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The First Total Synthesis of Sporiolide A

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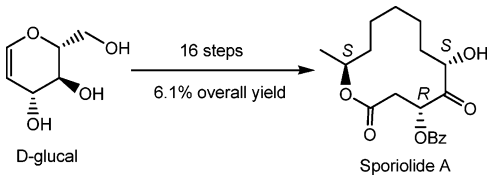

The first total synthesis of the natural cytotoxic agent sporiolide A has been accomplished from D-glucal in 16 steps with 6.1% overall yield. Carbohydrates were applied as the chiral templates to manipulate the absolute configuration during the synthesis. Pyridinium chlorochromate (PCC)-promoted transformation of the cyclic enol-ether to lactone, followed by Yamaguchi esterification and intramolecular ring closure metathesis, greatly facilitates synthesis of the target compound.

Introduction

Marine fungi are attracting increasing attention as a potential source of new pharmaceuticals and pharmaceutical leads.[1] These leading compounds include fungal metabolites containing 12-membered lactone rings such as sporiolides [A (**1**), B (**2**)] and pandangolide 1 (**3**) isolated from the cultured broth of *Cladosporium* sp. from an Okinawan marine brown alga *Actinotrichia fragilis* and the Red Sea sponge *Niphates rowi* (Figure 1).[2] Sporiolides A and B exhibit cytotoxicity against L1210 cells with IC_{50} values of 0.13 and 0.81 μg/mL, respectively. Importantly, sporiolide A shows antifungal activity against *Candida albicans* (MIC 16.7 μg/mL), *Cryptococcus neoformans* (8.4 μg/mL), *Aspergillus niger* (16.7 μg/mL), and *Neurospora crassa* (8.4 μg/mL), together with antibacterial activity against *Micrococcus luteus* (16.7 μg/mL). In 2004, Kobayashi and co-workers proposed a chemical structure of sporiolide A corresponding to 3-*O*-benzoyl pandangolide 1 based on spectroscopic data,[3] although the absolute configuration of pandangolide 1 was not determined until 2005.[4] The potential biological importance, as well as the uncertainty of its absolute structural configuration, marked sporiolide A as a synthetic target for us. Herein, we report our efforts leading to the first total synthesis of sporiolide A (**1**) using chiral carbohydrate templates.

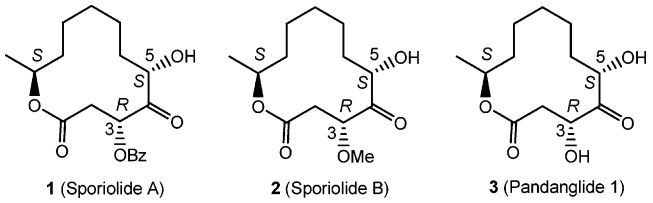

FIGURE 1. Structures of macrolides from marine-derived fungus *Cladosporium* species.

Results and Discussion

As outlined in Scheme 1, we decided to prepare sporiolide A (**1**) from olefinic intermediate **4** that we envisaged would be made available from intramolecular ring closure metathesis (RCM) of diene **5** after esterification of acid **6** and alcohol **7**. Key intermediate **6a** could be derived from cyanated D-xylose derivative **8** to afford the proposed absolute configurations at

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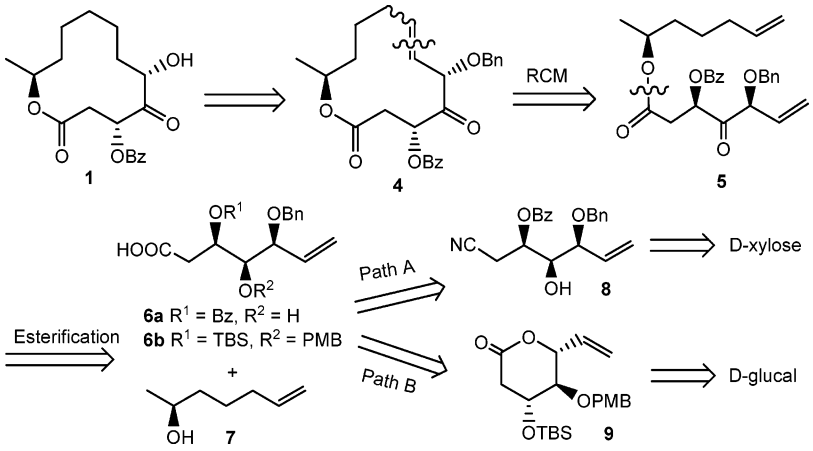
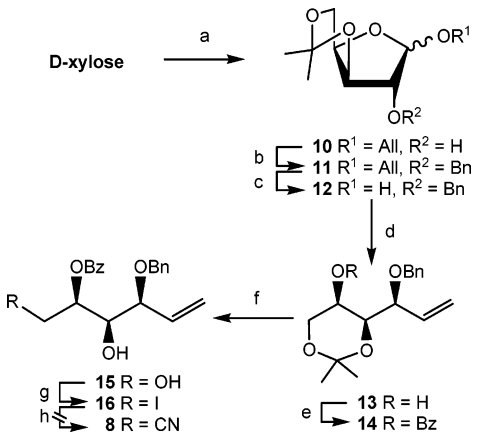
SCHEME 1. Retrosynthetic Analysis of Sporiolide A (1)



