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Natural Product Synthesis

Total Synthesis of Sporolide B**

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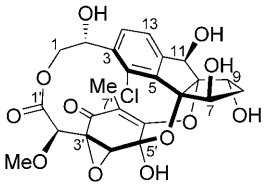
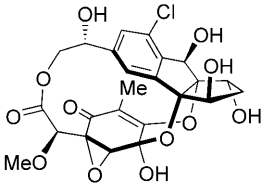
Sporolides A (**1a**) and B (**1b**) are two highly unusual natural products reported by the research group of Fenical in 2005.[1] Isolated from the marine actinomycete *Salinospora tropica*, these molecules possess no obvious biological activity, yet their intriguing molecular architectures imply the 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 to better understand the biosynthetic origins of the sporolides A and B, as well as their postulated enediyne precursor, we embarked on the total synthesis of these molecules. Herein, 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.



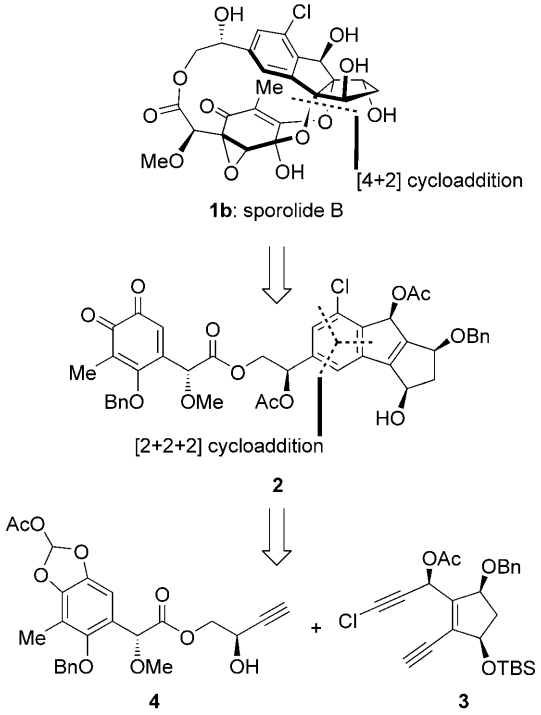
1a: sporolide A



1b: sporolide B

The unprecedented 24-carbon 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 cagelike 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



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

based on two key retrosynthetic disconnections: 1) 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 2) 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 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] ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, −78 °C), affording, upon benzylation (NaH, BnBr, THF), vinyl iodide **6** (ca. 10:1 diastereomeric ratio, 95% combined yield).[10] Carboxymethylation of the latter

