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Synthesis of sporiolide B from D-glucal

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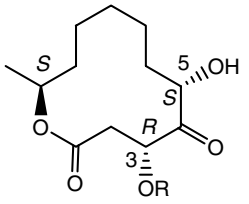
Abstract—A total synthesis of the 12-membered ring natural macrolide, sporiolide B, was achieved from D-glucal in 17 steps with 4.8% overall yield. The required stereochemical configuration at C-3 and C-5 in sporiolide B was easily introduced by applying a Mitsunobu reaction on the chiral template D-glucal. Yamaguchi esterification and ring closing metathesis greatly improved the access to the target compound.

Keywords: Total synthesis; Macrolides; Sporiolide B; D-Glucal; Natural products

1. Introduction

Marine microorganisms, such as bacteria, fungi, and microalgae, which have proved to be a rich source of structurally novel and biologically active secondary metabolites, are attracting increasing attention as a potential source of new pharmaceuticals and pharmaceutical leads.[1] In 2004, from the culture broth of a fungus *Cladosporium* sp. separated from an Okinawan marine brown alga *Actinotrichia fragilis*, Kobayashi reported the isolation of a 12-membered ring macrolide sporiolide B (**1**) and proposed that structurally it corresponds to the 3-*O*-methyl ether of pandangolide 1 (**2**)[2] based on spectroscopic analyses (Chart 1).[3]

Sporiolide B exhibits cytotoxicity against L1210 cells ($IC_{50} = 0.81$ μg/mL) and antibacterial activity against *Micrococcus luteus* (MIC = 16.7 μg/mL). Attracted by its various biological activities, we already completed the first total synthesis of sporiolide B from D-xylose in 3.5% overall yield.[4] In our ongoing project, we needed to synthesize larger quantities of sporiolide B for bioactivity screening. However, in large scale preparations with our previous procedure, we realized that a number of toxic reagents ($HgAc_2$ and KCN) were used. We thus decided to explore an alternative strategy toward the target molecule. Herein, a facile total synthesis of sporiolide B from 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal) as starting material is now reported.



1 R = Me (Sporiolide B)
2 R = H (Pandangolide 1)

Chart 1. Structures of sporiolide B (**1**) and pandangolide 1 (**2**).

2. Results and discussion

As outlined in Chart 2, sporiolide B (**1**) could be prepared from the lactone precursor **3** available from intramolecular ring closure metathesis of diene **4** after Yamaguchi esterification of alcohol **5** and acid **6**. Key intermediate **6** could be derived from the well functionalized lactone **7**, which would be prepared from commercially available D-glucal.

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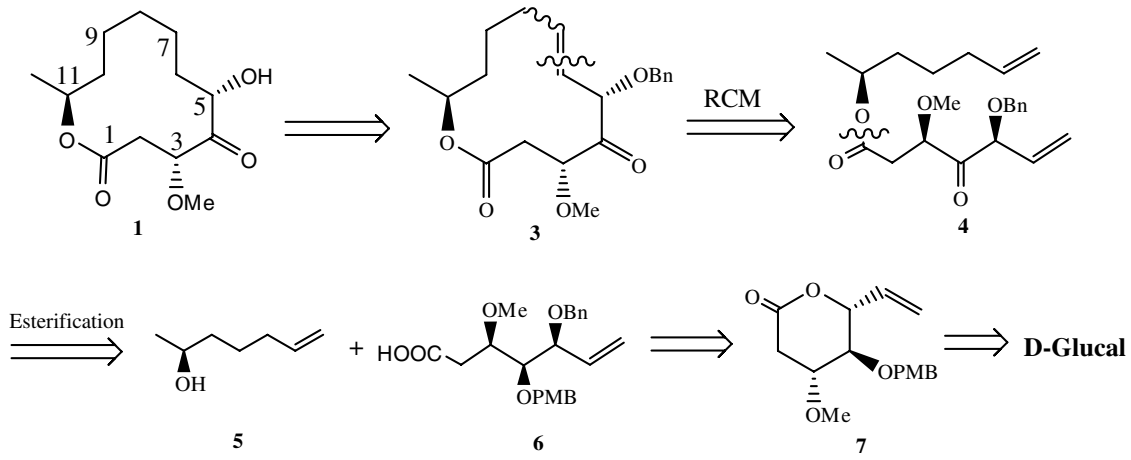
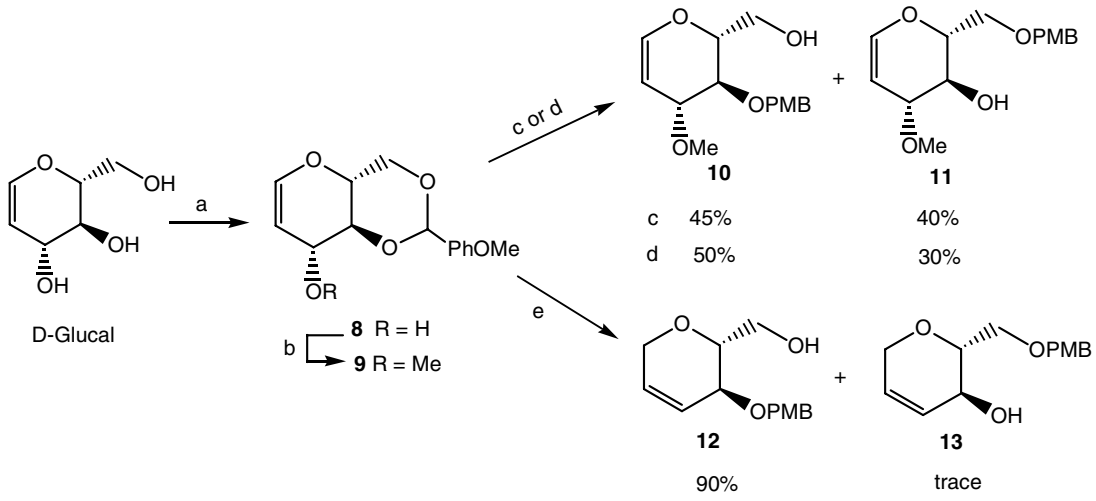