SCHEME 2. Attempted Synthesis of Sporiolide A from d-Xylose[a]



[a] Reagents and conditions: (a) ref 5; (b) BnBr, NaH, DMF, 2 h, 95% (α/β = 1.5/1); (c) (i) t-BuOK, DMSO, 80 °C, 15 min; (ii) $Hg(OAc)_2$, THF/H_2O, 30 min, 84% for two steps (α/β = 2/1); (d) BuLi, Ph_3PCH_3Br, THF, −50 °C to rt, 12 h, 75%; (e) BzCl, Pyr, DMAP, 2 h, 98%; (f) TsOH·H_2O, MeOH/H_2O, 3 h, 95%; (g) Ph_3P, I_2, imidazole, THF, 12 h, 81%; (h) KCN, DMF, rt to 150 °C.

C-3 and C-5 in sporiolide A (path A, Scheme 1). Alternatively, as our subsequent investigation would make clear, acid **6b** could be obtained from the appropriately functionalized lactone **9**, which could be prepared from commercially available D-glucal (path B, Scheme 1).

Initially, we tried to prepare key intermediate **8** starting from D-xylose as illustrated in Scheme 2. Thus, benzylation of known D-xylofuranosyl derivative **10**[5] and subsequent deallylation (*t*-BuOK in DMSO and $Hg(OAc)_2$ in THF/H_2O)[6] gave hemiacetal **12** in good yield (80% from **10**). Standard Wittig reaction of **12** with methyltriphenylphosphonium bromide in anhydrous THF at −50 °C generated olefin **13**, in which the hydroxyl group was benzoylated using BzCl and pyridine (→**14**). Acid hydrolysis of **14** with TsOH hydrate (→**15**) and regioselective iodination[7] with Ph_3P and I_2 furnished iodide **16** in an isolated yield of 57% over 4 steps. Attempted S_N2 substitution of iodide to the cyano group with KCN using many known procedures was fruitless.[8] However, in a model study, this transformation was successfully carried out when methyl ether was used in place of the benzoate group. Furthermore, if the benzoate group was replaced by 4-methoxybenzyl ether, the desired compound failed to form under the same reaction conditions. Since the literature[9] suggested that this problem might be hard to overcome, we focused our attention on path B of Scheme 1, as shown in Scheme 3.

D-Glucal was regioselectively silylated at the 3- and 6-positions according to a literature method[10] to give compound **17**, which was then treated with PMBCl and NaH in DMF, affording fully protected glucal **18** (75% yield from D-glucal). Regioselective desilylation of **18** with HF−pyridine complex[11] gave **19**, providing a free primary hydroxyl, which was then oxidized by Swern oxidation and alkenated under Witttig reaction conditions (→**20**). This D-glucal derivative **20** was subjected to pyridinium chlorochromate (PCC)-promoted transformation of cyclic enol ether to lactone[12] at 45 °C in the presence of silica gel to give key intermediate **9** in 74% yield. Treatment of **9** with NaOMe in MeOH was formed methyl ester **21**, in which free OH was blocked by a benzyl group using benzyltrichloroacetimdate[13] and trimethylsilyltrifluoromethanesulfonate (TMSOTf), affording compound **22**. Hydrolysis of **22** with LiOH, followed by esterification with (*S*)-6-hepten-2-ol (**7**)[14] under Yamaguchi's conditions,[15] afforded diene derivative **23**, which was subjected to desilylation with tetrabutylammonium fluoride (TBAF) (→**24**), benzoylation with BzCl in pyridine (→**25**), cleavage of PMB group with DDQ[16] (→ **26**), and Dess−Martin periodinane oxidation,[17] to form ketone diene intermedi-

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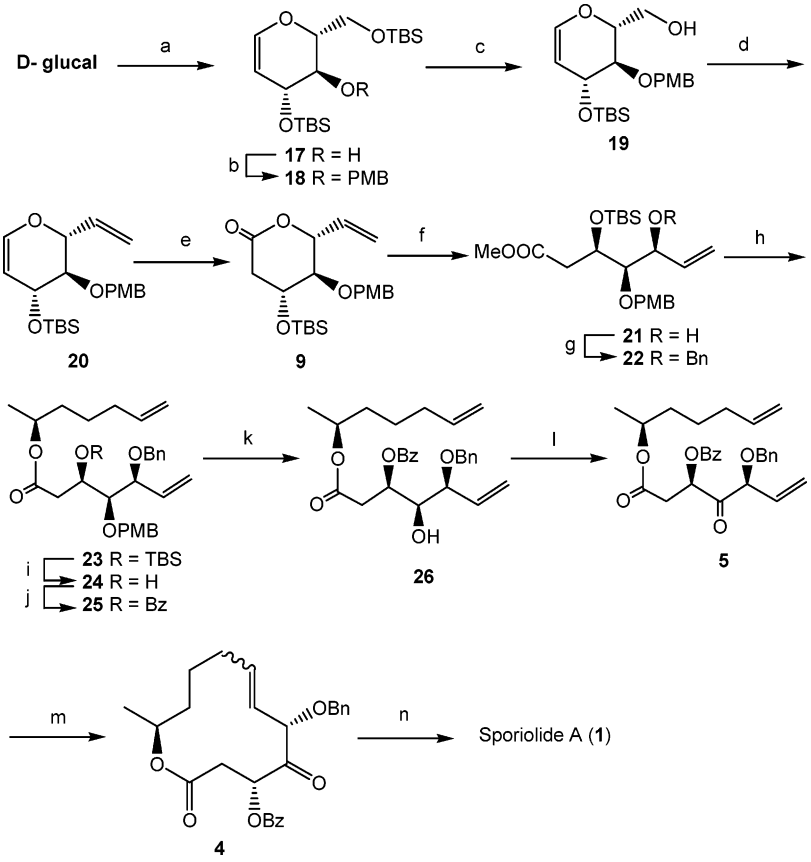
SCHEME 3. Total Synthesis of Sporiolide A (1)[a]