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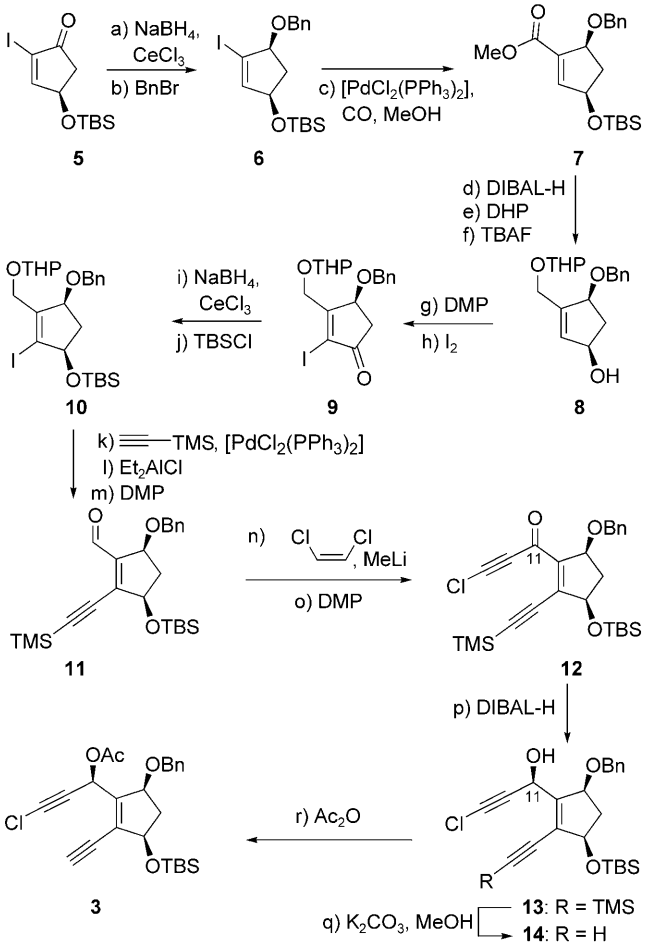
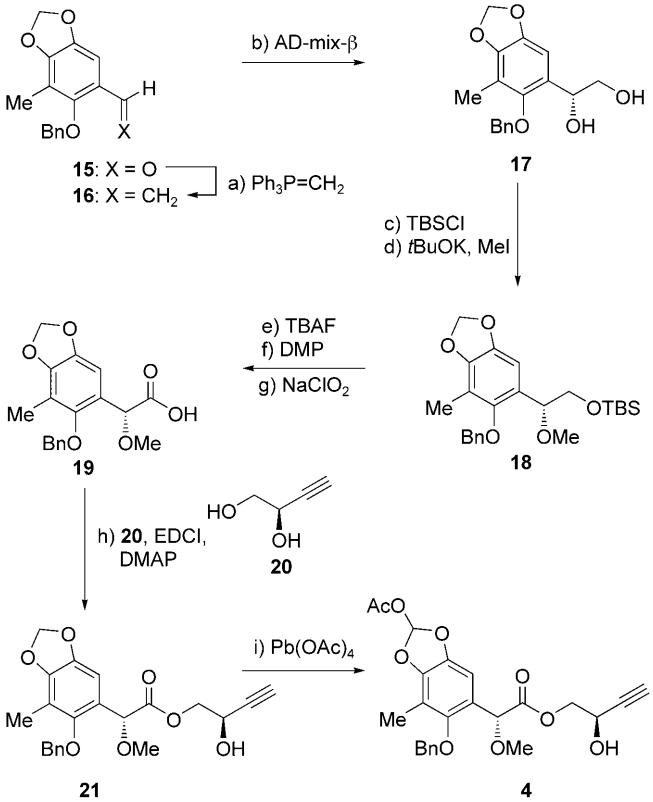


Scheme 2. Construction of building block **3**. Reagents and conditions: a) $NaBH_4$ (1.2 equiv), $CeCl_3 \cdot 7H_2O$ (1.2 equiv), MeOH, −78 °C, 1 h; b) NaH (60% in mineral oil, 1.5 equiv), THF, 0 °C, 30 min; then BnBr (1.5 equiv), TBAI (0.2 equiv), THF, 0→25 °C, 16 h, 95% over two steps; c) $[PdCl_2(PPh_3)_2]$ (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→−10 °C, 1 h, 95%; e) DHP (1.5 equiv), $TsOH \cdot H_2O$ (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% over three steps; h) I_2 (3.0 equiv), CH_2Cl_2/pyridine (1:1), 25 °C, 15 h, 80%; i) $NaBH_4$ (1.2 equiv), $CeCl_3 \cdot 7H_2O$ (1.2 equiv), MeOH, −78 °C, 1 h; j) TBSCl (2.0 equiv), imidazole (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 3 h, 94% over two steps; k) TMS-acetylene (1.2 equiv), $[PdCl_2(PPh_3)_2]$ (0.02 equiv), CuI (0.04 equiv), Et_2NH, 25 °C, 16 h, 98%; l) Et_2AlCl (1.8 M in toluene, 2.0 equiv), CH_2Cl_2, −25→25 °C, 2 h, 99%; m) DMP (1.2 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 79%; n) *cis*-1,2-dichloroethylene (4.5 equiv), MeLi (1.6 M in Et_2O, 3.0 equiv), Et_2O, 0 °C, 30 min; then **11**, Et_2O, 0 °C, 10 min; o) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 93% over two steps; p) DIBAL-H (1.0 M in toluene, 1.5 equiv), toluene, −78 °C, 30 min, 81%; q) K_2CO_3 (1.5 equiv), MeOH, 25 °C, 1 h, 99%; r) Ac_2O (1.5 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 30 min, 98%. DHP = 3,4-dihydro-2*H*-pyran, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, TBAF = tetra-*n*-butylammonium fluoride, TBAI = tetra-*n*-butylammonium iodide, THF = tetrahydrofuran, THP = tetrahydropyranyl, TMS = trimethylsilyl, Ts = 4-toluenesulfonyl.