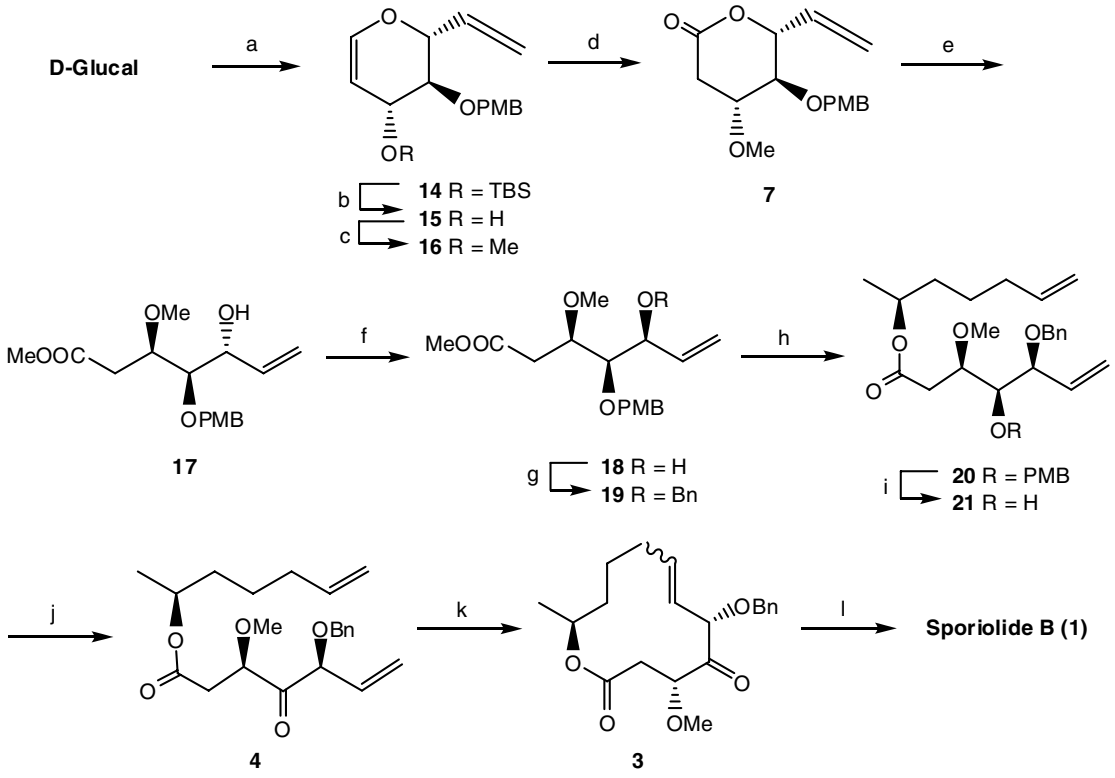
Chart 2. Retrosynthetic analysis of sporiolide B (**1**).



Scheme 1. Attempted cleavage of *p*-anisaldehyde acetal by regioselective reduction. Reagents and conditions: (a) Ref. 5; (b) MeI, NaH, DMF, 2 h; 95%; (c) DIBAL-H, DCM, −78 °C to rt, 2 h, 45% for **10**, 40% for **11**; (d) $LiAlH_4$, $AlCl_3$, THF, 75 °C, 6 h, 50% for **10,** 30% for **11**; (e) $NaCNBH_3$, TMSCl, MeCN, 4 h, 90% for **12**.

Initially, we tried to prepare **10** from **9**, which was obtained by methylation of the known D-glucal derivative **8**,[5] through regioselective reductive cleavage of *p*-anisaldehyde acetal as illustrated in Scheme 1. Unfortunately, a poor selectivity was obtained using either DIBAL-H[5,6] or $LiAlH_4$–$AlCl_3$[7] as reducing agents. When **9** was treated with $NaCNBH_3$–TMSCl,[8] **12** involving double bond migration was obtained unexpectedly in an excellent yield (90%), and its structure was confirmed unambiguously by ^1H NMR spectroscopy.

