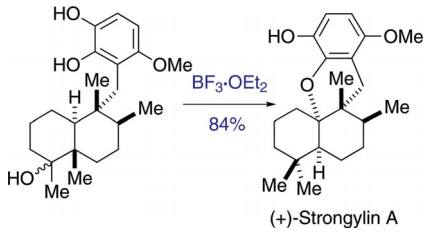
EurJOC European Journal of Organic Chemistry

Natural Product Synthesis

(+)-Strongylin A has been synthesized for the first time by starting from (+)-5-methyl-Wieland–Miescher ketone (16% overall yield in 14 steps). The characteristic tetracyclic core structure was constructed in a domino dehydroxylation/rearrangement/cyclization reaction.



Keywords: Natural products / Total synthesis / Terpenoids / Configuration determination / Cascade reactions / Diastereoselectivity

DOI: 10.1002/ejoc.201300438

Total Synthesis of (+)-Strongylin A, a Rearranged Sesquiterpenoid Hydroquinone from a Marine Sponge

Takaaki Kamishima,[a] Takuya Kikuchi,[a] and Tadashi Katoh*[a]

Keywords: Natural products / Total synthesis / Terpenoids / Configuration determination / Cascade reactions / Diastereoselectivity

A biologically attractive and structurally unique marine natural product, (+)-strongylin A (**1**), was synthesized for the first time by starting from a known *trans*-decalone derivative (19% overall yield in 11 steps). The synthetic method involved the following key steps: (i) stereocontrolled hydrogenation of an *exo*-olefinic decalin to install the C8 stereogenic centre present in the required decalin segment; (ii) coupling of the decalin segment with an aromatic moiety to assemble the desired carbon skeleton; and (iii) sequential BF_3·Et_2O-induced dehydroxylation/rearrangement/cyclization of a decalin tertiary alcohol to directly produce target compound **1**. This total synthesis has established the absolute configuration of the natural product.

Introduction

Recently, a wide variety of natural products with unique structural features and attractive biological activities have been isolated from marine sponges.[1] Many of these natural products have received considerable attention owing to their potential for use as new therapeutic agents.[2] In most cases, however, biological studies, including those focussing on structure–activity relationships, have been severely restricted, probably because of the scarcity of samples and/or the structural diversity of the natural products derived from marine sponges.[1,2] As a consequence, the development of efficient and flexible methods for the synthesis of bioactive marine natural products and their analogues is desirable and worthwhile from the viewpoint of medicinal/pharmaceutical chemistry.

Strongylin A (**1**, Figure 1) was first isolated from the Caribbean sponge *Strongylophora hartmani* by Wright et al. in 1991,[3] and subsequently from the Bahamian sponge *Xestospongia wiedenmayeri* by scientists from the Schering–Plough Corporation (now Merck & Co., Inc.) in 1995.[4] This marine natural product has been shown to have antiproliferative activity against P388 murine leukaemia cells (IC_{50} = 13 μg/mL) and antiviral activity against the human influenza A/PR/8/34 (H1N1) virus in vitro (IC_{50} = 6.5 μg/mL).[3] The constitutional structure and relative stereochemistry of **1** have been determined by extensive spectroscopic studies, including 2D NMR experiments,[3,4] but the absolute configuration has not been assigned. This natural product consists of a benzo[*d*]xanthene skeleton (ABCD ring system) containing four contiguous asymmetric centres and three quaternary carbon atoms, with the characteristic feature of *cis*-fused AB and BC rings, an ether bond at the bridgehead of the AB ring junction, and a mono-*O*-methylated hydroquinone moiety (D ring).[3,4] Closely related natural products with similar tetracyclic core structures have been isolated. These include aureol (**2**) from the Caribbean sponge *Smenospogia aurea* in 1980,[5] smenoqualone (**3**)

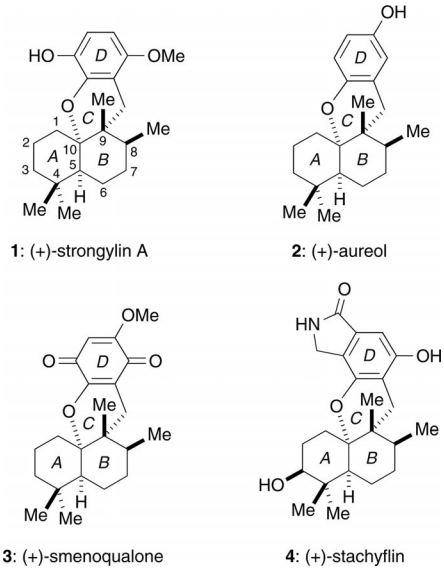


Figure 1. Representative examples of sesquiterpenoid natural products having a tetracyclic benzo[*d*]xanthene skeleton (ABCD ring system).

[a] Laboratory of Synthetic and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, 981-8558, Japan
Fax: +81-22-727-0135
E-mail: katoh@tohoku-pharm.ac.jp
Homepage: http://www.tohoku-pharm.ac.jp/laboratory/iyakugo/index.html

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300438.