[a] Reagents and conditions: (a) ref 10, 90%; (b) PMBCl, NaH, DMF, 2 h, 83%; (c) HF/Pyr, THF, 2 h, 78%; (d) (i) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C to rt, 2 h; (ii) BuLi, Ph_3PCH_3Br, THF, −50 °C to rt, 3 h, 75% over two steps; (e) PCC, silica gel, CH_2Cl_2, 45 °C, 6 h, 74%; (f) NaOMe, MeOH, 3 h, 83%; (g) $BnOC(NH)CCl_3$, TMSOTf, CH_2Cl_2, 3 h, 75%; (h) (i) LiOH, THF/MeOH/H_2O, 12 h; (ii) (*S*)-6-hepten-2-ol, 2,4,6-trichlorobenzoyl chloride, TEA, DMAP, THF, 18 h, 79% in two steps; (i) TBAF, THF, 4 h, 83%; (j) BzCl, Pyr, DMAP, 4 h, 95%; (k) DDQ, CH_2Cl_2/ H_2O, 2 h, 90%; (l) Dess−Martin periodinane, CH_2Cl_2, 3 h, 82%; (m) 30% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 24 h, 72% (*E*/*Z* = 2/1); (n) H_2, Pd/C, MeOH, 24 h, 91%.

ate **5** in 58% yield over four steps. Diene **5** was then exposed to the Grubbs catalyst [$PHCH{=}RuCl(PCy_3)_2$, 30 mol/%, 1.4×10^{-4} M in CH_2Cl_2][18] to undergo an intramolecular ring closure metathesis (RCM) to produce macrolide **4** in a form of *E*,*Z* mixture (*E*/*Z* = 2/1). Final hydrogenation of **4** with H_2 in the presence of Pd/C reduced both benzyl and double bond to accomplish the total synthesis of sporiolide A, identical in all physical data to that reported for the natural product.[3]

In summary, we have finished the first total synthesis of sporiolide A in 16 steps and 6.1% overall yield. The required stereochemical configurations at C-3 and C-5 in sporiolide A were successfully secured by using D-glucal as the chiral template. PCC-promoted transformation of the cyclic enol ether to lactone, Yamaguchi esterification, and Grubbs ring closure metathesis greatly facilitated the synthesis of our target. As exemplified in this study, carbohydrate moieties provide versatile synthons in asymmetric synthesis of natural products.[19] This report provides an attractive method for the preparation of other natural macrolides, such as pandangolide 1a, pandangolides 1 and 2, and sporiolide B.[1d,20] The screening of cytotoxic activities toward other cell lines are currently under investigation and will be reported in due course.

Experimental Section

3,6-*O*-Di-*tert*-butyldimethylsilyl-4-*O*-*p*-methoxybenzyl-D-glucal (18). To a stirred solution of **17** (5.5 g, 14.7 mmol) in anhydrous DMF (30 mL) was added NaH (720 mg, 30 mmol) portionwise at 0 °C. After 30 min, *p*-methoxybenzyl chloride (2.4 mL, 18 mmol) was added dropwise under the same reaction conditions. The mixture was kept stirring at room temperature for 2 h, poured into ice−water (30 mL), and extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the residue on column chromatography (petroleum ether−EtOAc, 25:1) afforded **18** (6.0 g, 83%) as a colorless syrup: $[\alpha]^{25}_D$ −20 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.10 (s, 6H), 0.90 (s, 9H), 0.93 (s, 9H), 3.62 (t, 1H, *J* = 6.5 Hz), 3.80 (s, 3H), 3.84 (s, 1H), 3.87 (t, 1H, *J* = 6.6 Hz), 3.94 (dd, 1H, *J* = 4.4, 11.1 Hz), 4.32 (d, 1H, *J* = 5.9 Hz), 4.62 (dd, 1H, *J* = 2.4, 8.3 Hz), 4.64 (d, 1H, *J* = 10.7 Hz), 4.75 (d, 1H, *J* = 10.8 Hz), 6.30 (d, 1H, *J* = 6.1 Hz), 6.87 (d, 2H, *J* = 8.2 Hz), 7.26 (d, 2H, *J* = 8.2 Hz); ^{13}C

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NMR ($CDCl_3$) δ −5.4, −5.2, −4.6, −4.4, 18.0, 18.4, 25.8, 25.9, 55.2, 61.9, 69.0, 73.5, 76.2, 78.0, 103.2, 113.8, 129.5, 130.6, 143.4, 159.2. Anal. Calcd for $C_{26}H_{46}O_5Si_2$: C, 63.11; H, 9.37; Found: 63.39; H, 9.31.