To solve this problem, we turned our attention to another synthetic route as shown in Scheme 2. Silylated **14** was easily obtained from D-glucal in five steps according to our previous report.[9] Thus, desilylation with TBAF gave alcohol **15**, which was methylated with MeI and NaH resulting in the glucal derivative **16**. Compound **16** was subjected to PCC oxidation[10] at 45 °C in the presence of silica gel to give the key lactone **7** in good yield (67% in three steps). Treatment of **7** with NaOMe in MeOH gave the methyl ester **17**, in which the free (*R*)-OH was inverted into the precursor (*S*)-benzoate under Mitsunobu reaction conditions.[11] Debenzoylation of this precursor with NaOMe in methanol (→**18**), followed by benzylation with benzyl 2,2,2-trichloroacetimidate (→**19**),[12] and hydrolysis with LiOH, furnished acid **6**. Esterification of **6** with (*S*)-6-hepten-2-ol (**5**)[13] under Yamaguchi's conditions[14] afforded the diene derivative **20** (78% from **19**), which was subjected to PMB cleavage with DDQ[15] and Dess–Martin periodinane[16] oxidation, to give the key intermediate **4** in 77% yield and two steps. Diene **4** was then exposed to the Grubbs catalyst [$PHCH{=}RuCl(PCy_3)_2$, 30 mol %][17] undergoing an intramolecular ring closure metathesis (RCM) to produce macrolactone **3** as a *E*,*Z* mixture (*E*/*Z* = 2:1). Final hydrogenation of **3** with H_2 in the presence of Pd/C simultaneously cleaved the benzyl ether and



Scheme 2. Reagents and conditions: (a) Ref. 10, 44%; (b) TBAF, THF, 2 h, 95%; (c) MeI, NaH, DMF, 2 h, 95%; (d) PCC, silica gel, DCM, 45 °C, 6 h, 70%; (e) NaOMe, MeOH, 3 h, 83%; (f) (i) Ph_3P, DEAD, PhCOOH, THF, 2 h; (ii) NaOMe, MeOH, 3 h, 81% in two steps; (g) $BnOC(NH)CCl_3$, TMSOTf, DCM, 3 h, 75%; (h) (i) LiOH, THF/water, 12 h; (ii) (*s*)-6-hepten-2-ol, 2,4,6-trichlorobenzoyl chloride, TEA, DMAP, THF, 18 h, 78% in two steps; (i) DDQ, DCM/water, 2 h, 93%; (j) Dess–Martin periodinane, DCM, 3 h, 83%; (k) 30% $PhCH{=}RuCl_2(PCy_3)_2$, DCM, refluxing, 24 h, 70% ($E/Z = 2{:}1$); (l) H_2, Pd/C, MeOH, 12 h, 81%.

saturated the double bond yielding sporiolide B, identical in every respect to the natural product.[3]

The effects of sporiolide B against human MDA231, BEL-7402, and Hela cell growth were investigated with different methods.[3,18] Unfortunately, under these testing conditions, sporiolide B did not show significant inhibition on proliferation of either human MDA231, BEL-7402, or Hela cell lines at 0.25–1.0 μg/mL for 24, 48, and 72 h, respectively.

In summary, we have achieved the total synthesis of sporiolide B in 17 steps and 4.8% overall yield. The required stereochemical configuration at C-3 and C-5 in sporiolide B was successfully controlled by using a Mitsunobu reaction to invert the stereochemistry at C-5 of a glucal-derived compound. Yamaguchi esterification and ring closing metathesis greatly improved the target synthesis.

3. Experimental

3.1. General methods

Optical rotations were determined at 25 °C with a Perkin–Elmer Model 241-Mc automatic polarimeter, and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR, and ^{1}H–^{1}H, ^{1}H–^{13}C COSY spectra were recorded with a Bruker ARX 400 spectrometer for solns in $CDCl_3$. Chemical shifts are given in parts per million downfield from internal Me_4Si. Mass spectra were measured using a MALDI TOF mass spectrometer with α-cyano-4-hydroxycinnamic acid (CCA) as matrix, or recorded with a VG PLATFORM mass spectrometer using the ESI(−) technique to introduce the sample. TLC was performed on silica gel HF_{254} with detection by charring with 30% H_2SO_4 in MeOH or in some cases by UV detection. Column chromatography was conducted by elution of a column of silica gel (100–200 mesh) with EtOAc–petroleum ether (60–90 °C). Solns were concentrated at <60 °C under diminished pressure.

3.2. (2*R*,3*S*)-2-Hydroxymethyl-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran (12)

To a stirred soln of **8**[5] (2.2 g, 8.4 mmol) in anhyd DMF (15 mL) was added NaH (400 mg, 16.4 mmol) at 0 °C, 30 min later, methyl iodide (0.6 mL, 9 mmol) was added dropwise under the same reaction conditions. After stirring at rt for 2 h, the reaction mixture was poured into ice water (30 mL) and extracted with EtOAc

(2 × 50 mL). The combined organic layers were dried over anhyd Na_2SO_4 and concentrated under diminished pressure. Purification of the residue on column chromatography (7:1 petroleum ether–EtOAc) afforded **9** (2.2 g, 95%) as a solid. To a stirred soln of **9** (0.5 g, 1.8 mmol) in anhyd MeCN (10 mL) at 0 °C was added TMSCl (1.5 mL, 10.8 mmol) portionwise, and then $NaCNBH_3$ (754 mg, 10.8 mmol) was added under the same conditions. The resulting mixture was diluted with CH_2Cl_2 (50 mL) 4 h later and washed with satd aq $NaHCO_3$ and aq NaCl. After drying over anhyd Na_2SO_4 and concentration under diminished pressure, the residue was purified by column chromatography (3:1 petroleum ether–EtOAc) to give **12** (400 mg, 90%) as a colorless syrup: $[\alpha]_D^{25}$ −10 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.26 (d, 2H, *J* 8.5 Hz, Ph), 6.88 (d, 2H, *J* 8.6 Hz, Ph), 5.93 (d, 1H, *J* 10.4 Hz, H-3), 5.85 (d, 1H, *J* 10.5 Hz, H-2), 4.60, 4.47 (2d, 2H, *J* 11.2 Hz, PhCH_2), 4.24–4.15 (m, 2H, H-1a and H-1b), 3.99 (d, 1H, *J* 8.7 Hz, H-4), 3.86 (dd, 1H, *J* 2.9, 11.6 Hz, H-6b), 3.81 (s, 3H, OCH_3), 3.68 (dd, 1H, *J* 5.6, 11.6 Hz, H-6a), 3.49–3.45 (m, 1H, H-5), 1.86 (br s, 1H, O*H*). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.33; H, 7.31.