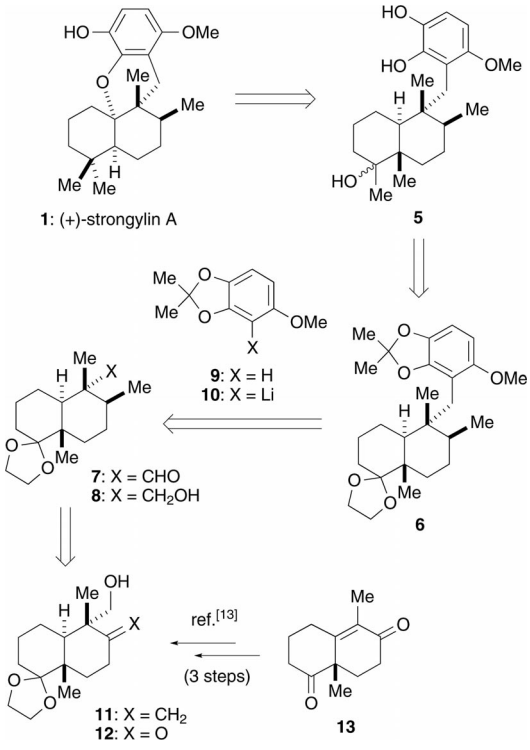
from the marine sponge *Smenospongia sp.* in 1992,[6] and stachyflin (**4**) from a culture broth of *Stachybotrys sp.* RF-7260 in 1997.[7] Natural products **2** and **4** have also been shown to have remarkable biological properties, such as antiproliferative[5] and antiviral activities,[5,7] whereas the biological activity of **3** has not been disclosed.

Unique structural features coupled with attractive biological activities have made these natural products exceptionally intriguing and timely targets for total synthesis. There have been reports on the total synthesis of natural (+)-**2**,[8,9] unnatural (–)-**2** and (–)-**3**,[10] and natural (+)-**4**.[11] However, the total synthesis of **1** has not been reported to date. An enantioselective approach to the tetracyclic core structure of this family has been reported.[12] In this study, we describe the first total synthesis of naturally occurring (+)-**1** in an enantiomerically pure form using a synthetic strategy developed in our laboratory.[8,11] This total synthesis verified the absolute configuration of (+)-**1**, which is as shown in Figure 1.

Results and Discussion

Synthetic Plan

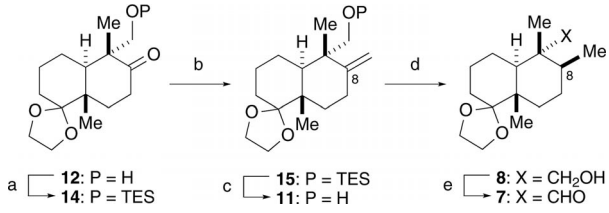
Our retrosynthetic analysis of (+)-strongylin A (**1**) is outlined in Scheme 1, and is based on our previous syntheses of (+)-aureol (**2**)[8] and (+)-stachyflin (**4**).[11] A key element of this approach is the acid-induced dehydroxylation/rearrangement/cyclization of tertiary alcohol **5** to directly produce target molecule **1** in one step. We believed that this cascade reaction would proceed stereoselectively to install the requisite *cis*-fused decalin ring junction (**5** → [**I** → **II** → **III**] → **1**; Scheme 4). A second crucial step is the coupling reaction of an appropriately functionalized *trans*-decalin **7** (accessible from the corresponding alcohol, i.e., **8**) with trioxy-substituted aryllithium compound **10** (accessible from known trioxybenzene derivative **9**) to assemble the carbon skeleton, represented by intermediate **6**. Intermediate **6** could be converted into intermediate **5**, a precursor for the key cascade reaction, by deprotection and functional-group manipulation. Intermediate **8**, in turn, was to be produced by stereoselective hydrogenation of *exo*-olefin **11**, which is accessible from known *trans*-decalone **12**.[13] Starting material **12** is readily prepared from enantiomerically pure (+)-5-methyl-Wieland–Miescher ketone (**13**) in a three-step sequence according to the method reported by Smith et al.[13]



Scheme 1. Retrosynthetic analysis of (+)-strongylin (**1**).

Synthesis of Decalin Segment 7

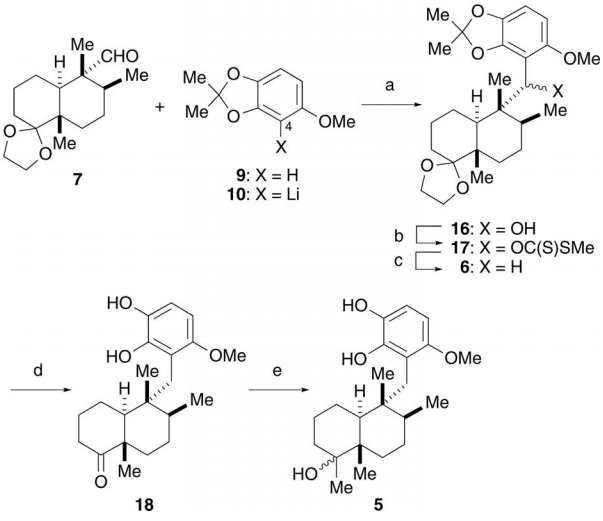
The synthesis of **7** from **12** (> 99% *ee*),[13] is shown in Scheme 2. Initial attempts to realize the direct conversion of **12** into **11** under conventional Wittig methylenation conditions[14] were unsuccessful, probably because of the presence of the sensitive hydroxy group in **12**. Therefore, we decided to carry out the conversion of **12** into **11** in a stepwise process. Thus, protection of the hydroxy group followed by Wittig methylenation[14] of the resulting triethylsilyl (TES) ether (i.e., **14**) and deprotection of the TES group in the resulting *exo*-olefin (i.e., **15**) provided the desired *exo*-olefin (i.e., **11**) in 69% yield over the three steps. To form the C8 stereogenic centre, compound **11** was subjected to hydroxy-group-directed hydrogenation by using Crabtree's catalyst {$[Ir(COD)(PCy_3)(py)]^+[PF_6]^-$; 2.5 mol-%},[15] which resulted in the formation of **8** with complete stereoselectivity and in almost quantitative yield (98%). When the hydrogenation was carried out by using a conventional Pd/C catalyst in methanol, an inseparable mixture of stereoisomers (β-Me/α-Me, 2:1) was produced in a lower yield (72%). Oxidation of **8** with tetra-*n*-propylammonium perruthenate (TPAP)[16] then gave decalin segment **7** in 94% yield.