compound under palladium-catalyzed conditions ($[PdCl_2(PPh_3)_2]$ cat., CO, MeOH) led to methyl ester **7** (95% yield), whose reduction (DIBAL-H, 95% yield), protection as a THP ether (DHP, $TsOH \cdot H_2O$), and desilylation (TBAF) furnished allylic alcohol **8**. Oxidation of **8** with Dess–Martin periodinane[11] (DMP) gave the corresponding enone (83% overall yield over the last three steps), which was iodinated (I_2, CH_2Cl_2/pyridine (1:1)), affording iodoenone **9** in 80% yield. Luche reduction of the latter ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, −78 °C) proceeded stereoselectively (ca. 5:1 diastereomeric ratio)[10] and afforded, upon silylation (TBSCl, imidazole, DMAP), vinyl iodide **10** in 94% yield over the two steps. Sonogashira coupling of **10** with TMS-acetylene ($[PdCl_2(PPh_3)_2]$ cat., CuI cat., Et_2NH, 98% yield) and subsequent removal of the THP protecting group (Et_2AlCl, −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



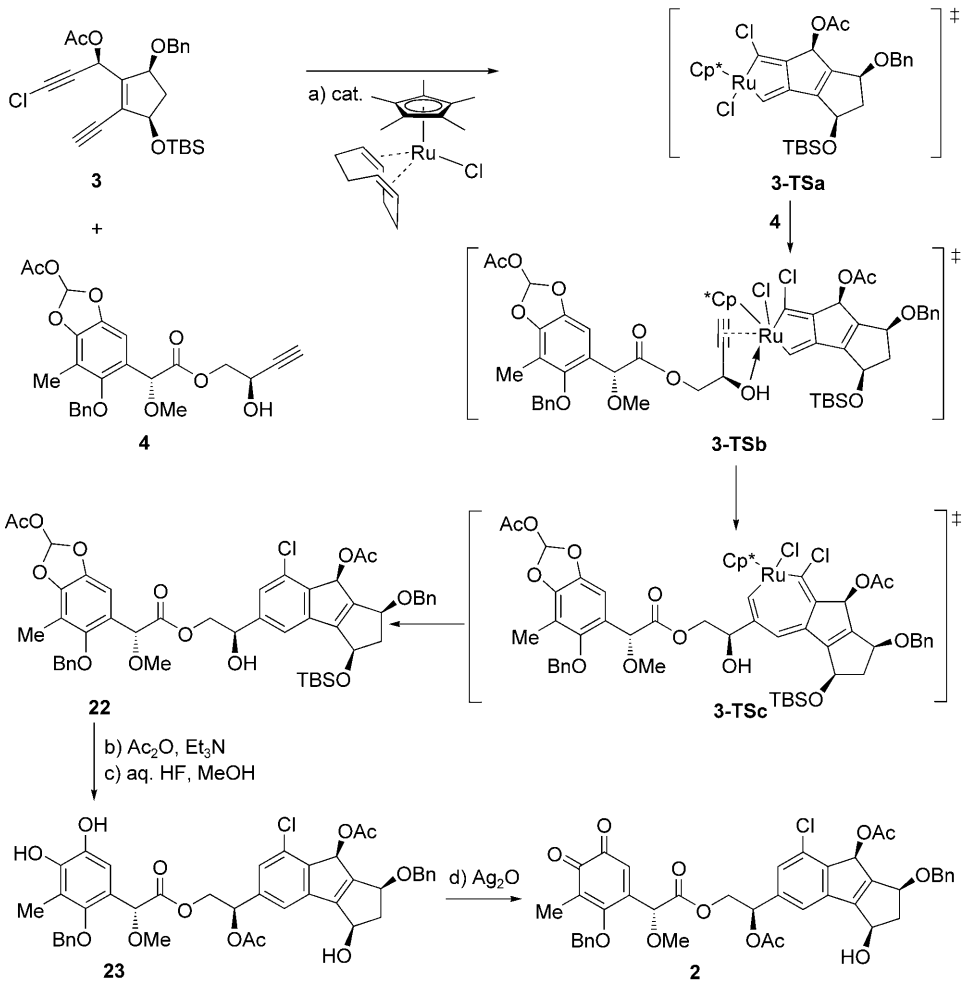
Scheme 3. Construction of building block **4**. Reagents and conditions: a) $MePPh_3Br$ (1.5 equiv), KHMDS (1.0 M in toluene, 1.2 equiv), THF, 0 °C, 30 min; then **15**, THF, −78→0 °C, 30 min, 98%; b) AD-mix-β (1.4 g per mmol **16**), *t*BuOH/H_2O (1:1), 25 °C, 8 h, 96%; c) TBSCl (1.5 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 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), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 78%; g) $NaClO_2$ (4.5 equiv), $NaH_2PO_4 \cdot 2H_2O$ (3.0 equiv), 2-methyl-2-butene (2.5 equiv), *t*BuOH/H_2O (1:1), 25 °C, 30 min, 96%; h) **20** (1.3 equiv), EDCI (1.2 equiv), DMAP (0.2 equiv), CH_2Cl_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, HMDS = bis(trimethylsilyl)amide.

