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The first total synthesis of sporiolide B

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Abstract—The first total synthesis of natural cytotoxic agent, sporiolide B, is described. D-Xylose was used as the chiral template to pre-control the absolute configuration during the synthesis. Yamaguchi esterification and ring closing metathesis greatly facilitate the target compound accomplishment.

Kobayashi and co-workers at Hokkaido University recently reported a new cytotoxic 12-membered macrolide, designated sporiolide B (**1**).[1] It was isolated from the cultured broth of a fungus *Cladosporium* sp., which was separated from an Okinawan marine brown alga *Actinotrichia fragilis*. The spectroscopic data based structure elucidation supposed that sporiolide B corresponds to 3-*O*-methyl pandangolide 1 (**2**), a hexaketide lactone whose absolute configuration has been determined very recently.[2] Sporiolide B exhibits cytotoxicity against L1210 cells ($IC_{50} = 0.81$ μg/mL) and antibacterial activity against *Micrococcus luteus* (MIC = 16.7 μg/mL). The biological potential as well as the uncertainty of its absolute structural configuration marked it as a synthetic target for us. We report herein the first total synthesis of sporiolide B starting from D-xylose.

As outlined in Scheme 1, we decided to prepare sporiolide B (**1**) by intercepting olefinic intermediate **3** that we envisaged would be made available from ring closing metathesis (RCM) of diene **4** after esterification of alcohol **5** and acid **6** (or its precursor **7**). Key intermediate **6** (or **7**) could be derived from D-xylose in order to keep the proposed absolute configurations at C-3 and C-5 in sporiolide B (Fig. 1).

The synthesis began with the preparation of acid **6** as illustrated in Scheme 2. Thus, benzylation of known D-xylofuranosyl derivative **8**,[3] followed by one-pot allyl isomerization (*t*-BuOK in DMSO) and cleavage ($Hg(OAc)_2$ in THF/H_2O),[4] gave hemiacetal **10** in a good yield (80% from **8**). The standard Wittig reaction of **10** and methyltriphenylphosphonium bromide in anhydrous THF at −50 °C generated olefin **11**, in which the secondary alcohol was subsequently methylated with MeI and NaH in DMF (→**12**). The acid hydrolysis of **12** with TsOH hydrate (→**13**), and regioselective iodination[5] with Ph_3P and I_2 furnished iodide **14** in a 52% isolated yield over four steps. S_N2 substitution of iodide with KCN,[6] followed by acid hydrolysis in methanol gave methyl ester **15**. The secondary hydroxyl of **15** was oxidized with Dess–Martin periodinane[7] to give ketone **16** in an excellent yield (90%). Unfortunately, free acid formation from **16** was troublesome under basic conditions[8] and the double bond migrated analogue **17** was gained unambiguously. This migration was confirmed by a correlated quartet (δ 6.49 ppm, J = 7.1 Hz, $=CHCH_3$) and doublet (δ 1.79 ppm, $J = 7.1$ Hz, $CH_3CH=$) in NMR spectra.

Alternatively, the secondary hydroxyl group of **15** was protected by 4-methoxybenzyl (PMB) using 4-methoxybenzyl trichloroacetimidate[9] in the presence of TMSOTf to give **18**, which was hydrolyzed with LiOH, furnished acid **7**. The esterification of acid **7** and (*S*)-6-hepten-2-ol (**5**)[10] under Yamaguchi's conditions[11] afforded diene derivative **19** (70% from **15**), which was subjected to cleavage of PMB group with DDQ[12] and oxidation with Dess–Martin periodinane, to form key intermediate **4** in a 77% yield in two steps. Diene **4** was then exposed to the Grubbs catalyst [$PHCH{=}RuCl(PCy_3)_2$, 30 mol %, 1.4×10^{-4} M in