3.3. (2*R*,3*S*,4*R*)-3-(4-Methoxybenzyloxy)-2-vinyl-3,4-dihydro-2*H*-pyran-4-ol (15)

To a soln of silyl ether **14**[9] (4.5 g, 12 mmol) in THF (50 mL) was added TBAF (24 mL of a 1 M soln in THF, 24 mmol) at 0 °C. The mixture was stirred under these conditions for 30 min, followed by additional 2 h stirring at rt, at the end of which time, TLC indicated completion of the reaction. Then the reaction mixture was concentrated under diminished pressure and the residue was subjected to column chromatography (4:1 petroleum ether–EtOAc) to furnish **15** (3.0 g, 95%) as a colorless syrup: $[\alpha]_D^{25}$ −17 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.28 (d, 2H, *J* 8.1 Hz, Ph), 6.89 (d, 2H, *J* 7.7 Hz, Ph), 6.39 (d, 1H, *J* 6.0 Hz, OC*H*=CH), 6.05–5.92 (m, 1H, C*H*=CH_2), 5.47 (d, 1H, *J* 17.3 Hz, CH=CH_aH_b), 5.34 (d, 1H, *J* 10.6 Hz, CH=CH_aH_b), 4.78 (dd, 1H, *J* 2.6, 6.0 Hz, OCH=C*H*), 4.74 (d, 1H, *J* 11.3 Hz, PhC*H*), 4.61 (d, 1H, *J* 11.2 Hz, PhC*H*), 4.35 (t, 1H, *J* 7.2 Hz, C*H*OPMB), 4.28 (s, 1H, OC*H*CH=CH_2), 3.80 (s, 3H, OCH_3), 3.43 (t, 1H, *J* 6.9 Hz, C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 144.6, 134.5, 130.5, 130.0 (2C), 118.6, 114.4 (2C), 103.2, 80.5, 78.1, 73.8, 68.7, 55.7 (OCH_3). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 69.09; H, 6.84.

3.4. (2*R*,3*S*,4*R*)-4-Methoxy-3-(*p*-methoxybenzyloxy)-2-vinyl-3,4-dihydro-2*H*-pyran (16)

To a stirred soln of **15** (1.1 g, 4.2 mmol) in anhyd DMF (15 mL) was added NaH (200 mg, 8.2 mmol) portionwise at 0 °C and 30 min later, methyl iodide (0.3 mL, 4.5 mmol) was added dropwise under the same conditions. After stirring at rt for 2 h, the reaction mixture was poured into ice water (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under diminished pressure. Purification of the residue by column chromatography (7:1 petroleum ether–EtOAc) afforded **16** (1.1 g, 95%) as a solid: $[\alpha]_D^{25}$ −18 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.27 (d, 2H, *J* 8.4 Hz, Ph), 6.87 (d, 2H, *J* 8.3 Hz, Ph), 6.41 (d, 1H, *J* 6.1 Hz, OC*H*=C), 6.07–5.93 (m, 1H, C*H*=CH_2), 5.40 (d, 1H, *J* 17.2 Hz, CH=CH_aH_b), 5.29 (d, 1H, *J* 10.5 Hz, CH=CH_aH_b), 4.86 (dd, 1H, *J* 2.5, 6.1 Hz, OCH=C*H*), 4.71 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.62 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.29 (t, 1H, *J* 7.5 Hz, C*H*OPMB), 3.96 (d, 1H, *J* 6.0 Hz, OC*H*CH=CH_2), 3.80 (s, 3H, OCH_3 in PMB), 3.49 (dd, 1H, *J* 6.7, 8.5 Hz, C*H*OMe), 3.39 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 143.7, 133.7, 129.6, 128.9 (2C), 118.6, 113.1 (2C), 99.2, 98.8, 77.1, 76.6, 72.4, 55.8 (PhO*C*H_3), 54.5 (O*C*H_3). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.81; H, 7.22.

3.5. (4*R*,5*S*,6*R*)-4-Methoxy-5-(*p*-methoxybenzyloxy)-6-vinyl-tetrahydropyran-2-one (7)

To a soln of **16** (880 mg, 3.2 mmol) in CH_2Cl_2 (100 mL) was added PCC (2.1 g, 9.6 mmol) and silica gel (2.6 g). The stirred suspension was refluxed for 6 h, then cooled and filtered through Celite. The Celite pad was washed several times with EtOAc and the combined filtrates were concentrated. The crude product was purified by column chromatography (4:1 petroleum ether–EtOAc) to give **7** (650 mg; 70%) as a colorless syrup: $[\alpha]_D^{25}$ −15 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.25 (d, 2H, *J* 8.2 Hz, Ph), 6.90 (d, 2H, *J* 8.2 Hz, Ph), 5.98–5.82 (m, 1H, C*H*=CH_2), 5.43 (d, 1H, *J* 17.2 Hz, CH=CH_aH_b), 5.30 (d, 1H, *J* 10.6 Hz, CH=CH_aH_b), 4.62 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.61–4.57 (m, 1H, C*H*OPMB), 4.55 (d, 1H, *J* 11.0 Hz, PhC*H*), 3.81 (s, 3H, PhOCH_3), 3.76 (dd, 1H, *J* 3.6, 7.8 Hz, OC*H*CH=CH_2), 3.54 (dd, 1H, *J* 3.4, 7.5 Hz, C*H*OMe), 3.36 (s, 3H, OCH_3), 2.83 (dd, 1H, *J* 4.5, 16.3 Hz, COCH_aH_b), 2.73 (dd, 1H, *J* 4.2, 16.4 Hz, COCH_aH_b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7 (C=O), 158.3, 132.9, 128.9 (2C), 128.0, 117.8, 113.2 (2C), 98.8, 79.1, 77.8, 71.6, 56.0 (PhO*C*H_3), 54.5 (O*C*H_3), 32.4 (CO*C*H_2). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.35; H, 6.82.