growing molecule by treatment of aldehyde **11** with a preformed solution of lithiochloroacetylene (*cis*-1,2-dichloroethylene, MeLi, Et_2O, 0 °C) and furnished the expected secondary alcohol, which, however, possessed the undesired configuration at C11.[12] This configuration was inverted through an oxidation/reduction protocol. Thus, oxidation of this alcohol with DMP led to ketone **12** (93% overall yield over the last two steps), which was reduced stereoselectively (chelation controlled, ca. 7:1 diastereomeric ratio) with DIBAL-H (toluene, −78 °C)[12] and afforded 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** (K_2CO_3, MeOH, 99% yield), and subsequent acetylation (Ac_2O, Et_3N, DMAP, 98% yield), led to the targeted acetoxy chloroacetylene **3** through 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 ($Ph_3P{=}CH_2$, −78→0 °C, 98% yield) and afforded styrene derivative **16**, which entered a highly enantioselective Sharpless asymmetric dihydroxylation reaction[14] (AD-mix-β, 96% yield, 98% *ee*) and furnished, after sequential silylation (TBSCl, Et_3N, DMAP, 99% yield) and methylation (*t*BuOK, MeI, 95% yield), fully protected pentasubstituted aryl system **18**. The latter compound was converted into 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 $NaClO_2$ (96% yield). Coupling of **19** with acetylenic alcohol **20**,[15] as facilitated by EDCI and DMAP, led to the selective formation of hydroxy ester **21** (73% yield). Treatment 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 hydroxy group in **4** to provide favorable conditions for the desired outcome of the reaction, which included 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). The highly productive process that led rapidly and exclusively to the desired *meta*-chloro isomer may be explained by inspection of transition states **3-TSa**, **3-TSb**, and **3-TSc**, via which this reaction is presumed to proceed.

In preparation for the next challenging task, namely the forging of the cyclic framework of the sporolide molecule through the proposed [4+2] cycloaddition reaction,[6] compound **22** was converted into *o*-quinone **2** via catechol