3-*O*-*tert*-Butyldimethylsilyl-4-*O*-*p*-methoxybenzyl-D-glucal (19). To a solution of **18** (5.8 g, 11.7 mmol) in THF (120 mL) was added HF/Pyr (70%, 7 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature, stirred for 2 h, diluted with EtOAc (100 mL), and neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was further extracted with EtOAc (100 mL). After being washed with brine and dried over anhydrous Na_2SO_4, the organic layer was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether−EtOAc, 4:1) to give **19** (3.5 g, 78%) as a colorless syrup: $[\alpha]^{25}_D$ −18 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.92 (s, 9H), 3.38 (d, 1H, J = 7.7 Hz), 3.50 (d, 1H, J = 3.9 Hz), 3.81 (s, 3H), 3.91 (t, 1H, J = 7.3 Hz), 4.62 (s, 2H), 4.76 (d, 1H, J = 6.5 Hz), 5.56 (d, 1H, J = 3.2 Hz), 5.82 (dd, 1H, J = 4.1, 9.7 Hz), 6.12 (dd, 1H, J = 3.2, 9.6 Hz), 6.88 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.4, 17.9, 25.8, 55.2, 61.9, 68.6, 73.5, 76.4, 77.0, 103.7, 113.7, 129.6, 131.2, 143.4, 159.4. Anal. Calcd for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found: C, 63.50; H, 8.44.

(2*R*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-3-(*p*-methoxybenzyloxy)-2-vinyl-2,3-dihydro-2*H*-pyran (20). To a stirred solution of oxalyl chloride (1.1 mL, 13 mol) in dry CH_2Cl_2 (20 mL) at −78 °C was added DMSO (2.1 mL, 28 mmol) dropwise under N_2 atmosphere. The reaction mixture was stirred under these conditions for 30 min, and a solution of alcohol **19** (3.4 g, 8.9 mmol) in dry CH_2Cl_2 (30 mL) was then added slowly. After 1 h of stirring at −78 °C, Et_3N (8.3 mL, 60 mol) was added, and the reaction was stirred for another 30 min at ambient temperature, quenched with saturated aqueous NH_4Cl (30 mL), and extracted with CH_2Cl_2 (30 mL). The combined organic phase was washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish the aldehyde, which was directly used in the next step without further purification. In a parallel reaction flask, a 2.5 M solution of n-BuLi in hexane (5.6 mL, 14 mmol) was added under N_2 atmosphere to a stirred suspension of methyltriphenylphosphonium bromide (4.2 g, 11.6 mmol) in dry THF (40 mL) at −50 °C. The mixture was allowed to warm to room temperature, stirred for 1 h, and cooled to −50 °C again. To this mixture a solution of above crude aldehyde in dry THF (30 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 2 h, quenched with aqueous NH_4Cl, and extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether−EtOAc, 10:1) to give **20** (2.5 g, 75% yield over two steps) as a colorless syrup: $[\alpha]^{25}_D$ −18 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.92 (s, 9H), 3.42 (t, 1H, J = 6.5 Hz), 3.80 (s, 3H), 4.28 (t, 1H, J = 7.5 Hz), 4.35 (d, 1H, J = 6.0 Hz), 4.58 (d, 1H, J = 10.7 Hz), 4.66−4.68 (m, 1H), 4.70 (d, 1H, J = 11.0 Hz), 5.26 (d, 1H, J = 10.5 Hz), 5.40 (d, 1H, J = 17.3 Hz), 5.97−6.06 (m, 1H), 6.32 (d, 1H, J = 6.0 Hz), 6.86 (d, 2H, J = 8.3 Hz), 7.26 (d, 2H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.6, −4.5, 18.0, 25.8, 55.2, 69.1, 73.8, 78.1, 80.1, 103.9, 113.7, 118.0, 129.6, 130.2, 134.6, 143.2, 159.2. Anal. Calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 67.23; H, 8.50.

(4*R*,5*R*,6*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-(*p*-methoxybenzyloxy)-6-vinyltetrahydropyran-2-one (9). To a solution of compound **20** (840 mg, 2.2 mmol) in CH_2Cl_2 (100 mL) was added the mixture of PCC (1.5 g, 6.6 mmol) and silica gel (1.8 g). The stirred suspension was refluxed for 6 h and 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 (petroleum ether−EtOAc, 6:1) to give **9** (650 mg, 74%) as a colorless syrup: $[\alpha]^{25}_D$ −14 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 2.55 (dd, 1H, J = 4.8, 16.6 Hz), 2.89 (dd, 1H, J = 4.2, 16.6 Hz), 3.46 (t, 1H, J = 4.8 Hz), 3.81 (s, 3H), 4.17 (dd, 1H, J = 4.3, 8.6 Hz), 4.56 (d, 1H, J = 11.1 Hz), 4.62 (d, 1H, J = 11.1 Hz), 4.66 (t, 1H, J = 6.2 Hz), 5.25 (d, 1H, J = 10.5 Hz), 5.37 (d, 1H, J = 17.2 Hz), 5.90−5.98 (m, 1H), 6.88 (d, 2H, J = 8.1 Hz), 7.23 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.8, 17.8, 25.6, 36.9, 55.3, 68.8, 72.7, 79.8, 81.0, 113.9, 117.8, 129.3, 129.5, 134.4, 159.5, 169.1. Anal. Calcd for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 63.95; H, 8.18.