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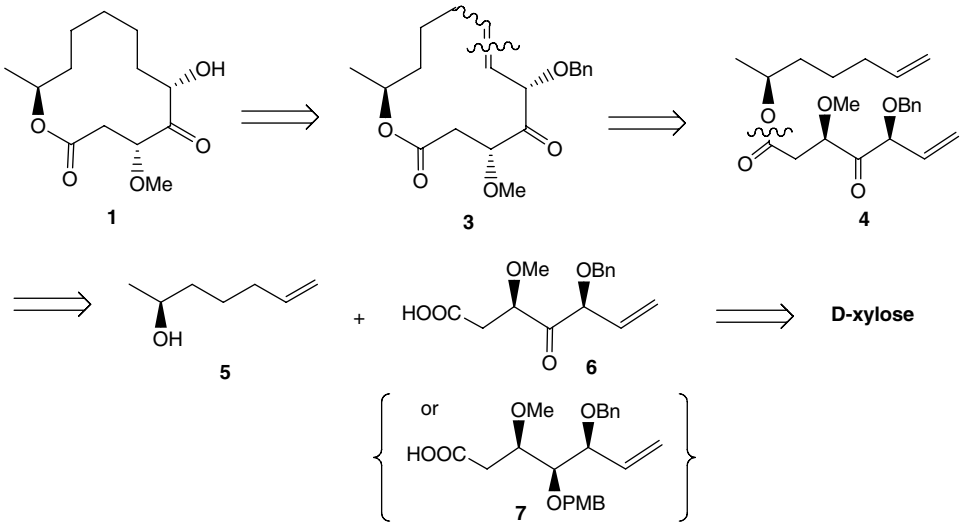


Scheme 1. Retrosynthetic analysis of sporiolide B (**1**).

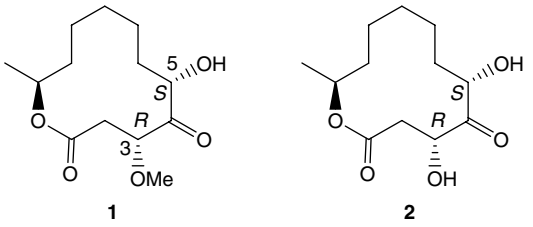
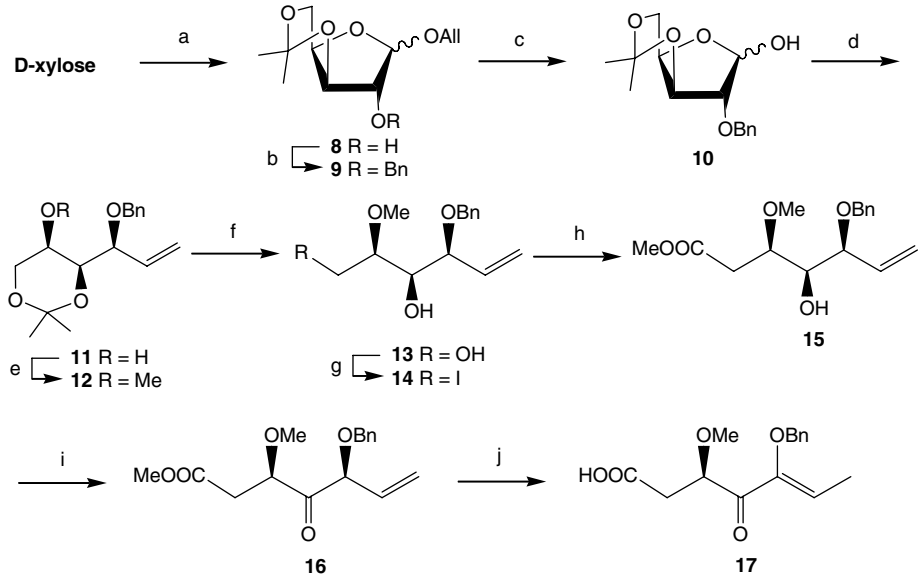