Scheme 2. Synthesis of decalin segment **7**. (a) TESCl, imidazole, CH_2Cl_2, room temp., 1 h; (b) $Ph_3PCH_3^+Br^-$, *t*BuOK, benzene, reflux, 1 h; (c) TBAF, THF, room temp., 1 h, 69% (3 steps); (d) H_2 (1 atm), Crabtree's catalyst (2.5 mol-%), CH_2Cl_2, room temp., 1 h, 98%; (e) TPAP, NMO, CH_2Cl_2/MeCN, 4 Å MS, room temp., 1 h, 94%. TES = triethylsilyl, TBAF = tetrabutylammonium fluoride, Crabtree's catalyst = $[Ir(COD)(PCy_3)(py)]^+[PF_6]^-$ (COD = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine), TPAP = tetra-*n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

Synthesis of Intermediate 5

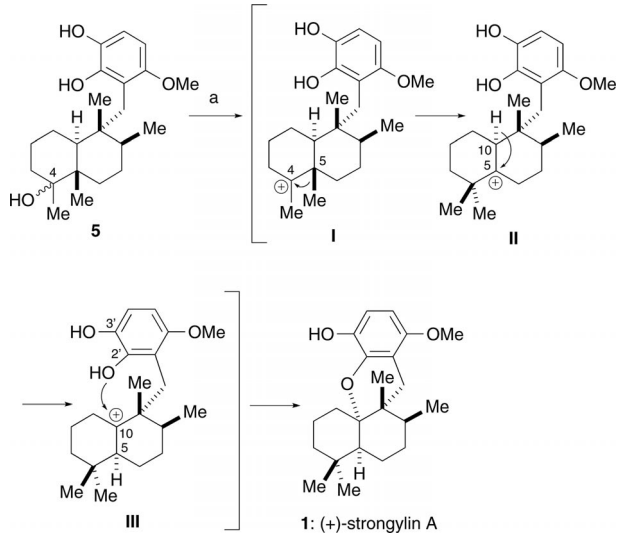
Having synthesized decalin segment **7**, we approached the synthesis of intermediate **5**, a precursor of the key cascade reaction (Scheme 3). The crucial coupling reaction of sterically hindered decalin aldehyde **7** with an appropriately functionalized aromatic portion such as **9** to construct the desired carbon skeleton was investigated. Site-selective lithiation at the C4 position in **9** was achieved by treatment with *t*BuLi in THF at 0 °C for 30 min,[17] and the aryllithium compound generated in situ (i.e., **10**) was allowed to react with **7** at 0 °C rising to room temperature over 1 h to give the expected coupling product (i.e., **16**) in excellent yield (94%) as an inseparable mixture of epimeric alcohols (ca. 4:1, as assessed by 400 MHz ^{1}H NMR spectroscopy). The removal of the hydroxy group from **16** was achieved by the Barton–McCombie procedure,[18] and the desired deoxygenated product (i.e., **6**) was formed in 78% overall yield via methyl xanthate **17**. Exposure of **6** to concentrated hydrochloric acid in refluxing ethanol resulted in simultaneous deprotection of the acetonide and ethylene acetal moieties to give the desired ketone (i.e., **18**)[19] in 71% yield. Finally, nucleophilic addition of a methyl anion to the carbonyl group in **18** was performed by using a Grignard reagent [MeMgBr (5 equiv.), THF, 0 °C to room temp.], and intermediate **5**[19] was formed in 70% yield as an inseparable mixture of epimeric alcohols (ca. 1.7:1, as estimated by 400 MHz ^{1}H NMR spectroscopy).[20]



Scheme 3. Synthesis of advanced key intermediate **5**. (a) 5-methoxy-2,2-dimethylbenzo[*d*][1,3]dioxole (**9**), *t*BuLi, THF, 0 °C, 30 min; at 0 °C, add **7**, 0 °C to room temp., 1 h, 94%; (b) NaN(SiMe$_3$)$_2$, CS$_2$, MeI, THF, –78 to –65 °C, 3 h; (c) *n*Bu$_3$SnH, AIBN, benzene, reflux, 5 h, 78% (2 steps); (d) HCl (12 M), EtOH, reflux, 5 h, 71%; (e) MeMgBr, THF, 0 °C to room temp., 1 h, 70%. AIBN = 2,2′-azobis(isobutyronitrile).

Synthesis of (+)-Strongylin A (1)

With key intermediate **5** in hand, we directed our attention to the crucial acid-induced cascade dehydroxylation/rearrangement/cyclization process to complete the synthesis (Scheme 4). The desired cascade event was successfully achieved by treating **5** with an excess of $BF_3{\cdot}Et_2O$ (10 equiv.) in CH_2Cl_2 at –78 to 0 °C for 3 h, and **1** was formed in high yield (84%) as a single stereoisomer. The spectroscopic properties of **1** (IR, ^{1}H and ^{13}C NMR, and MS) were identical to those of natural **1**. The optical rotation of synthetic **1** {$[a]_D^{23}$ = +83.3 (c = 0.024, CH_2Cl_2)} was in good agreement with that of natural **1** {ref.[3] $[a]_D^{20}$ = +72 (c = 0.023, CH_2Cl_2)}, which confirmed the absolute configuration of **1**.



Scheme 4. Synthesis of (+)-strongylin A (**1**). (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 to 0 °C, 3 h, 84%.