Methyl (3*R*,4*R*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-4-(*p*-methoxybenzyloxy)hept-6-enoate (21). To a solution of compound **9** (629 mg, 1.6 mmol) in anhydrous MeOH (15 mL) was added 1 N NaOMe in MeOH until pH 9−10. The reaction mixture was stirred at room temperature for 3 h under these conditions, neutralized with Amberlite IR-120 (H^+), and filtered. The filtrate was concentrated to dryness under diminished pressure and purified by silica gel column chromatography (petroleum ether−EtOAc, 5:1) to give **21** (550 mg, 83%) as a colorless syrup: $[\alpha]^{25}_D$ −10 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 2.56 (dd, 1H, J = 5.0, 16.5 Hz), 2.89 (dd, 1H, J = 4.3, 16.5 Hz), 3.46 (t, 1H, J = 5.1 Hz), 3.49 (s, 3H), 3.81 (s, 3H), 4.17 (dd, 1H, J = 4.4, 8.7 Hz), 4.56 (d, 1H, J = 11.1 Hz), 4.62 (d, 1H, J = 11.1 Hz), 4.66 (t, 1H, J = 6.3 Hz), 5.25 (d, 1H, J = 10.6 Hz), 5.37 (d, 1H, J = 17.2 Hz), 5.90−5.98 (m, 1H), 6.88 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.8, 17.9, 25.6, 37.0, 51.6, 55.3, 68.8, 72.7, 79.8, 81.0, 113.8, 117.9, 129.5, 129.7, 134.4, 159.6, 172.2. Anal. Calcd for $C_{22}H_{36}O_6Si$: C, 62.23; H, 8.55. Found: C, 62.01; H, 8.64.

Methyl (3*R*,4*R*,5*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-(*p*-methoxybenzyloxy)hept-6-enoate (22). To a solution of **21** (509 mg, 1.2 mmol) and benzyltrichloroacetimidate (460 mg, 1.8 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added TMSOTf (9.0 μL, 0.02 mmol) under N_2 protection. The reaction mixture was monitored by TLC until all starting material was consumed and then quenched with Et_3N and concentrated to dryness. The residue was subjected to the silica gel column chromatography (petroleum ether−EtOAc, 6:1) to give **22** (463 mg, 75%) as a colorless syrup: $[\alpha]^{25}_D$ −12 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.86 (s, 9H), 2.42 (dd, 1H, J = 8.8, 15.1 Hz), 2.63 (dd, 1H, J = 2.9, 15.3 Hz), 3.62 (s, 3H), 3.68−3.70 (m, 1H), 3.80 (s, 3H), 4.10 (d, 1H, J = 9.6 Hz), 4.26−4.32 (m, 2H), 4.56 (d, 1H, J = 11.3 Hz), 4.58 (d, 1H, J = 12.1 Hz), 4.73 (d, 1H, J = 11.3 Hz), 5.33 (d, 1H, J = 17.1 Hz), 5.38 (d, 1H, J = 10.4 Hz), 5.95−6.04 (m, 1H), 6.85 (d, 2H, J = 8.0 Hz), 7.25−7.40 (m, 7H); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.7, 17.9, 25.7, 38.3, 51.4, 55.2, 69.7, 69.7, 72.9, 80.2, 82.2, 113.6, 119.8, 127.3, 127.5, 128.2, 129.4, 130.8, 135.6, 138.7, 159.1, 172.6. Anal. Calcd for $C_{29}H_{42}O_6Si$: C, 67.67; H, 8.22. Found: C, 67.91; H, 8.13.

(*S*)-Hept-6-en-2-yl (3*R*,4*R*,5*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-4-(*p*-methoxybenzyloxy)hept-6-enoate (23). The methyl ester **22** (437 mg, 0.85 mmol) was dissolved in THF/MeOH/H_2O (15 mL, 2:1:1) and cooled with ice−water bath. $LiOH\cdot H_2O$ (105 mg, 2.5 mmol) was added 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 phase was dried over anhydrous Na_2SO_4 and concentrated to afford acid intermediate. Without further purification, the crude acid was dissolved in anhydrous THF (15 mL) and treated with triethylamine (0.12 mL, 0.9 mmol) and 2,4,6-trichlorobenzoyl chloride (0.13 mL, 0.85 mmol), successively. After being stirred at room temperature for 1 h, a solution of (*S*)-6-hepten-2-ol (113 mg, 1.0 mmol) and DMAP (110 mg, 0.9 mmol) in THF (5 mL) were added. The reaction mixture was stirred at room temperature for another 18 h and was then quenched by aqueous NH_4Cl. The water phase was separated and extracted with EtOAc (2 × 25 mL). The combined organic extracts were dried and evaporated. Purification of the residue by silica gel column chromatography (petroleum ether−EtOAc, 7:1) gave **23** (400 mg, 79% over two steps) as a colorless syrup: $[\alpha]^{25}_D$ −17 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.23 (d, 3H, J = 6.2 Hz), 1.36−1.56 (m, 3H),

