First Stereoselective Total Synthesis of Sporostatin and Determination of Absolute Configuration

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Abstract: The first simple and efficient total synthesis of sporostatin has been accomplished in five steps starting from (*S*)-propylene oxide. The synthesis utilizes simple reactions such as esterification, cross-metathesis, and intramolecular Friedel–Crafts reaction as key steps.

Key words: homoallyl alcohol, cross-metathesis, intramolecular Friedel–Crafts reaction

Sporostatin (M5032, **1**), isolated from the fungus of *Sporormiella* sp. is an inhibitor of cyclic adenosine 3′,5′-monophosphate phosphodiesterase (cAMP-PDE).[1] It constitutes a ten-membered macrolide derivative with 1,3-dihydroxybenzene ring and is structurally related to xestodecalactones A, B, C (**2**, **3a**,**b**) and curvularins (**4**, **5a**,**b**), which in turn were isolated from fungi (Figure 1).[2] Inhibitory activities of sporostatin (**1**) against cAMP-PDE from bovine heart expressed in terms of 50% inhibition (IC_{50}) was 41 μg/mL and it was noncompetitive against cAMP. It was found to be a specific inhibitor of epidermal growth factor (EGF) receptor, tyrosine kinase in vitro.

Recently, syntheses of the structurally similar xestodecalactones A, B, and C have been reported,[2] however, sporostatin has not been synthesized so far, and its absolute configuration also had not been determined.

We report herein the first total synthesis of sporostatin with high stereoselectivity. The absolute configuration of sporostatin was determined as *S* by its total synthesis. In our retrosynthetic analysis (Scheme 1), we envisioned that the target molecule could be achieved by intramolecular acylation of the acid **9**. The *trans* geometry of the double bond in compound **9** could be achieved from **8** through cross-metathesis with acrylic acid **12**. Compound

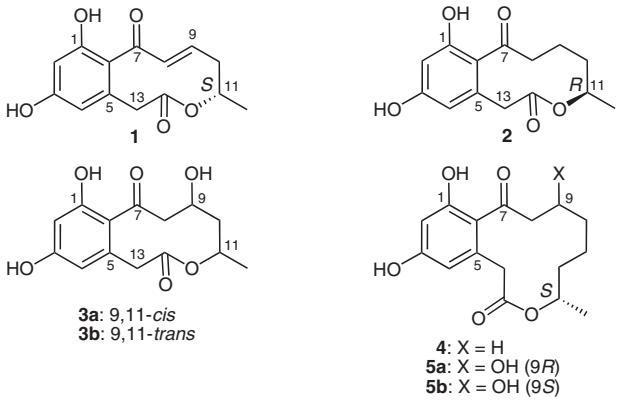
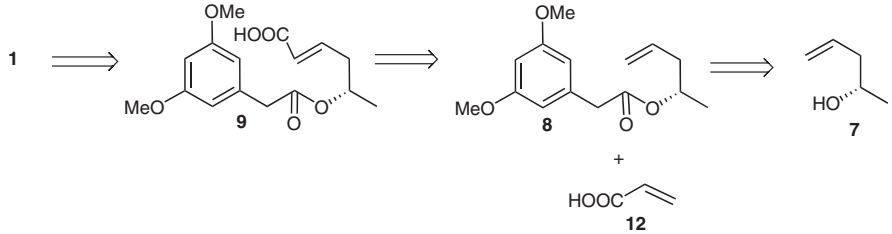


Figure 1 Sporostatin (**1**), xestodecalactone A (**2**), xestodecalactone B, C (**3a**,**b**), curvularins (**4**, **5a**,**b**)

8 was considered to be obtained from esterification of homoallylic alcohol **7** and the aromatic fragment **11**.

The synthesis of sporostatin is described in Scheme 2. Accordingly, the synthesis began with (*S*)-propylene oxide **6**. Ring opening[4] of chiral epoxide **6** (obtained via Jacobsen's HKR methodology)[5] with vinyl magnesium bromide in the presence of CuCN gave homoallylic alcohol **7**.[6] The esterification of **7** with 3,5-dimethoxyphenyl acetic acid in the presence of DCC and DMAP resulted in compound **8** in 97% yield. The cross-metathesis reaction of **8** with acrylic acid (3 equiv) in the presence of the Hoveyda–Grubbs catalyst (**HG**, 5 mol%, CH_2Cl_2, 25 °C, 16 h) gave the corresponding α,β-unsaturated carboxylic acid **9** in 82% yield with *E*/*Z* ratio of 20:1.[7] The desired macrolide **10** was obtained in 41% yield when the carboxylic acid **9** was subjected to an intramolecular Friedel–Crafts reaction with a mixture of trifluoroacetic acid and