It is noteworthy that this cascade reaction proceeded smoothly and cleanly in a completely stereocontrolled manner. This can be rationalized by the mechanism shown in Scheme 4. Thus, an initial coordination–activation between the Lewis acid and the C4 tertiary hydroxy group in **5** causes the hydroxy group to leave, and results in the formation of a first intermediate carbocation **I**, which is transformed into a second intermediate carbocation **II** by the migration of the C5 methyl group to the C4 carbocation centre. Intermediate **II** then undergoes a 1,2-hydride shift from the C10 position to the C5 carbocation centre on the α-face of the molecule to deliver a third intermediate carbocation **III**. Finally, the C10 carbocation centre in this intermediate is trapped by the C2′ hydroxy group in the aromatic moiety to produce the desired cyclized product (i.e., **1**). We believe that this cascade sequence proceeds in a stepwise manner under kinetically controlled conditions.

Conclusions

We accomplished the first total synthesis of naturally occurring (+)-strongylin A (**1**) in a highly efficient way starting from the known *trans*-decalone **12**, accessible from (+)-5-methyl-Wieland–Miescher ketone (**13**; 19% overall yield in 11 steps from **12**; 16% overall yield in 14 steps from **13**). The key steps of the synthesis were (i) the highly stereoselective hydrogenation of *exo*-olefinic decalin **11** to establish the

C8 stereogenic centre in the decalin segment (**11** → **8**, Scheme 2); (ii) the coupling reaction of decalin segment **7** with aromatic portion **10** to construct the carbon skeleton (**7** + **10** → **16**, Scheme 3); and (iii) the acid-induced cascade dehydroxylation/rearrangement/cyclization of tertiary alcohol **5** to stereoselectively construct the tetracyclic core structure in one step, leading to target molecule **1**. This total synthesis has verified the absolute configuration of **1**. Importantly, because of its generality and flexibility, this synthesis has the potential to produce additional analogues of **1** in enantiomerically pure form. Efforts to achieve this are currently underway.

Experimental Section

General Methods: All reactions involving air- and moisture-sensitive reagents were carried out by using oven-dried glassware and standard syringe/septum cap techniques. Routine monitoring of reactions was carried out by using glass-supported Merck silica gel 60 F_{254} TLC plates. Flash column chromatography was performed on Kanto Chemical Silica Gel 60N (spherical, neutral 40–50 nm) with the solvents indicated. All solvents and reagents were used as supplied, with the following exceptions: tetrahydrofuran (THF) was freshly distilled from Na metal/benzophenone under argon; benzene and CH_2Cl_2 were distilled from calcium hydride under argon. Optical rotations were measured with a JASCO DIP-370 automatic digital polarimeter. Melting points were taken with a Yanaco MP-3 micro melting point apparatus. ^1H and ^{13}C NMR spectra were measured with a JEOL AL-400 (400 MHz) spectrometer. Chemical shifts are expressed in ppm by using Me_4Si (δ = 0 ppm) as internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br.). Infrared (IR) spectroscopic measurements were carried out with a JASCO FTIR-4100 spectrometer. Low- and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-DX 303/JMA-DA 5000 SYSTEM high-resolution mass spectrometer.

[(4a′*S*,5′*S*,8a′*S*)-5′,8a′-Dimethyl-6′-methyleneoctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalen-5′-yl)]methanol (11): Triethylsilyl chloride (2.83 mL, 17 mmol) was added dropwise to a stirred solution of (4a′*R*,5′*R*,8a′*S*)-5′-hydroxymethyl-5′,8a′-dimethylhexahydro-2′*H*-spiro[1,3-dioxolane-2,1′-naphthalen-6′(7′*H*)-one] (**12**; 3.79 g, 14 mmol) and imidazole (3.84 g, 56 mmol) in anhydrous CH_2Cl_2 (47 mL) at 0 °C under argon, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with NH_4Cl (saturated aq.; 20 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (2 × 70 mL). The combined extracts were washed with brine (2 × 50 mL), then dried with $MgSO_4$. Concentration of the solvent in vacuo gave (4a′*R*,5′*R*,8a′*S*)-5′,8a′-dimethyl-5′-[(triethylsilyloxy)methyl]hexahydro-2′*H*-spiro[1,3-dioxolane-2,1′-naphthalen-6′(7′*H*)-one] (**14**; 5.51 g, 14 mmol), which was used in the next reaction without purification.

A stirred suspension of *t*BuOK (15.8 g, 0.14 mol) and methyltriphenylphosphonium bromide (50.4 g, 0.14 mol) in anhydrous benzene (300 mL) was heated at reflux under argon for 2 h. A solution of **14** (5.51 g, 14 mmol) in anhydrous benzene (20 mL) was added to the above the mixture at 0 °C. The resulting solution was heated at reflux under argon for 1 h. After cooling, the reaction was quenched with H_2O (100 mL) at 0 °C, and the mixture was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine (2 × 100 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was diluted with EtOAc/hexane (1:20; 100 mL). The resulting mixture was filtered through a short pad of silica gel. The filtrate was concentrated in vacuo to give {[(4a′*S*,5′*S*,8a′*S*)-5′,8a′-dimethyl-6′-methyleneoctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalen-5′-yl)]methoxy}triethylsilane (**15**; 5.03 g, 13 mmol), which was used in the next reaction without purification.