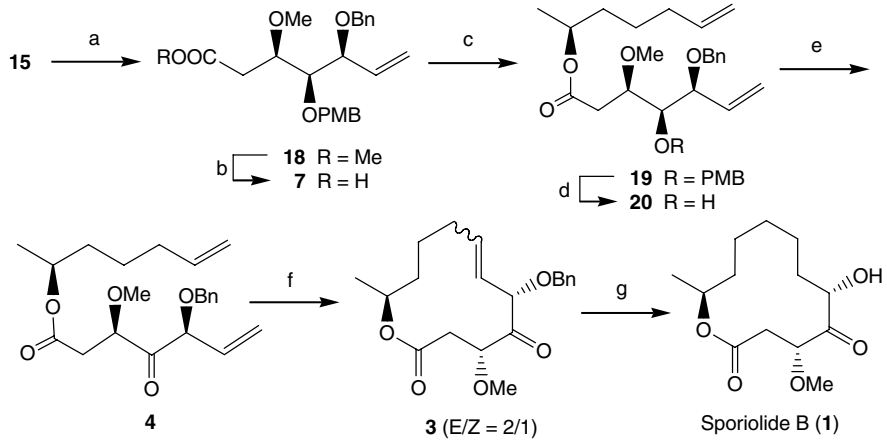
Figure 1. Chemical structures of sporiolide B (**1**) and pandangolide 1 (**2**).

CH_2Cl_2][13] undergoing a ring closing metathesis (RCM) to produce macrolide **3** in a form of *E*,*Z* mixture (*E*/*Z* = 2/1). The hydrogenation of **3** with H_2 in the presence of Pd/C reduced both benzyl group and double bond to accomplish the total synthesis of sporiolide B, identical in all physical data to that of reported for the natural product[14] (Scheme 3).

In summary, we have accomplished the first total synthesis of sporiolide B in 15 linear steps and a 3.5% overall yield. The required stereochemical configurations at C-3 and C-5 in sporiolide B were pre-controlled by using D-xylose as the chiral template. Yamaguchi esterification and ring closing metathesis greatly facilitate the target accomplishment. The current report also provides an attractive way for the preparation of other natural products, such as pandangolide 1a, pandangolide 1, and sporiolide A.[1,2,15]



Scheme 2. Reagents and conditions: (a) Ref. 3; (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% over two steps (α/β = 2/1); (d) *n*-BuLi, Ph_3PCH_3Br, THF, −50 °C to rt, 12 h, 75%; (e) MeI, NaH, DMF, 2 h, 96%; (f) $TsOH{\cdot}H_2O$, $MeOH/H_2O$, 3 h, 95%; (g) Ph_3P, I_2, Imidazole, THF, 12 h, 76%; (h) (i) KCN, $MeOH/H_2O$, 12 h; (ii) aq 6 N HCl, $MeOH/H_2O$, 80 °C, 6 h, 63% in two steps; (i) Dess–Martin periodinane, CH_2Cl_2, 3 h, 90%; (j) LiOH, THF/H_2O, 12 h, 85%.



Scheme 3. Reagents and conditions: (a) $PMBOC(NH)CCl_3$, TMSOTf, CH_2Cl_2, 2 h, 75%; (b) LiOH, THF/H_2O, 12 h; (c) (*S*)-6-hepten-2-ol, 2,4,6-trichlorobenzoyl chloride, TEA, DMAP, THF, 18 h, 78% in two steps; (d) DDQ, CH_2Cl_2/H_2O, 2 h, 93%; (e) Dess–Martin periodinane, CH_2Cl_2, 3 h, 83%; (f) 30% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 24 h, 70% ($E/Z = 2/1$); (g) H_2, Pd/C, MeOH, 12 h, 81%.