Scheme 1 Retrosynthetic analysis of sporostatin

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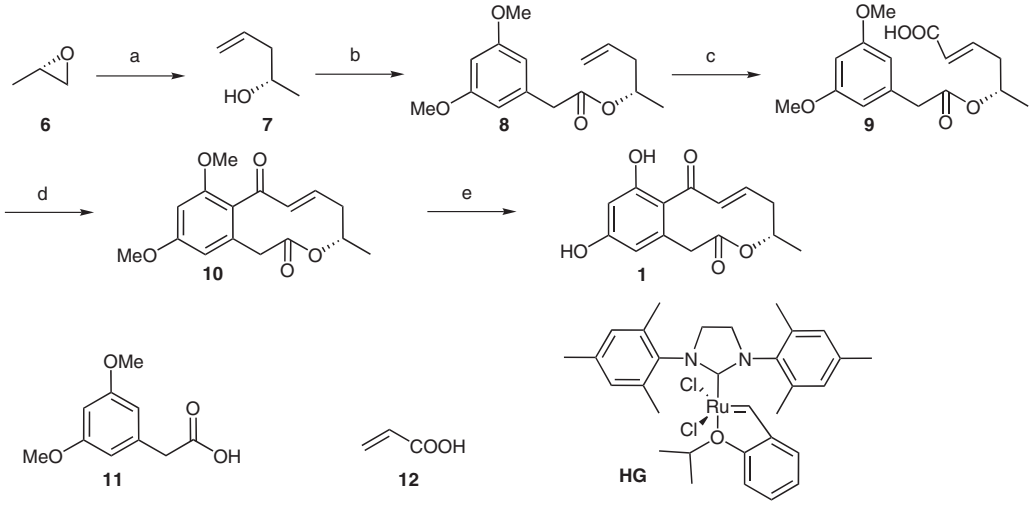

Scheme 2 *Reagents and conditions*: (a) CH_2=CHMgBr, CuBr, THF, –78 °C to –40 °C, 6 h, 80%; (b) **11**, DCC, DMAP, CH_2Cl_2, 3 h, r.t., 97%; (c) **12**, **HG** (5 mol%), CH_2Cl_2, 25 °C, 82%; (d) TFA, TFAA, reflux, 41%; (e) AlI_3, $Bu_4N^+I^-$, benzene, r.t., 95%.

trifluoroacetic anhydride at 60 °C for 30 minutes.[3,8,9] Deprotection of the methoxy groups of **10** using freshly prepared AlI_3[2,10] furnished the target molecule **1** in 94% yield whose melting point and spectroscopic data were identical with the natural product.[1b] The specific rotation of synthetic sporostatin (**1**) is –18.8, which is exactly the same value to that reported by Yaginuma et al.[1b] thereby confirming the stereogenic center at C11 carbon as *S*.[11]

In summary, we have described a simple and concise total synthesis of sporostatin employing very simple and easily accessible reactions such as Cu(I)-mediated ring opening of chiral epoxide with vinyl magnesium bromide, esterification, cross-metathesis reaction, and intramolecular Friedel–Crafts reaction as key steps. The stereochemistry at C11 in sporostatin (**1**) was determined as *S*.

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(11) **(*S*)-1,3-Dihydroxy-8-methyl-8,9-dihydro-5*H*-7-oxabenzocyclodecene-6,12-dione (Sporostatin, 1)**
Iodine (0.52 g, 2.06 mmol) was added to a mixture of aluminum (0.074 g, 2.76 mmol) in dry benzene. The mixture was refluxed for 1 h, cooled to r.t., and then *n*-Bu4N$^+$I$^-$ (0.0032 g, 0.0089 mmol) and compound **10** (0.020 g, 0.688 mmol) in dry benzene (8 mL) were added. The mixture was stirred for 45 min at 10 °C and quenched with H_2O. After acidification with 2 M HCl, the mixture was extracted with

EtOAc (3 × 10 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on SiO_2 (hexanes–EtOAc, 1:1) to afford the sporostatin (**1**, 0.017 mg, 95%) as white solid, mp 198–200 °C; $[\alpha]_D^{25}$ –18.8 (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, DMSO): δ = 13.59 (s, 1 H), 10.75 (s, 1 H), 6.80 (d, 1 H, *J* = 15.8 Hz), 6.32 (s, 1 H), 6.22 (s, 1 H), 5.92–5.98 (m, 1 H), 5.01–5.11 (m, 1 H), 4.07 (d, 1 H, *J* = 16.8 Hz), 3.82–3.90 (m, 1 H), 2.54–2.58 (m, 1 H), 1.36 (d, 3 H, *J* = 6.5 Hz). ^{13}C NMR (75 MHz, DMSO): δ = 198, 173.1, 167.4, 163.7, 140.0, 138.2, 136.3, 114.5, 111.7, 102.1, 74.9, 43.9, 41.6, 19.6. IR (neat): ν = 3424, 2255, 2128, 1739, 1650, 1376 cm^{-1}. MS (LC-MS): *m/z* = 263 $[M + 1]^+$. HRMS: *m/z* calcd for $C_{14}H_{15}O_4$: 263.0919; found: 263.0916.