Tetrabutylammonium fluoride (TBAF; 1.0 M in THF; 42.3 mL, 42 mmol) was added dropwise to a stirred solution of **15** (5.03 g, 13 mmol) in THF (70 mL) at 0 °C, and stirring was continued at room temperature for 1 h. The reaction was quenched with NH_4Cl (saturated aq.; 50 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (2 × 100 mL). The combined extracts were washed with brine (2 × 50 mL), then dried with $MgSO_4$. Concentration of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 10:1 → 5:1 → 3:1) to give **11** (2.60 g, 69% over three steps) as a white solid. Recrystallization from hexane/EtOAc gave colourless prisms. M.p. 84–86 °C. $[\alpha]_D^{22}$ = –6.2 (*c* = 1.07 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.14 (s, 3 H), 1.34–1.71 (m, 9 H), 1.93 (dd, *J* = 2.9, 12.2 Hz, 1 H), 2.16 (dt, *J* = 4.9, 14.1 Hz, 1 H), 2.32–2.39 (m, 1 H), 3.40 (d, *J* = 11.7 Hz, 1 H), 3.51 (d, *J* = 11.7 Hz, 1 H), 3.82–3.91 (m, 4 H), 4.72 (s, 1 H), 4.85 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 19.5, 21.5, 22.8, 29.3, 30.2, 31.1, 42.0, 43.0, 44.5, 64.8, 65.2, 66.7, 106.6, 113.2, 153.5 ppm. IR (KBr): $\tilde{\nu}$ = 3445, 2982, 2937, 1636, 1474, 1457, 1443, 1282, 1208, 1185, 1140, 1118, 1105, 1065, 1042, 1010, 985, 950, 927, 905, 892, 865, 747, 696, 651 cm^{-1}. $C_{16}H_{26}O_3$ (266.19): calcd. C 72.14, H 9.84; found C 72.14, H 9.91.

[(4a′*S*,5′*R*,6′*S*,8a′*S*)-5′,6′,8a′-Trimethyloctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalen-5′-yl)]methanol (8): $[Ir(COD)(PCy_3)(py)]^+$-$[PF_6]^-$ (Crabtree's catalyst; 37.8 mg, 47 μmol) was added to a solution of **11** (502 mg, 1.9 mmol) in anhydrous CH_2Cl_2 (6.3 mL). The mixture was degassed by ultrasonic means, and then it was stirred under H_2 (ballon) at room temperature for 1 h. The reaction mixture was concentrated in vacuo to give a residue, which was purified by column chromatography (hexane/EtOAc, 5:1) to give **8** (495 mg, 98%) as a colourless viscous liquid. $[\alpha]_D^{22}$ = –13.0 (*c* = 1.08 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.56 (s, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H), 1.05 (s, 3 H), 1.21–1.70 (m, 12 H), 1.81 (dd, *J* = 2.4, 12.7 Hz, 1 H), 3.30 (d, *J* = 11.7 Hz, 1 H), 3.38 (d, *J* = 11.7 Hz, 1 H), 3.81–3.95 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 15.9, 16.9, 20.4, 23.0, 26.7, 30.0, 30.4, 34.4, 40.5, 41.8, 43.4, 64.8, 65.3, 65.9, 113.4 ppm. IR (neat): $\tilde{\nu}$ = 3418, 2870, 2360, 2340, 1478, 1457, 1380, 1335, 1282, 1240, 1133, 1111, 1088, 950, 933, 908, 863, 752, 693 cm^{-1}. HRMS (FAB): calcd. for $C_{16}H_{29}O_3$ [M + H]$^+$ 269.2117; found 269.2121.

(4a′*S*,5′*R*,6′*S*,8a′*S*)-5′,6′,8a′-Trimethyloctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalene-5′-carbaldehyde) (7): Tetra-*n*-propylammonium perruthenate (TPAP; 22 mg, 62 μmol) was added to a stirred solution of **8** (330 mg, 1.2 mmol) in anhydrous CH_2Cl_2/MeCN (5:1; 12 mL) containing *N*-methylmorpholine *N*-oxide (NMO; 288 mg, 2.5 mmol) and molecular sieves (4 Å; 615 mg) at room temperature. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and the molecular sieves were removed by filtration through a short pad of Celite. Concentration of the filtrate in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 15:1) to give **7** (309 mg, 94%) as a colourless oil. $[\alpha]_D^{25}$ = –11.3 (*c* = 0.87 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.67 (d, *J* = 6.8 Hz, 3 H), 0.89 (s, 3 H), 1.05 (s, 3 H), 1.27–1.70 (m, 11 H), 1.91 (dd, *J* = 2.9, 12.2 Hz, 1 H), 3.85–4.00 (m, 4 H), 9.16 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.9, 16.5, 16.6, 22.7, 23.3, 25.5, 29.8, 30.6, 34.5, 41.9, 42.3, 53.4, 64.9, 65.3, 112.9, 206.7 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2868, 2680, 2360, 2341,

1724, 1457, 1384, 1335, 1284, 1212, 1179, 1129, 1114, 1093, 1064, 1050, 1016, 985, 939, 898 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{26}O_3$ $[M]^+$ 266.1882; found 266.1877.