Acknowledgments

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14. Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (^1H, ^{13}C NMR, and mass or elemental analysis) consistent with their structures. Selected spectral data for compound **16**: ^1H NMR ($CDCl_3$): δ 2.58 (dd, 1H, $J = 8.1$, 16.3 Hz), 2.81 (dd, 1H, $J = 4.2$, 16.3 Hz), 3.34 (s, 3H), 3.68 (s, 3H), 4.48 (dd, 1H, $J = 4.2$, 8.1 Hz), 4.55 (d, 1H, $J = 11.8$ Hz), 4.62 (d, 1H, $J = 6.6$ Hz), 4.68 (d, 1H, $J = 11.8$ Hz), 5.42 (d, 1H, $J = 10.4$ Hz), 5.49 (d, 1H, $J = 17.3$ Hz), 5.86–5.88 (m, 1H), 7.30–7.39 (m, 5H); For compound **17**: ^1H NMR ($CDCl_3$): δ 1.79 (d, 3H, $J = 7.1$ Hz), 2.55 (dd, 1H, $J = 8.5$, 16.0 Hz), 2.65 (dd, 1H, $J = 4.6$, 15.8 Hz), 3.29 (s, 3H), 4.62 (dd, 1H, $J = 4.7$, 8.4 Hz), 4.87 (s, 2H), 6.49 (q, 1H, $J = 7.1$ Hz), 7.31–7.41 (m, 5H); For compound **19**: ^1H NMR ($CDCl_3$): δ 1.21 (d, 3H, $J = 6.0$ Hz), 1.41–1.55 (m, 4H), 2.04 (dd, 2H, $J = 6.7$, 13.3 Hz), 2.47–2.60 (m, 2H), 3.32 (s, 3H), 3.55–3.57 (m, 1H), 3.80 (s, 3H), 3.95–3.97 (m, 1H), 4.02 (t, 1H, $J = 6.8$ Hz), 4.36 (d, 1H, $J = 11.7$ Hz), 4.48 (d, 1H, $J = 10.9$ Hz), 4.62 (d, 1H, $J = 10.8$ Hz), 4.65 (d, 1H, $J = 9.6$ Hz), 4.90–4.98 (m, 2H), 5.00 (d, 1H, $J = 17.4$ Hz), 5.38 (d, 1H, $J = 18.0$ Hz), 5.42 (d, 1H, $J = 9.0$ Hz), 5.75–5.77 (m, 1H), 5.94–5.96 (m, 1H), 6.84 (d, 2H, $J = 8.0$ Hz), 7.24–7.34 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 19.91, 24.54, 33.40, 35.27, 36.51, 55.19, 58.63, 70.86, 70.92, 74.04, 77.54, 80.06, 81.79, 113.59, 114.70, 119.35, 127.40, 127.65, 128.24, 129.78, 130.44, 133.29, 136.15, 138.36, 138.42, 159.17, 171.47; For compound **20**: ^1H NMR ($CDCl_3$): δ 1.20 (d, 3H, $J = 6.1$ Hz), 1.36–1.55 (m, 4H), 2.04 (dd, 2H, $J = 6.8$, 13.6 Hz), 2.55–2.67 (m, 2H), 3.34 (s, 3H), 3.49 (d, 1H, $J = 6.5$ Hz), 3.81 (t, 1H, $J = 7.4$ Hz), 3.99 (br s, 1H), 4.36 (d, 1H, $J = 11.7$ Hz), 4.63 (d, 1H, $J = 11.6$ Hz), 4.91–4.96 (m, 2H), 5.38 (d, 1H, $J = 17.3$ Hz), 5.43 (d, 1H, $J = 10.2$ Hz), 5.74–5.76 (m, 1H), 5.84–5.86 (m, 1H), 6.84 (d, 2H, $J = 8.0$ Hz), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.92, 24.57, 33.42, 35.27, 37.04, 58.68, 70.18, 71.14, 74.69, 76.11, 80.53, 114.74, 120.17, 127.62, 127.96, 128.34, 136.10, 138.08, 138.38, 171.29; For compound **4**: ^1H NMR ($CDCl_3$): δ 1.20 (d, 3H, $J = 6.1$ Hz), 1.34–1.53 (m, 4H), 2.04 (dd, 2H, $J = 7.0$, 13.8 Hz), 2.52 (dd, 1H, $J = 8.4$, 16.1 Hz), 2.77 (dd, 1H, $J = 3.7$, 16.1 Hz), 3.34 (s, 3H), 4.48 (dd, 1H, $J = 3.6$, 8.2 Hz), 4.54 (d, 1H, $J = 11.9$ Hz), 4.62 (d, 1H, $J = 6.7$ Hz), 4.67 (d, 1H, $J = 11.8$ Hz), 4.92–4.97 (m, 2H), 5.00 (d, 1H, $J = 17.2$ Hz), 5.42 (d, 1H, $J = 10.3$ Hz), 5.50 (d, 1H, $J = 17.3$ Hz), 5.75–5.77 (m, 1H), 5.87–5.89 (m, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.88, 24.52, 33.41, 35.26, 37.08, 58.67, 71.38, 71.57, 80.53, 83.11, 114.73, 120.14, 127.87, 127.96, 128.49, 132.34, 137.21, 138.38, 169.93, 206.55; For compound **3** (*Z*-isomer): ^1H NMR ($CDCl_3$): δ 1.20 (d, 3H, $J = 6.1$ Hz), 1.44–1.53 (m, 4H), 2.08 (dd, 2H, $J = 9.7$, 16.9 Hz), 2.70 (dd, 1H, $J = 9.3$, 14.8 Hz), 2.91 (dd, 1H, $J = 2.6$, 14.8 Hz), 3.40 (s, 3H), 4.34 (dd, 1H, $J = 2.7$, 9.4 Hz), 4.52 (d, 1H, $J = 11.5$ Hz), 4.62 (d, 1H, $J = 11.7$ Hz), 4.83 (dd, 1H, $J = 6.3$, 11.8 Hz), 4.89 (d, 1H, $J = 8.7$ Hz), 5.62 (t, 1H, $J = 9.5$ Hz), 5.80–5.82 (m, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.61,