3.6. Methyl (3*R*,4*R*,5*R*)-5-hydroxy-3-methoxy-4-(*p*-methoxybenzyloxy)-hept-6-enoate (17)

To a soln of **7** (600 mg, 2.0 mmol) in anhyd MeOH (15 mL) was added M NaOMe in MeOH until pH 9–

10. The reaction mixture was stirred at rt for 3 h, then neutralized with Amberlite IR-120 (H^+), and filtered. The filtrate was concentrated to dryness under diminished pressure. Purification of the residue by column chromatography (4:1 petroleum ether–EtOAc) gave **17** (550 mg, 83%) as a colorless syrup: $[\alpha]_D^{25}$ −20 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.26 (d, 2H, *J* 8.6 Hz, Ph), 6.88 (d, 2H, *J* 8.6 Hz, Ph), 6.00–5.90 (m, 1H, C*H*=CH_2), 5.44 (d, 1H, *J* 17.2 Hz, CH=C$H_a$$H_b$), 5.25 (d, 1H, *J* 10.5 Hz, CH=$CH_a$$H_b$), 4.64, 4.50 (2d, 2H, *J* 11.3 Hz, PhCH_2), 4.39 (t, 1H, *J* 5.3 Hz, C*H*OPMB), 4.02–3.98 (m, 1H, OC*H*CH=CH_2), 3.81 (s, 3H, PhOCH_3), 3.65 (s, 3H, CH_3OOC), 3.45 (dd, 1H, *J* 3.4, 5.9 Hz, C*H*OMe), 3.33 (br s, 1H, O*H*), 3.38 (s, 3H, OCH_3), 2.69 (dd, 1H, *J* 5.9, 16.1 Hz, $COCH_a$$H_b$), 2.61 (dd, 1H, *J* 7.0, 16.1 Hz, $COCH_a$$H_b$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1 (O=*C*OMe), 159.4, 137.9, 129.8 (2C), 129.6, 116.1, 113.9 (2C), 78.8, 78.4, 72.3, 72.0, 58.0 (COO*C*H_3), 55.3 (PhO*C*H_3), 51.7 (OCH_3), 34.7 (OOC*C*H_2). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.67; H, 7.60.

3.7. Methyl (3*R*,4*R*,5*S*)-5-hydroxy-3-methoxy-4-(*p*-methoxybenzyloxy)-hept-6-enoate (18)

To a soln of **17** (520 mg, 1.6 mmol) in dry THF (15 mL) was added Ph_3P (839 mg, 3.2 mmol), benzoic acid (391 mg, 3.2 mmol), and diethylazodicarboxylate (DEAD, 0.50 mL, 3.2 mmol) at 0 °C. The resulting mixture was stirred at rt for 2 h. After removing the solvent under diminished pressure, the residue was dissolved in EtOAc (100 mL) and washed with N aq HCl, satd aq $NaHCO_3$, and aq NaCl. After drying over anhyd Na_2SO_4 and concentration under diminished pressure, the residue was dissolved in anhyd MeOH (15 mL), and M NaOMe in MeOH was added until pH 9–10. The reaction mixture was stirred at rt for 3 h under these conditions, neutralized with Amberlite IR-120 (H^+), filtered, and concentrated. The residue was purified by silica gel column chromatography (4:1 petroleum ether–EtOAc) to yield **18** (421 mg, 81%) as a colorless syrup: $[\alpha]_D^{25}$ −14 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.25 (d, 2H, *J* 8.4 Hz, Ph), 6.89 (d, 2H, *J* 8.4 Hz, Ph), 6.05–5.96 (m, 1H, C*H*=CH_2), 5.46 (d, 1H, *J* 17.0 Hz, CH=C$H_a$$H_b$), 5.28 (d, 1H, *J* 10.5 Hz, CH=$CH_a$$H_b$), 4.66, 4.51 (2d, 2H, *J* 11.0 Hz, PhCH_2), 4.44–4.40 (m, 1H, C*H*OPMB), 4.02 (t, 1H, *J* 6.9 Hz, OC*H*CH=CH_2), 3.80 (s, 3H, PhOCH_3), 3.68 (s, 3H, CH_3OOC), 3.48 (dd, 1H, *J* 3.6, 6.5 Hz, C*H*OMe), 3.40 (s, 3H, OCH_3), 2.70–2.55 (m, 2H, $COCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0 (O=*C*OMe), 159.5, 137.8, 129.8 (2C), 129.5, 116.2, 113.8 (2C), 78.8, 78.3, 72.3, 71.9, 58.1 (COO*C*H_3), 55.2 (PhO*C*H_3), 51.8 (OCH_3), 34.6 (OOC*C*H_2). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.70; H, 7.35.