(5-Methoxy-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yl)[(4a′*S*,5′*R*,6′*S*,8a′*S*)-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalen-5′-yl)]methanol (16): *t*BuLi (1.5 M in pentane; 2.7 mL, 4.1 mmol) was added dropwise to a stirred solution of 5-methoxy-2,2′-dimethylbenzo[*d*][1,3]dioxole (**9**; 739 mg, 4.1 mmol) in anhydrous THF (8.2 mL) at 0 °C under argon. After 30 min, a solution of **7** (362 mg, 1.4 mmol) in anhydrous THF (6.8 mL) was added dropwise to the above mixture at 0 °C, and the resulting solution was stirred at room temperature for a further 1 h. The reaction was quenched with NH_4Cl (saturated aq.; 15 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (2 × 40 mL). The combined extracts were washed with brine (2 × 20 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 20:1 → 6:1) to give **16** (ca. 4:1 diastereomeric mixture; 571 mg, 94%) as a pale yellow amorphous solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.58 (d, J = 6.3 Hz, 3/5 H), 0.77 (s, 3/5 H), 0.85 (s, 12/5 H), 0.95 (d, J = 6.8 Hz, 12/5 H), 1.06 (s, 12/5 H), 1.09 (s, 3/5 H), 1.12–1.68 (m, 12 H), 1.63 (s, 3/5 H), 1.64 (s, 24/5 H), 1.69 (s, 3/5 H), 1.94–2.05 (m, 8/5 H), 2.29–2.33 (m, 2/5 H), 3.75–3.96 (m, 4 H), 3.76 (s, 3/5 H), 3.77 (s, 12/5 H), 4.86 (d, J = 10.7 Hz, 4/5 H), 5.34 (s, 1/5 H), 6.20 (d, J = 8.3 Hz, 1/5 H), 6.22 (d, J = 8.8 Hz, 4/5 H), 6.53 (d, J = 8.3 Hz, 1/5 H), 6.54 (d, J = 8.3 Hz, 4/5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 13.1, 16.6, 17.3, 18.1, 18.9, 21.8, 22.9, 23.2, 23.5, 25.8 (2 C), 25.9, 27.9, 29.0, 29.5, 29.9, 30.7, 30.9, 33.1, 35.5, 41.8, 42.3, 43.8, 44.5, 46.5, 46.7, 55.6 (2 C), 65.2, 65.3, 101.5, 101.7, 105.5, 113.5, 113.6, 117.8, 141.3, 141.4, 146.0, 152.9 ppm. IR (neat): $\tilde{\nu}$ = 2933, 2359, 2340, 1715, 1698, 1682, 1651, 1557, 1539, 1506, 1456, 1385, 1252, 1214, 1129, 1078, 1060, 995, 979, 898, 790 cm^{-1}. HRMS (FAB): calcd. for $C_{26}H_{39}O_6$ $[M + H]^+$ 447.2747; found 447.2736.

(4a′*S*,5′*R*,6′*S*,8a′*S*)-5′-{(5-Methoxy-2,2-dimethylbenzo[*d*][1,3]dioxol-4-yl)methyl}-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro(1,3-dioxolane-2,1′-naphthalene) (6): $NaN(SiMe_3)_2$ (1.0 M in THF; 1.6 mL, 1.6 mmol) was added dropwise to a stirred solution of **16** (153 mg, 0.32 mmol) in anhydrous THF (3.2 mL) at –78 °C under argon. After 30 min, CS_2 (0.39 mL, 6.5 mmol) was added dropwise to the mixture at –78 °C, and the resulting mixture was stirred at –65 °C for 1 h. MeI (0.41 mL, 6.5 mmol) was added dropwise to the mixture at –65 °C, and the resulting mixture was stirred at the same temperature for a further 1 h. The reaction was quenched with NH_4Cl (saturated aq.; 10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 15 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 10:1) to give methyl xanthate **17** (142 mg, 0.26 mmol) as a yellow amorphous solid.

nBu$_3$SnH (0.36 mL, 1.3 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN; 22 mg, 0.13 mmol) were added successively to a stirred solution of **17** (142 mg, 0.26 mmol) in anhydrous benzene (8.8 mL) at room temperature. To degas the reaction mixture, it was frozen by using liquid nitrogen, then the reaction vessel was placed under vacuum for 30 min and then filled with dry argon. The mixture was heated at reflux under argon for 5 h. After cooling, the reaction mixture was concentrated in vacuo to give a residue, which was purified by column chromatography (hexane/EtOAc, 1:0 → 15:1) to give **6** (108 mg, 78% over 2 steps) as a colourless viscous liquid. $[\alpha]_D^{21}$ = –5.0 (c = 1.64 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (s, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 1.04 (s, 3 H), 1.23–1.68 (m, 11 H), 1.61 (s, 3 H), 1.66 (s, 3 H), 1.92 (d, J = 12.6 Hz, 1 H), 2.54 (d, J = 14.0 Hz, 1 H), 2.62 (d, J = 14.0 Hz, 1 H), 3.65–3.89 (m, 4 H), 3.70 (s, 3 H), 6.19 (d, J = 8.2 Hz, 1 H), 6.51 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 17.3, 18.9, 22.4, 23.6, 26.2, 26.4, 28.4, 30.2, 31.3, 35.3, 38.4, 42.8, 44.4, 46.0, 56.1, 65.2, 65.6, 101.4, 105.2, 112.6, 114.1, 117.3, 141.3, 148.4, 154.6 ppm. IR (neat): $\tilde{\nu}$ = 2985, 2870, 2834, 2362, 2341, 1716, 1698, 1684, 1635, 1558, 1540, 1520, 1507, 1462, 1437, 1382, 1337, 1212, 1179, 1162, 1104, 1046, 1024, 950, 936, 836, 799 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{38}O_5$ $[M]^+$ 430.2719; found 430.2712.