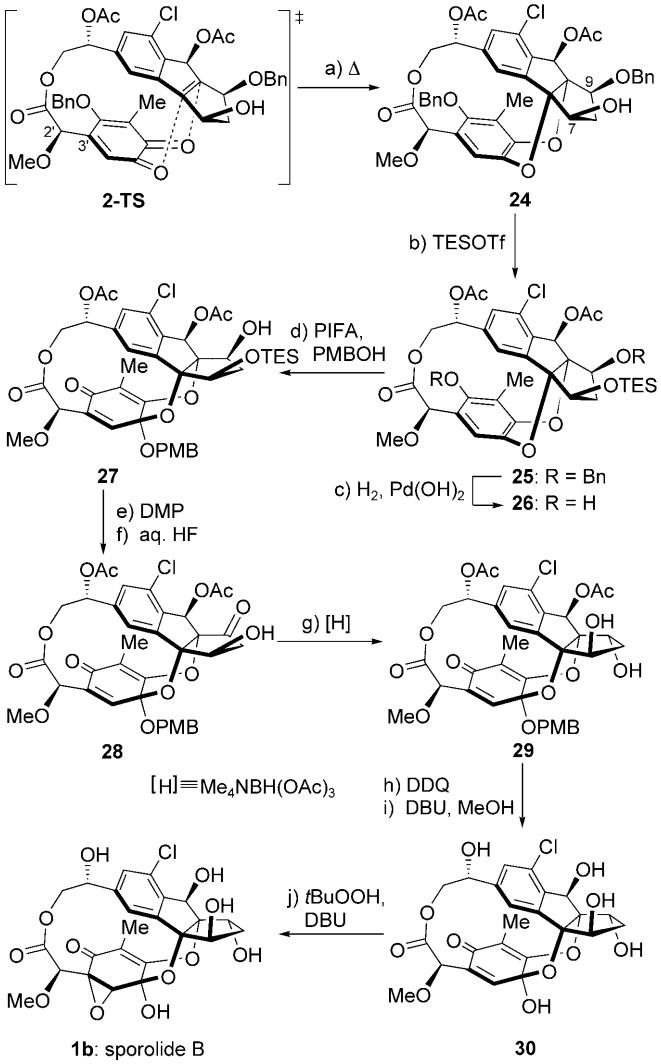


Scheme 4. Synthesis of *o*-quinone **2**. Reagents and conditions: a) **3** (1.0 equiv), **4** (1.1 equiv), [Cp*RuCl(cod)] (0.07 equiv), DCE, 25 °C, 30 min, 87%; b) Ac_2O (2.0 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 30 min, 92%; c) HF (48% aqueous solution, excess), MeCN, 25 °C, 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 = cycloocta-l,5-diene, Cp* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane.

derivative **23** through sequential acetylation (Ac_2O, Et_3N, and DMAP, 92% yield), desilylation (aq.HF and MeOH, 74% yield), and oxidation (Ag_2O, 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 and afforded the desired product **24** (40% yield based on ca. 50% conversion),[17] apparently via 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 five-membered rings), an explanation for its regioselectivity (*o*-quinone rotation around the C2′–C3′ bond) remains elusive. Notably, the oxygen substituent at C9 within **24** and all its precursors have (by design) 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 hydroxy group at C7 playing a directing role in the reduction step. Therefore, subsequent steps had to accommodate, in addition to the obligatory dearomatization of the trioxygenated benzenoid ring, the two steps required for this inversion. To this end, a TES group was placed on the well positioned oxygen atom at C7 (TESOTf, Et_3N, 95% yield) before the two benzyl groups were removed (H_2, $Pd(OH)_2$ cat., 92% yield), affording hydroxy phenol **26** via intermediate **25**. Exposure of **26** to $PhI(OCOCF_3)_2$ in the presence of PMBOH in acetonitrile furnished *para*-ketal quinone **27** in 75% yield, thus providing the opening for the oxidation/reduction protocol to invert the configuration at C9. Indeed, oxidation of **27** (DMP, 90% yield) and subsequent removal of the TES protecting group (aq. HF, MeCN, 85% yield) gave, through the corresponding carbonyl compound, β-hydroxy ketone **28**, whose reduction with $Me_4NBH(OAc)_3$ (MeCN/AcOH 10:1) led to 1,3-diol **29** as a single stereoisomer in 85% yield. This compound was treated sequentially with DDQ (CH_2Cl_2/H_2O (10:1), 70% yield) and DBU (CH_2Cl_2/MeOH (3:1), 78% yield) to remove the PMB and acetate protecting groups, thus 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 CH_2Cl_2 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 (see the Supporting Information).

The regio- and stereocontrolled total synthesis of sporolide B (**1b**) described here 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 sporolide A (**1a**).



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), Et_3N (2.0 equiv), CH_2Cl_2, 0°C, 30 min, 95%; c) H_2 (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), K_2CO_3 (5.0 equiv), MeCN, 0°C, 30 min, 75%; e) DMP (2.0 equiv), CH_2Cl_2, 25°C, 1 h, 90%; f) HF (48% aqueous solution, excess), MeCN, 25°C, 2 h, 85%; g) $Me_4NBH(OAc)_3$ (10 equiv), MeCN/AcOH (10:1), 25°C, 2 h, 85%; h) DDQ (5.0 equiv), CH_2Cl_2/H_2O (10:1), 25°C, 5 h, 70%; i) DBU (10 equiv), CH_2Cl_2/MeOH (3:1), 40°C, 4 h, 78%; j) *t*BuOOH (10 equiv), DBU (5.0 equiv), CH_2Cl_2, 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, TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

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