3.8. Methyl (3*R*,4*S*,5*S*)-5-benzyloxy-3-methoxy-4-(*p*-methoxybenzyloxy)-hept-6-enoate (19)

To a soln of **18** (250 mg, 0.77 mmol) and benzyl 2,2,2-trichloroacetimidate (380 mg, 1.5 mmol) in dry CH_2Cl_2 (15 mL) at −25 °C was added TMSOTf (3.0 μL, 0.008 mmol) under N_2 atmosphere. The reaction was monitored by TLC until all the starting material was consumed, then quenched with Et_3N and concentrated to dryness. The residue was subjected to silica gel column chromatography (petroleum ether–EtOAc, 6:1) to give **19** (240 mg, 75%) as a colorless syrup: $[\alpha]_D^{25}$ −16 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.34–7.23 (m, 7H, Ph), 6.84 (d, 2H, *J* 8.4 Hz, Ph), 5.99–5.91 (m, 1H, C*H*=CH_2), 5.41 (d, 1H, *J* 17.1 Hz, CH=$CH_a$$H_b$), 5.40 (d, 1H, *J* 10.6 Hz, CH=C$H_a$$H_b$), 4.65, 4.62 (2d, 2H, *J* 11.4 Hz, PhCH_2), 4.46, 4.34 (2d, 2H, *J* 11.3 Hz, PhCH_2), 4.05 (t, 1H, *J* 6.9 Hz, C*H*OPMB), 3.96–3.92 (m, 1H, OC*H*CH=CH_2), 3.79 (s, 3H, PhOCH_3), 3.64 (s, 3H, CH_3OOC), 3.57 (dd, 1H, *J* 3.5, 6.3 Hz, C*H*OMe), 3.31 (s, 3H, OCH_3), 2.58–2.41 (m, 2H, $COCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6 (O=*C*OMe), 158.9, 138.6, 135.5, 130.4, 129.1 (2C), 127.6 (2C), 127.0 (2C), 126.8, 119.5, 113.5 (2C), 81.6, 80.1, 72.6, 70.0, 69.3, 58.1 (COO*C*H_3), 54.6 (PhO*C*H_3), 50.8 (OCH_3), 34.3 (OOC*C*H_2). Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.91; H, 7.21.

3.9. (*S*)-Hept-6-en-2-yl (3*R*,4*S*,5*S*)-5-benzyloxy-3-methoxy-4-(*p*-methoxybenzyloxy)-hept-6-enoate (20)

Methyl ester **19** (210 mg, 0.51 mmol) was dissolved in 4:1 THF–water (15 mL) and the soln was cooled in an ice-water bath. To this was added $LiOH{\cdot}H_2O$ (84 mg, 2 mmol), and the resulting mixture was stirred at room temperature for 12 h, neutralized with 1 N HCl, and then extracted with EtOAc. The combined organic phases were dried with anhyd Na_2SO_4 and concentrated to afford acid **6**. Without further purification, the crude acid was dissolved in anhyd THF (15 mL) and treated with Et_3N (82 μL, 0.6 mmol) and 2,4,6-trichlorobenzoyl chloride (78 μL, 0.5 mmol) successively. After stirring at rt for 1 h, a soln of (*S*)-6-hepten-2-ol (68 mg, 0.6 mmol) and DMAP (73 mg, 0.6 mmol) in THF (5 mL) was added. The reaction mixture was stirred at rt for another 18 h, then diluted with aq NH_4Cl. The aq soln was extracted with EtOAc (2 × 25 mL). The combined organic extracts was dried and evaporated. Purification of the residue by column chromatography (6:1 petroleum ether–EtOAc) gave **20** (196 mg, 78% in two steps) as a colorless syrup: $[\alpha]_D^{25}$ −22 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.34–7.24 (m, 7H, Ph), 6.84 (d, 2H, *J* 8.0 Hz, Ph), 5.97–5.92 (m, 1H, C*H*=CH_2), 5.78–5.74 (m, 1H, C*H*=CH_2), 5.42 (d, 1H, *J* 9.0 Hz CH=C$H_a$$H_b$), 5.38 (d, 1H, *J* 18.0 Hz, CH=$CH_a$$H_b$), 5.00 (d, 1H, *J* 17.4 Hz, CH=$CH_a$$H_b$), 4.98–4.90 (m, 2H, CH=C$H_a$$H_b$,

C*H*OOC), 4.65, 4.48 (2d, 2H, *J* 10.5 Hz, PhCH_2), 4.62, 4.36 (2d, 2H, *J* 11.2 Hz, PhCH_2), 4.02 (t, 1H, *J* 6.8 Hz, C*H*OPMB), 3.97–3.95 (m, 1H, OC*H*CH=CH_2), 3.80 (s, 3H, PhOCH_3), 3.57–3.55 (m, 1H, C*H*OMe), 3.32 (s, 3H, OCH_3), 2.60–2.47 (m, 2H, COCH_2), 2.04 (dd, 2H, *J* 6.7, 13.3 Hz, CH_2CH=CH_2), 1.55–1.41 (m, 4H, CH_2CH_2), 1.21 (d, 3H, *J* 6.0 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (O=*C*OCH), 159.2, 138.4 (2C), 136.2, 133.3, 130.4 (2C), 129.8, 128.2 (2C), 127.7, 127.4 (2C), 119.4, 114.7, 113.6 (2C), 81.8, 80.1, 77.5, 74.0, 70.9, 58.6 (O*C*H_3), 55.2 (PhO*C*H_3), 36.5, 35.3, 33.4, 24.5, 19.9. Anal. Calcd for $C_{30}H_{40}O_6$: C, 72.55; H, 8.12. Found: C, 72.81; H, 8.01.