(4a*S*,5*R*,6*S*,8a*S*)-5-(2,3-Dihydroxy-6-methoxybenzyl)-5,6,8a-trimethyloctahydronaphthalen-1(2*H*)-one (18): HCl (12 M; 0.5 mL, 6.0 mmol) was added to a stirred solution of **17** (52.2 mg, 0.12 mmol) in EtOH (2.0 mL) at 0 °C. The reaction mixture was heated at reflux for 5 h. After cooling, the reaction was quenched with $NaHCO_3$ (saturated aq.; 10 mL), and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (2 × 10 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 4:1) to give **18** (33.4 mg, 71%) as a pale yellow amorphous solid. $[\alpha]_D^{24}$ = –33.8 (c = 0.58 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3 H), 0.94 (d, J = 6.3 Hz, 3 H), 1.16 (s, 3 H), 1.22–1.73 (m, 8 H), 1.99–2.04 (m, 1 H), 2.14–2.23 (m, 2 H), 2.59 (dt, J = 7.3, 13.7 Hz, 1 H), 2.65 (d, J = 14.1 Hz, 1 H), 2.71 (d, J = 13.7 Hz, 1 H), 3.68 (s, 3 H), 5.01 (br. s, 1 H), 5.57 (s, 1 H), 6.22 (d, J = 8.8 Hz, 1 H), 6.67 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 18.4, 18.9, 22.5, 26.1, 27.5, 32.2, 34.3, 37.4, 37.6, 43.2, 49.5, 49.7, 55.2, 100.8, 112.7, 115.1, 136.7, 145.3, 153.8, 218.3 ppm. IR (neat): $\tilde{\nu}$ = 2923, 2853, 1684, 1558, 1540, 1488, 1456, 1379, 1313, 1287, 1254, 1160, 1128, 1082, 958, 940, 938, 842, 821 cm^{-1}. HRMS (EI): calcd. for $C_{21}H_{30}O_4$ $[M]^+$ 346.2122; found 346.2144.

3-{[(1*R*,2*S*,4a*S*,8a*S*)-5-Hydroxy-1,2,4a,5-tetramethyldecahydronaphthalen-1-yl]methyl}-4-methoxybenzene-1,2-diol (5): MeMgBr (3.0 M in Et_2O; 96 μL, 0.29 mmol) was added dropwise to a stirred solution of **18** (20 mg, 58 μmol) in anhydrous THF (5.7 mL) at 0 °C under argon, and stirring was continued at room temperature for 1 h. The reaction was quenched with HCl (1 M; 3 mL) at 0 °C, and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with $NaHCO_3$ (saturated aq.; 2 × 10 mL) and brine (2 × 10 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 3:1 → 1:1) to give **5** (ca. 1:1.7 diastereomeric mixture; 14.7 mg, 70%) as a white amorphous solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 3 H), 0.88 (d, J = 3.4 Hz, 5.1/2.7 H), 0.93 (d, J = 6.3 Hz, 3/2.7 H), 0.98 (s, 5.1/2.7 H), 1.04 (s, 5.1/2.7 H), 1.12 (s, 3/2.7 H), 1.16–1.91 (m, 13 H), 2.60–2.72 (m, 2 H), 3.70 (s, 3 H), 4.88 (s, 1/2.7 H), 5.3 (s, 1.7/2.7 H), 5.49 (s, 1/2.7 H), 5.58 (s, 1.7/2.7 H), 6.23–6.27 (m, 1 H), 6.64–6.69 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 17.1 (2 C), 17.9, 18.5 (2 C), 22.5, 22.9, 23.2, 23.5, 23.6, 23.8, 28.0, 29.7, 31.3, 31.4, 34.8, 35.3, 37.2, 37.8, 38.1, 41.9, 42.2, 42.4, 55.3, 76.8, 100.9, 112.5, 115.9, 137.2, 145.2, 153.8, 153.9 ppm. IR (neat): $\tilde{\nu}$ = 3545, 3445, 2933, 2353, 2320, 1748, 1732, 1716, 1698, 1683, 1652, 1558, 1540, 1487, 1472, 1457, 1375, 1338, 1288, 1252, 1172, 1082, 997 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{34}O_4$ $[M]^+$ 362.2457; found 362.2458.

(4a*S*,7*S*,7a*R*,13a*S*)-9-Methoxy-4,4,7,7a-tetramethyl-1,2,3,4,4a,5,6,7,7a,8-decahydrobenzo[*d*]xanthen-12-ol [(+)-Strongylin A] (1): $BF_3{\cdot}OEt_2$ (51 μL, 0.39 mmol) was added to a stirred solution of **5** (14.2 mg, 39 μmol) in anhydrous CH_2Cl_2 (1.3 mL) at –78 °C under argon, and the resulting mixture was gradually warmed to 0 °C over 3 h. The reaction was quenched with NH_4Cl

(saturated aq.; 2 mL) at 0 °C, and the resulting mixture was extracted with $CHCl_3$ (3× 5 mL). The combined extracts were washed with brine (2× 3 mL), then dried with $MgSO_4$. Evaporation of the solvent in vacuo gave a residue, which was purified by column chromatography (hexane/EtOAc, 20:1) to give **1** (11.3 mg, 84%) as a white amorphous solid. $[\alpha]_D^{23}$ = +83.3 (*c* = 0.024 in CH_2Cl_2), {lit.[3] $[\alpha]_D^{20}$ = +72.0 (*c* = 0.023 in CH_2Cl_2)}. The ^1H and ^{13}C NMR, IR, and MS spectra (see below) were identical to those of natural (+)-strongylin A. ^1H NMR (400 MHz, [D$_6$]benzene): δ = 0.64 (s, 3 H), 0.82 (s, 3 H), 0.88 (d, *J* = 7.3 Hz, 3 H), 1.10 (s, 3 H), 1.19–1.40 (m, 7 H), 1.52–1.67 (m, 3 H), 1.80–1.90 (m, 2 H), 2.33 (d, *J* = 17.6 Hz, 1 H), 3.23 (d, *J* = 18.0 Hz, 1 H), 3.41 (s, 3 H), 5.12 (s, 1 H), 6.12 (d, *J* = 8.8 Hz, 1 H), 6.96 (d, *J* = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]benzene): δ = 17.3, 18.8, 20.3, 22.6, 27.9, 29.2, 29.4, 32.1, 32.8, 33.4, 33.9, 38.2, 39.8, 43.9, 54.9, 83.8, 100.8, 110.7, 111.4, 139.6, 139.7, 151.3 ppm. IR (neat): $\tilde{\nu}$ = 3566, 2934, 2873, 1717, 1618, 1464, 1385, 1323, 1304, 1119, 1090, 1055, 1024, 1011, 978, 947, 887, 877, 851 cm^{-1}. HRMS (EI): calcd. for $C_{22}H_{32}O_4$ $[M]^+$ 344.2351; found 344.2357.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

This study was supported by a Grant-in-Aid for the Strategic Research Foundation Program at Private Universities (2010–2014) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (MEXT) and a Grant-in-Aid for Scientific Research (C) (No. 24590017) from MEXT.