1.60−1.63 (m, 1H), 2.09 (dd, 2H, J = 6.8, 13.4 Hz), 2.43 (dd, 1H, J = 8.3, 15.8 Hz), 2.69 (dd, 1H, J = 3.6, 15.8 Hz), 3.77 (dd, 1H, J = 3.9, 4.8 Hz), 3.86 (s, 3H), 4.16 (dd, 1H, J = 2.6, 8.3 Hz), 4.36−4.39 (m, 2H), 4.62 (d, 1H, J = 10.9 Hz), 4.65 (d, 1H, J = 11.1 Hz), 4.78 (d, 1H, J = 11.1 Hz), 4.90−4.95 (m, 1H), 5.01 (d, 1H, J = 10.2 Hz), 5.05 (d, 1H, J = 18.4 Hz), 5.40 (d, 1H, J = 17.5 Hz), 5.43 (d, 1H, J = 10.7 Hz), 5.80−5.86 (m, 1H), 6.01−6.10 (m, 1H), 6.91 (d, 2H, J = 8.4 Hz), 7.26−7.39 (m, 7H); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.7, 17.9, 19.8, 24.6, 25.8, 33.5, 35.3, 38.7, 55.2, 69.3, 69.7, 70.8, 72.9, 80.2, 82.2, 113.6, 114.7, 119.7, 127.2, 127.4, 128.2, 129.4, 130.8, 135.6, 138.4, 138.8, 159.0, 171.7. Anal. Calcd for $C_{35}H_{52}O_6Si$: C, 70.43; H, 8.78. Found: C, 70.72; H, 8.91.

(*S*)-Hept-6-en-2-yl (3*R*,4*S*,5*S*)-5-Benzyloxy-3-hydroxy-4-(*p*-methoxybenzyloxy)hept-6-enoate (24). To a solution of silyl ether **23** (358 mg, 0.6 mmol) in THF (10 mL) was added TBAF (1.2 mL of 1 M solution in THF, 1.2 mmol) at 0 °C. The mixture was stirred under these conditions for 30 min, followed by an additional 4 h of stirring at room temperature. At the end of which time TLC indicated the reaction complete. Then the reaction mixture was concentrated under vacuum and the residue was subjected to column chromatography (petroleum ether−EtOAc, 4:1) to furnish **24** (240 mg, 83%) as a colorless syrup: $[\alpha]^{25}_D$ −18 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3H, J = 6.2 Hz), 1.36−1.55 (m, 3H), 1.57−1.60 (m, 1H), 2.04 (dd, 2H, J = 7.0, 13.8 Hz), 2.43−2.50 (m, 2H), 3.09 (br s, 1H), 3.39−3.41 (m, 1H), 3.80 (s, 3H), 4.08 (t, 1H, J = 6.5 Hz), 4.32 (br s, 1H), 4.40 (d, 1H, J = 11.4 Hz), 4.44 (d, 1H, J = 11.4 Hz), 4.60 (d, 1H, J = 11.9 Hz), 4.63 (d, 1H, J = 11.9 Hz), 4.89−4.96 (m, 2H), 4.99 (d, 1H, J = 17.5 Hz), 5.39 (d, 1H, J = 16.6 Hz), 5.41 (d, 1H, J = 10.8 Hz), 5.74−5.80 (m, 1H), 5.81−5.91 (m, 1H), 6.85 (d, 2H, J = 8.3 Hz), 7.20−7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 19.9, 24.6, 33.4, 35.3, 38.9, 55.2, 68.1, 70.7, 71.0, 73.2, 80.4, 81.1, 113.7, 114.7, 119.5, 127.7, 127.9, 128.4, 129.8, 135.6, 137.7, 138.4, 159.3, 171.4. Anal. Calcd for $C_{29}H_{38}O_6$: C, 72.17; H, 7.94. Found: C, 71.90; H, 8.05.