3.10. (*S*)-Hept-6-en-2-yl (3*R*,4*S*,5*S*)-5-benzyloxy-4-hydroxy-3-methoxy-hept-6-enoate (21)

A soln of ester **20** (170 mg, 0.33 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with water (1 mL) and DDQ (150 mg, 0.66 mmol), and then stirred at rt for 2 h. Satd aq $NaHCO_3$ was added, and the aq layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over anhyd Na_2SO_4 and concentrated to dryness. Column chromatography of the residue (4:1 petroleum ether–EtOAc) gave **21** (120 mg, 93%) as a colorless syrup: $[\alpha]_D^{25}$ −25 (*c* 0.5, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 7.34–7.26 (m, 5H, Ph), 5.86–5.82 (m, 1H, C*H*=CH_2), 5.77–5.73 (m, 1H, C*H*=CH_2), 5.43 (d, 1H, *J* 10.2 Hz, CH=C$H_a$$H_b$), 5.38 (d, 1H, *J* 17.3 Hz, CH=$CH_a$$H_b$), 5.00 (d, 1H, *J* 17.3 Hz, CH=$CH_a$$H_b$), 4.96–4.91 (m, 2H, CH=C$H_a$$H_b$, C*H*OOC), 4.63, 4.36 (2d, 2H, *J* 11.6 Hz, PhCH_2), 3.99 (br s, 1H, C*H*OH), 3.81 (t, 1H, *J* 7.4 Hz, OC*H*CH=CH_2), 3.49 (d, 1H, *J* 6.5 Hz, C*H*OMe), 3.34 (s, 3H, OCH_3), 2.67–2.55 (m, 2H, COCH_2), 2.04 (dd, 2H, *J* 6.8, 13.6 Hz, CH_2CH=CH_2), 1.55–1.36 (m, 4H, CH_2CH_2), 1.20 (d, 3H, *J* 6.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (O=*C*OCH), 138.4, 138.1, 136.1, 128.3 (2C), 128.0 (2C), 127.6, 120.2, 114.7, 80.5, 76.1, 74.7, 71.1, 70.2, 58.7 (OCH_3), 37.0, 35.3, 33.4, 24.6, 19.9. Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.89; H, 8.48.

3.11. (*S*)-Hept-6-en-2-yl (3*R*,5*S*)-5-benzyloxy-3-methoxy-4-oxo-hept-6-enoate (4)

To a soln of **21** (970 mg, 2.6 mmol) in dry CH_2Cl_2 (150 mL), Dess–Martin periodinane (1.65 g, 3.9 mmol) was added and the reaction mixture was stirred for 3 h at rt. After extraction with satd aq $NaHCO_3$, the organic layer was separated, dried, and concentrated. The residue was subjected to column chromatography on silica gel (6:1 petroleum ether–EtOAc) to furnish compound **4** (802 mg, 83%) as a colorless syrup: $[\alpha]_D^{25}$ −30 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.40–7.30 (m, 5H, Ph), 5.90–5.86 (m, 1H, C*H*=CH_2), 5.77–5.74 (m, 1H, C*H*=CH_2), 5.50 (d, 1H, *J* 17.3 Hz, CH=$CH_a$$H_b$), 5.42 (d, 1H, *J* 10.3 Hz, CH=C$H_a$$H_b$), 5.00 (d, 1H, *J* 17.2 Hz, CH=$CH_a$$H_b$), 4.97–4.92 (m, 2H, CH=C$H_a$$H_b$, C*H*OOC), 4.62 (d, 1H, *J* 6.7 Hz, OC*H*CH=CH_2), 4.67, 4.54 (2d, 2H, *J* 11.9 Hz, PhCH_2), 4.48 (dd, 1H, *J* 3.6, 8.2 Hz, C*H*OMe), 3.34 (s, 3H, OCH_3), 2.77 (dd, 1H, *J* 3.7, 16.1 Hz, COC$H_a$$H_b$), 2.52 (dd, 1H, *J* 8.4, 16.1 Hz, COC$H_a$$H_b$), 2.04 (dd, 2H, *J* 7.0, 13.8 Hz, CH_2CH=CH_2), 1.53–1.43 (m, 4H, CH_2CH_2), 1.20 (d, 3H, *J* 6.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6 (C=O), 169.9 (O=*C*OCH), 138.4, 137.2, 132.3, 128.5 (2C), 128.0, 127.9 (2C), 120.1, 114.7, 83.1, 80.5, 71.6, 71.4, 58.7 (OCH_3), 37.1, 35.3, 33.4, 24.5, 19.9. Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.91; H, 7.88.

