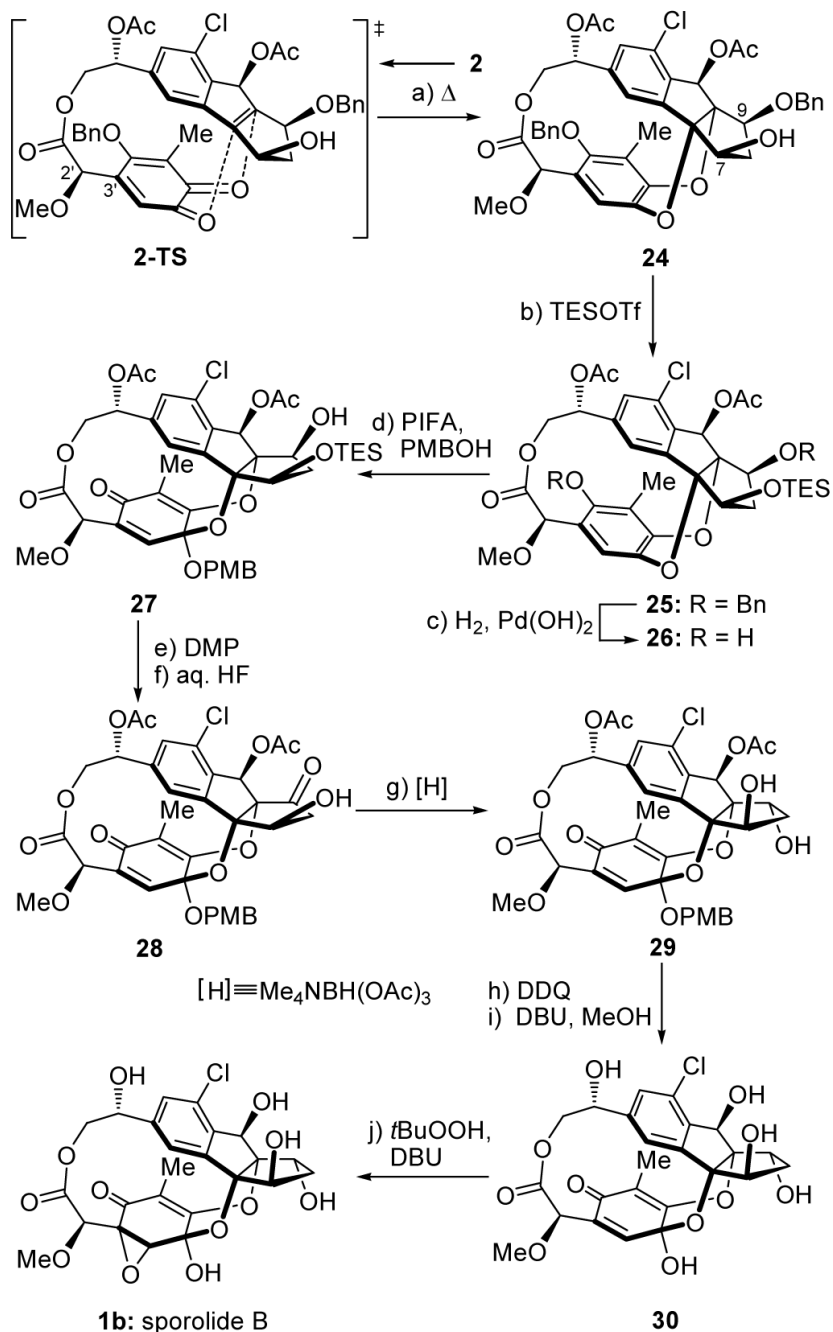
**Scheme 3.**

Construction of building block **4**. Reagents and conditions: a) MePPh₃Br (1.5 equiv), KHMDS (1.0 M in toluene, 1.2 equiv), THF, 0 °C, 30 min; then **15**, THF, -78 → 0 °C, 30 min, 98 %; b) AD-mix β (1.4 g per mmol **16**), *t*BuOH/H₂O (1:1), 25 °C, 8 h, 96 %; c) TBSCl (1.5 equiv), Et₃N (1.5 equiv), 4-DMAP (0.1 equiv), CH₂Cl₂, 25 °C, 8 h, 99 %; d) *t*BuOK (3.0 equiv), MeI (4.0 equiv), MeCN, 0 → 25 °C, 16 h, 95 %; e) TBAF (1.0 M in THF, 1.5 equiv), THF, 25 °C, 16 h, 99 %; f) DMP (1.5 equiv), NaHCO₃ (5.0 equiv), CH₂Cl₂, 25 °C, 1 h, 78 %; g) NaClO₂ (4.5 equiv), NaH₂PO₄·2H₂O (3.0 equiv), 2-methyl-2-butene (2.5 equiv), *t*BuOH/H₂O (1:1), 25 °C, 30 min, 96 %; h) **20** (1.3 equiv), EDCI (1.2 equiv), 4-DMAP (0.2 equiv), CH₂Cl₂, 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, KHMDS = potassium bis(trimethylsilyl)amide.

**Scheme 4.**

Synthesis of *o*-quinone **2**. Reagents and conditions: a) **3** (1.0 equiv), **4** (1.1 equiv), $\text{Cp}^*\text{RuCl}(\text{COD})$ (0.07 equiv), DCE, 25 °C, 30 min, 87 %; b) Ac_2O (2.0 equiv), Et_3N (2.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 0 °C, 30 min, 92 %; c) HF (48 % aqueous solution, excess), MeCN, 25 °C, 30 min; then MeOH (excess), 25 °C, 3 h, 74 %; d) Ag_2O (2.5 equiv), CH_2Cl_2 , 25 °C, 30 min, 94 %. COD = 1,5-cyclooctadiene, Cp^* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane.

**Scheme 5.**

Completion of the total synthesis of sporolide B (**1b**). Reagents and conditions: a) toluene, 110 °C, 1.5 h, 40 % (based on 50 % recovered starting material); b) TESOTf (1.5 equiv), Et₃N (2.0 equiv), CH₂Cl₂, 0 °C, 30 min, 95 %; c) H₂ (balloon pressure), Pd(OH)₂ (10 % on carbon, 2.0 equiv), EtOAc, 25 °C, 4 h, 92 %; d) PIFA (1.5 equiv), PMBOH (10 equiv), K₂CO₃ (5.0 equiv), MeCN, 0 °C, 30 min, 75 %; e) DMP (2.0 equiv), CH₂Cl₂, 25 °C, 1 h, 90 %; f) HF (48 % aqueous solution, excess), MeCN, 25 °C, 2 h, 85 %; g) Me₄NBH(OAc)₃ (10 equiv), MeCN/AcOH (10:1), 25 °C, 2 h, 85 %; h) DDQ (5.0 equiv), CH₂Cl₂/H₂O (10:1), 25 °C, 5 h, 70 %; i) DBU (10 equiv), CH₂Cl₂/MeOH (3:1), 40 °C, 4 h, 78 %; j) *t*BuOOH (10 equiv), DBU (5.0 equiv), CH₂Cl₂, 40 °C, 3 h, 63 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-

dichloro-5,6-dicyano-1,4-benzoquinone, PIFA = phenyliodine(III) bis(trifluoroacetate), PMB = 4-methoxybenzyl, Tf = trifluoromethanesulfonyl.