(*S*)-Hept-6-en-2-yl (3*R*,4*S*,5*S*)-3-Benzoyloxy-5-benzyloxy-4-(*p*-methoxybenzyloxy)hept-6-enoate (25). To the solution of **24** (216 mg, 0.45 mmol) in pyridine (5 mL) were added benzoyl chloride (0.06 mL, 0.67 mmol) and a catalytic amount of DMAP at 0 °C. The mixture was stirred at room temperature for 3 h and coevaporated with toluene under diminished pressure. Purification of the residue on silica gel column chromatography (petroleum ether−EtOAc, 8:1) afforded **25** (250 mg, 95%) as a colorless syrup: $[\alpha]^{25}_D$ −17 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.12 (d, 3H, J = 6.1 Hz), 1.29−1.45 (m, 3H), 1.50−1.54 (m, 1H), 1.97 (dd, 2H, J = 7.2, 14.0 Hz), 2.72−2.85 (m, 2H), 3.79 (s, 3H), 3.81 (dd, 1H, J = 3.6, 5.8 Hz), 3.96 (t, 1H, J = 6.7 Hz), 4.28 (d, 1H, J = 11.4 Hz), 4.53 (d, 1H, J = 10.9 Hz), 4.56 (d, 1H, J = 10.3 Hz), 4.68 (d, 1H, J = 10.9 Hz), 4.86 (t, 1H, J = 6.1 Hz), 4.91 (d, 1H, J = 11.4 Hz), 4.95 (d, 1H, J = 19.1 Hz), 5.35 (d, 1H, J = 11.4 Hz), 5.36 (d, 1H, J = 16.1 Hz), 5.67−5.74 (m, 1H), 5.76−5.81 (m, 1H), 5.87−5.96 (m, 1H), 6.83 (d, 2H, J = 8.3 Hz), 7.18−7.29 (m, 7H), 7.38 (t, 2H, J = 7.6 Hz), 7.53 (t, 1H, J = 7.1 Hz), 7.97 (d, 2H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 19.7, 24.5, 33.4, 35.2, 36.3, 55.2, 70.2, 70.5, 71.3, 73.8, 80.2, 80.4, 113.6, 114.7, 119.7, 127.4, 127.9, 128.2, 129.7, 129.8, 130.1, 130.1, 132.8, 135.6, 138.0, 138.3, 159.2, 165.6, 170.1. Anal. Calcd for $C_{36}H_{42}O_7$: C, 73.70; H, 7.22. Found: C, 73.43; H, 7.13.

(*S*)-Hept-6-en-2-yl (3*R*,4*S*,5*S*)-3-Benzoyloxy-5-benzyloxy-4-hydroxyhept-6-enoate (26). A solution of ester **25** (224 mg, 0.38 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated with DDQ (173 mg, 0.76 mmol) in the presence of water (1 mL). The mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO4 and concentrated to dryness. Column chromatography of the residue (petroleum ether−EtOAc, 5:1) gave **26** (160 mg, 90%) as a colorless syrup: $[\alpha]^{25}_D$ −17 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, 3H, J = 6.1 Hz), 1.29−1.47 (m, 3H), 1.50−1.54 (m, 1H), 1.97 (dd, 2H, J = 6.9, 13.4 Hz), 2.53 (br s, 1H), 2.87 (d, 2H, J = 6.5 Hz), 3.83−3.89 (m, 2H), 4.27 (d, 1H, J = 11.2 Hz), 4.52 (d, 1H, J = 11.2 Hz), 4.87 (t, 1H, J = 6.0 Hz), 4.92 (d, 1H, J = 11.6 Hz), 4.95 (d, 1H, J = 18.7 Hz), 5.36 (d, 1H, J = 17.4 Hz), 5.41 (d, 1H, J = 10.3 Hz), 5.68−5.75 (m, 1H), 5.80 (t, 1H, J = 6.3 Hz), 5.85−5.94 (m, 1H), 7.14−7.24 (m, 5H), 7.39 (t, 2H, J = 7.4 Hz), 7.54 (t, 1H, J = 7.0 Hz), 7.97 (d, 2H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 24.5, 33.4, 35.2, 36.8, 69.6, 70.7, 71.5, 73.8, 81.0, 114.7, 120.7, 127.6, 128.1, 128.2, 128.3, 129.7, 130.1, 132.9, 135.2, 137.6, 138.4, 165.5, 170.2. Anal. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35. Found: C, 72.42; H, 7.26.

(*S*)-Hept-6-en-2-yl (3*R*,5*S*)-3-Benzoyloxy-5-benzyloxy-4-oxohept-6-enoate (5). To a solution of **26** (149 mg, 0.32 mmol) in dry CH_2Cl_2 (15 mL) was added Dess−Martin periodinane (203 mg, 0.48 mmol) and the reaction mixture was stirred for 3 h at ambient temperature. After extraction with saturated aqueous $NaHCO_3$, the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel (petroleum ether−EtOAc, 9:1) to furnish compound **5** (121 mg, 82%) as a colorless syrup: $[\alpha]^{25}_D$ −17 (*c* 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 3H, J = 6.2 Hz), 1.33−1.48 (m, 3H), 1.51−1.55 (m, 1H), 2.01 (dd, 2H, J = 7.2, 14.1 Hz), 2.82 (dd, 1H, J = 9.0, 16.2 Hz), 3.07 (dd, 1H, J = 3.5, 16.1 Hz), 4.64 (d, 1H, J = 5.8 Hz), 4.66 (d, 1H, J = 10.8 Hz), 4.71 (d, 1H, J = 11.6 Hz), 4.91−4.96 (m, 2H), 4.98 (d, 1H, J = 17.7 Hz), 5.42 (d, 1H, J = 10.5 Hz), 5.49 (d, 1H, J = 17.2 Hz), 5.65−5.77 (m, 1H), 5.84−5.92 (m, 1H), 6.08 (dd, 1H, J = 3.4, 9.0 Hz), 7.28−7.37 (m, 5H), 7.43 (t, 2H, J = 7.6 Hz), 7.57 (t, 1H, J = 7.4 Hz), 8.01 (d, 2H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 24.6, 33.4, 35.2, 35.8, 71.9, 72.1, 73.3, 84.1, 114.8, 119.8, 127.9, 128.0, 128.4, 128.5, 129.1, 129.8, 132.3, 133.4, 137.0, 138.3, 165.5, 168.8, 203.1. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.04; H, 7.05.