3.12. Lactone 3

Diolefin **4** (550 mg, 1.4 mmol), dissolved in dry degassed CH_2Cl_2 (100 mL), was added dropwise within 2 h to a refluxing soln of ruthenium catalyst[17] (360 mg, 0.4 mmol) in dry degassed CH_2Cl_2 (2 L). The mixture was heated at reflux until complete consumption of the starting material (20–24 h, TLC monitoring). After solvent removal under diminished pressure, the residue was purified by column chromatography (8:1 petroleum ether–EtOAc) yielding first (*Z*)-**3** (120 mg, 23.5%) and then (*E*)-**3** (250 mg, 46.5%) as colorless syrups: for the *Z*-isomer, $[\alpha]_D^{25}$ −28 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35–7.26 (m, 5H, Ph), 5.83–5.79 (m, 1H, CH_2C*H*=CH), 5.62 (t, 1H, *J* 9.5 Hz, CH_2CH=C*H*), 4.89 (d, 1H, *J* 8.7 Hz, C*H*OOC), 4.83 (dd, 1H, *J* 6.3, 11.8 Hz, C*H*OBn), 4.62 (d, 1H, *J* 11.7 Hz, PhC*H*), 4.52 (d, 1H, *J* 11.5 Hz, PhC*H*), 3.40 (s, 3H, OCH_3), 4.34 (dd, 1H, *J* 2.7, 9.4 Hz, C*H*OMe), 2.91 (dd, 1H, *J* 2.6, 14.8 Hz, OOCC$H_a$$H_b$), 2.70 (dd, 1H, *J* 9.3, 14.8 Hz, OOCC$H_a$$H_b$), 2.08 (dd, 2H, *J* 9.7, 16.9 Hz, CH_2CH=CH), 1.53–1.44 (m, 4H, CH_2CH_2), 1.20 (d, 3H, *J* 6.1 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.6 (C=O), 169.1 (O=*C*OCH), 137.3, 128.3 (2C), 128.1, 128.0 (2C), 127.8, 125.3, 79.5, 76.1, 72.3, 71.1, 58.2 (OCH_3), 37.1, 32.7, 27.0, 22.7, 20.6; for the *E*-isomer, $[\alpha]_D^{25}$ −26 (*c* 0.5, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ 7.39–7.31 (m, 5H, Ph), 5.91–5.87 (m, 1H, CH_2C*H*=CH), 5.42 (dd, 1H, *J* 4.7, 15.7 Hz, CH_2CH=C*H*), 4.87 (t, 1H, *J* 5.6 Hz, C*H*OOC), 4.63 (d, 1H, *J* 11.9 Hz, PhC*H*), 4.61 (d, 1H, *J* 7.0 Hz, C*H*OBn), 4.54 (d, 1H, *J* 11.8 Hz, PhC*H*), 3.42 (s, 3H, OCH_3), 4.19 (dd, 1H, *J* 3.1, 6.7 Hz, C*H*OMe), 3.11 (dd, 1H, *J* 3.0, 16.2 Hz, OOCC$H_a$$H_b$), 2.85 (dd, 1H, *J* 6.7, 16.3 Hz, OOCC$H_a$$H_b$), 2.19–2.17 (m, 1H, C$H_a$$H_b$CH=CH), 1.92–1.89 (m, 1H, C$H_a$$H_b$CH=CH), 1.55–1.47 (m, 4H, CH_2CH_2), 1.14 (d, 3H, *J* 6.5 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3 (C=O), 169.0 (O=*C*OCH), 137.5, 133.7, 128.5 (2C), 127.9, 127.6 (2C), 124.4, 83.5, 79.6, 71.9, 71.2, 58.4 (OCH_3), 35.9, 32.1, 31.6, 21.7, 19.1;

ESI$^{(+)}$MS: m/z 347 $[M+H]^+$, 369 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{26}O_5$ (E, Z mixture): C, 69.34; H, 7.56. Found: C, 69.05; H, 7.46.

3.13. Sporiolide B (1)

To a suspension of Pd/C (5% Pd, 100 mg) in MeOH (50 mL) was added a soln of **3** (E/Z mixture, 250 mg, 0.72 mmol) in MeOH (20 mL). The mixture was allowed to stir at rt under H_2 atmosphere. After 12 h, the reaction mixture was filtered and concentrated under diminished pressure. The residue was subjected to column chromatography on silica gel (5:1 petroleum ether–EtOAc) to give sporiolide B (150 mg, 81%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −32 (c 0.5, MeOH); lit.[4] $[\alpha]_D^{25}$ −29 (c 0.5, $CHCl_3$), $[\alpha]_D^{25}$ −33 (c 0.5, MeOH); lit.[3] $[\alpha]_D^{25}$ −33 (c 0.3, MeOH); ^{1}H NMR ($CDCl_3$): δ 4.81–4.83 (m, 1H, H-11), 4.44 (d, 1H, J 8.7 Hz, H-3), 4.30 (d, 1H, J 5.7 Hz, H-5), 3.53 (s, 3H, OCH_3), 3.43 (t, 1H, J 12.6 Hz, H-2b), 2.60 (dd, 1H, J 8.8, 13.9 Hz, H-2a), 2.04–2.06 (m, 1H, H-6b), 1.58–1.69 (m, 2H, H-10b, H-6a), 1.48–1.57 (m, 2H, H-7b, H-9b), 1.38–1.47 (m, 2H, H-8b, H-9a), 1.25–1.36 (m, 2H, H-8a, H-10a), 1.23 (d, 3H, J 6.4 Hz, H-12), 1.07–1.09 (m, 1H, H-7a); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8 (C-4), 170.6 (C-1), 76.1 (C-5), 74.4 (C-3), 73.3 (C-11), 58.4 (OCH_3), 41.4 (C-2), 33.4 (C-10), 30.0 (C-6), 26.5 (C-8), 23.8 (C-9), 22.2 (C-7), 20.8 (C-12); MALDI-FTMS: calcd for $C_{13}H_{22}O_5$: 258.1467 $[M]^+$; found: 281.1403 $[M+Na]^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2007.04.013.

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