22.69, 26.98, 32.69, 37.14, 58.19, 71.11, 72.31, 76.13, 79.46, 125.30, 127.84, 128.01 ,128.12, 128.38, 128.44, 137.59, 137.28, 169.08, 205.57; For *E*-isomer: ^{1}H NMR ($CDCl_3$): δ 1.14 (d, 3H, $J = 6.5$ Hz), 1.47–1.55 (m, 4H), 1.91–1.93 (m, 1H), 2.17–2.19 (m, 1H), 2.85 (dd, 1H, $J = 6.7$, 16.3 Hz), 3.11 (dd, 1H, $J = 3.0$, 16.2 Hz), 3.42 (s, 3H), 4.19 (dd, 1H, $J = 3.1$, 6.7 Hz), 4.54 (d, 1H, $J = 11.8$ Hz), 4.61 (d, 1H, $J = 7.0$ Hz), 4.63 (d, 1H, $J = 11.9$ Hz), 4.87 (t, 1H, $J = 5.6$ Hz), 5.42 (dd, 1H, $J = 4.7$, 15.7 Hz), 5.88–5.90 (m, 1H), 7.31–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.10, 21.74, 31.57, 32.12, 35.90, 58.42, 71.20, 71.87, 79.59, 83.45, 124.39, 127.62, 127.92, 128.51, 133.66, 137.47, 168.97, 204.29; ESI(+)-MS: Calcd for $C_{20}H_{26}O_5$: 346.18 [M]; Found 347 $[M+H]^+$, 369 $[M+Na]^+$; For compound **1**, $[\alpha]_D^{25}$ −29 (*c* 0.5, $CHCl_3$), $[\alpha]_D^{25}$ −33 (*c* 0.5, MeOH); {reported value for **1** in Ref. 1: $[\alpha]_D^{25}$ −33 (*c* 0.3, MeOH)}; ^{1}H NMR ($CDCl_3$): δ 1.07–1.09 (m, 1H), 1.23 (d, 3H, $J = 6.4$ Hz), 1.25–1.36 (m, 2H), 1.38–1.47 (m, 2H), 1.48–1.57 (m, 2H), 1.58–1.69 (m, 2H), 2.04–2.06 (m, 1H), 2.60 (dd, 1H, $J = 8.8$, 13.9 Hz), 3.43 (t, 1H, $J = 12.6$ Hz), 3.53 (s, 3H), 4.30 (d, 1H, $J = 5.7$ Hz), 4.44 (d, 1H, $J = 8.7$ Hz), 4.81–4.83 (m, 1H); ^{13}C NMR ($CDCl_3$): 20.83, 22.15, 23.82, 26.54, 29.96, 33.42, 41.35, 58.41, 73.31, 74.37, 76.12, 170.63, 208.76; ESI(+)-MS: Calcd for $C_{13}H_{22}O_5$: 258.15 [M]; Found 281.3 $[M+Na]^+$.

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