Lactone (4). Diene **5** (97 mg, 0.21 mmol) was dissolved in dry, degassed CH_2Cl_2 (10 mL). This mixture was added dropwise within 1 h to a refluxing solution of ruthenium catalyst (54 mg, 0.06 mmol) in dry, degassed CH_2Cl_2 (470 mL). The reaction mixture was stirred under these conditions until the complete consumption of **5** (20−24 h, TLC monitoring). After removing solvent in vacuo, the residue was purified by silica gel column chromatography (petroleum ether−EtOAc, 9:1) to yield **4** (66 mg, 72%) as a mixture of *Z*,*E*-isomers (*Z*/*E* = 1/2): selected ^{1}H NMR ($CDCl_3$) for *E*-isomer, δ 1.18 (d, 3H, J = 6.5 Hz), 1.40−1.49 (m, 1H), 1.56−1.76 (m, 3H), 1.84 (dd, 1H, J = 11.2, 23.8 Hz), 2.30−2.33 (m, 1H), 2.97 (dd, 1H, J = 5.0, 17.9 Hz), 3.47 (dd, 1H, J = 3.3, 17.8 Hz), 4.57 (d, 1H, J = 7.9 Hz), 4.68 (s, 2H), 4.95−4.97 (m, 1H), 5.41 (dd, 1H, J = 3.9, 15.7 Hz), 5.84−5.91 (m, 1H), 5.96 (t, 1H, J = 3.8 Hz), 7.16−7.21 (m, 2H), 7.32−7.36 (m, 3H), 7.44 (t, 3H, J = 7.2 Hz), 8.12 (d, 2H, J = 7.9 Hz); for *Z*-isomer, δ 1.24 (d, 3H, J = 6.3 Hz), 1.40−1.49 (m, 1H), 1.56−1.76 (m, 3H), 2.07−2.12 (m, 1H), 2.14−2.19 (m, 1H), 2.83 (dd, 1H, J = 9.8, 15.0 Hz), 3.06 (dd, 1H, J = 2.9, 15.0 Hz), 4.42 (d, 1H, J = 11.6 Hz), 4.58 (d, 1H, J = 11.8 Hz), 4.73 (d, 1H, J = 8.3 Hz), 4.95−4.97 (m, 1H), 5.69 (t, 1H, J = 8.6 Hz), 5.89−5.93 (m, 1H), 6.10 (dd, 1H, J = 3.0, 9.8 Hz), 7.30−7.33 (m, 2H), 7.34−7.37 (m, 3H), 7.57 (t, 3H, J = 7.8 Hz), 8.02 (d, 2H, J = 7.9 Hz); selected ^{13}C NMR ($CDCl_3$) for *E*-isomer, δ 18.3, 20.3, 29.7, 32.3, 35.3, 71.2, 72.4, 72.5, 84.2, 124.4, 127.5, 128.1, 128.4, 128.6, 129.6, 129.9, 130.0, 132.5, 133.3, 137.1, 165.7, 168.8, 200.9; ESI(+)-MS calcd for $C_{26}H_{28}O_6$ 436.19 [M], found 437.5 $[M + H]^+$, 459.5 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{28}O_6$ (*E*,*Z* mixture): C, 71.54; H, 6.47. Found: C, 71.94; H, 6.39.

Sporiolide A (1). To a suspension of Pd/C (5% Pd, 15 mg) in MeOH (8 mL) was added a solution of **4** (45 mg, 0.1 mmol) in MeOH (4 mL). The mixture was allowed to stir at room temperature for 24 h under 4 atm of H_2 pressure, at the end of which of time TLC indicated that the reaction was complete. The mixture was filtered and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (petroleum ether−EtOAc, 7:1) to furnish sporiolide A (**1**, 33 mg, 91%) as white amorphous solid:

$[\alpha]^{25}_{D}$ −15 (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.16−1.21 (m, 1H), 1.23−1.28 (m, 1H), 1.30 (d, 3H, J = 5.8 Hz), 1.35−1.45 (m, 3H), 1.58−1.73 (m, 3H), 1.84−1.87 (m, 1H), 2.11−2.15 (m, 1H), 2.96 (d, 1H, J = 17.0 Hz), 3.50 (dd, 1H, J = 10.6, 17.2 Hz), 4.39 (t, 1H, J = 4.4 Hz), 4.92−4.95 (m, 1H), 5.96 (d, 1H, J = 10.0 Hz), 7.48 (t, 2H, J = 7.4 Hz), 7.62 (t, 1H, J = 7.1 Hz), 8.05 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.7, 26.5, 30.5, 33.3, 39.9, 68.0, 73.5, 75.6, 128.3, 128.6, 129.9, 133.8, 165.4, 168.2, 207.6; ESI(+)-MS calcd for $C_{19}H_{24}O_6$ 348.16 [M], found 371.57 $[M + Na]^+$. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.21; H, 6. 88.

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Supporting Information Available: Spectra for compounds **18**, **19**, **20**, **9**, **21**, **22**, **23**, **24**, **25**, **26**, **5**, **4**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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