[1] For recent reviews, see: a) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2013**, *30*, 237–323; b) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2012**, *29*, 144–222.

[2] For a recent review, see: M. Gordaliza, *Mar. Drugs* **2012**, *10*, 358–402.

[3] A. E. Wright, S. A. Rueth, S. S. Cross, *J. Nat. Prod.* **1991**, *54*, 1108–1111.

[4] S. J. Coval, M. A. Conover, R. Mierzwa, A. King, M. S. Puar, D. W. Phife, J.-K. Pai, R. E. Burrier, H.-S. Ahn, G. C. Boykow, M. Patel, S. A. Pomponi, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 605–610.

[5] P. Djura, D. B. Stierle, D. B. Sullivan, D. J. Faulkner, E. Arnold, J. Clardy, *J. Org. Chem.* **1980**, *45*, 1435–1441.

[6] M.-L. Bourguet-Kondracki, M.-T. Martin, M. Guyot, *Tetrahedron Lett.* **1992**, *33*, 8079–8080.

[7] a) T. Kamigauchi, T. Fujiwara, H. Tani, Y. Kawamura, I. Horibe (Shionogi & Co., Ltd., Japan), PCT WO 9711947 A1, **1997**; b) K. Minagawa, S. Kouzuki, J. Yoshimoto, Y. Kawamura, H. Tani, T. Iwata, Y. Terui, H. Nakai, S. Yagi, N. Hattori, T. Fujiwara, T. Kamigauchi, *J. Antibiot.* **2002**, *55*, 155–164; c) K. Minagawa, S. Kouzuki, T. Kamigauchi, *J. Antibiot.* **2002**, *55*, 165–171.

[8] a) J. Sakurai, T. Oguchi, K. Watanabe, H. Abe, S. Kanno, M. Ishikawa, T. Katoh, *Chem. Eur. J.* **2008**, *14*, 829–837; b) A. Suzuki, M. Nakatani, M. Nakamura, K. Kawaguchi, M. Inoue, T. Katoh, *Synlett* **2003**, 329–332; c) M. Nakamura, A. Suzuki, M. Nakatani, T. Fuchikami, M. Inoue, T. Katoh, *Tetrahedron Lett.* **2002**, *43*, 6929–6932.

[9] K. K. W. Kuan, H. P. Pepper, W. M. Bloch, J. H. George, *Org. Lett.* **2012**, *14*, 4710–4713.

[10] I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Díez, J. G. Urones, *Tetrahedron* **2010**, *66*, 8280–8290.

[11] a) J. Sakurai, T. Kikuchi, O. Takahashi, K. Watanabe, T. Katoh, *Eur. J. Org. Chem.* **2011**, 2948–2957; b) K. Watanabe, J. Sakurai, H. Abe, T. Katoh, *Chem. Commun.* **2010**, *46*, 4055–4057; c) M. Nakatani, M. Nakamura, A. Suzuki, M. Inoue, T. Katoh, *Org. Lett.* **2002**, *4*, 4055–4057.

[12] D. T. Ngoc, M. Albicker, L. Schneider, N. Cramer, *Org. Biomol. Chem.* **2010**, *8*, 1781–1784.

[13] A. B. Smith III, L. Kürti, A. H. Davulcu, Y. S. Cho, *Org. Process Res. Dev.* **2007**, *11*, 19–24.

[14] L. Fitjer, U. Quabeck, *Synth. Commun.* **1985**, *15*, 855–864.

[15] a) R. H. Crabtree, M. H. Davis, *J. Org. Chem.* **1986**, *51*, 2655–2661; b) P. G. Nell, *Synlett* **2001**, 160 and references cited therein.

[16] a) S. V. Ley in *Comprehensive Organic Synthesis* vol. 7 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 305–327; b) W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.

[17] G. Pavé, J.-M. Léger, C. Jarry, M.-C. Viaud-Massuard, G. Guillaument, *J. Org. Chem.* **2003**, *68*, 1401–1408.

[18] a) T. Kikuchi, M. Mineta, J. Ohtaka, N. Matsumoto, T. Katoh, *Eur. J. Org. Chem.* **2011**, 5020–5030; b) M. Inoue, W. Yokota, T. Katoh, *Synthesis* **2007**, 622–637; c) T. Katoh, T. Izuhara, W. Yokota, M. Inoue, K. Watanabe, A. Nobeyama, T. Suzuki, *Tetrahedron* **2006**, *62*, 1590–1608; d) M. Inoue, W. Yokota, M. G. Murugesh, T. Izuhara, T. Katoh, *Angew. Chem.* **2004**, *116*, 4303–4305; *Angew. Chem. Int. Ed.* **2004**, *43*, 4207–4209; e) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585.

[19] The 4-methoxybenzene-1,2-diol moiety present in this compound was found to be relatively stable, and no air oxidation was observed during the operation.

[20] Attempted Wittig methylenation of ketone **18** [$Ph_3P^+CH_3Br^-$, *t*BuOK or $NaN(SiMe_3)_2$, benzene or THF, 0 °C → reflux] was unsuccessful, presumably due to the influence of the two hydroxy groups in the aromatic ring. Therefore, we looked at a Grignard reaction followed by dehydroxylation to generate carbocation **I** (cf. Scheme 4).

Received: March 25, 2013
Published Online: ■

