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A Short, Catalytic, Asymmetric Synthesis of Diospongins A and B by a One-Pot, Sequential Hetero-Diels–Alder/Mukaiyama–Michael Reaction Process

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A new route to the diarylheptanoid diospongins A and B was developed. The key step is a novel, one-pot, sequential dirhodium(II) tetrakis[(*S*)-3-(benzo-fused phthalimido)-2-piperidinonate] [Rh_2(*S*-BPTPI)$_4$] catalyzed enantioselective hetero-Diels–Alder/TMSOTf-catalyzed Mukaiyama–Michael reaction process. The sign of the optical rotation of natural diospongin B was determined to be (+) and not (–) as was originally reported.

Introduction

Diospongins A (**1**) and B (**2**), isolated from the rhizomes of *Dioscorea spongiosa* by S. Kadota and co-workers in 2004, comprise a novel class of cyclic 1,7-diarylheptanoid natural products (Figure 1).[1] These compounds contain trisubstituted tetrahydropyran cores with different stereochemistries at the C3 position (diospongin numbering). Diospongin B (**2**) exhibits a potent inhibitory activity on bone resorption induced by parathyroid hormone in a bone organ culture system, and is regarded as a promising lead compound for the development of antiosteoporotic drugs; in contrast, diospongin A (**1**) did not show any activity.[1] In 2006, Jennings and co-workers accomplished the first asymmetric total synthesis of diospongins A and B by utilizing nucleophilic addition to a cyclic oxocarbenium ion, which unequivocally confirmed their structures.[2] Since then, a number of strategies for the total syntheses of **1** and **2** in both racemic and enantiomerically enriched forms have been developed.[3–6] These strategies include intramolecular oxy-Michael reaction,[3b,4a,4b] Pd^{II}-catalyzed stereospecific cyclization of chiral 1,5,7-trihydroxy-2-heptenes,[3a] Prins cyclization,[4c,5a] three-component dithiane linchpin coupling/stereocontrolled hydrogenation of 2,6-disubstituted dihydropyranones,[3c] and tandem cross-metathesis/thermal S_N2' reaction.[5b]

The hetero-Diels–Alder (HDA) reaction between dienes and aldehydes is regarded as one of the most straightforward routes to the tetrahydropyran core structure of diospongins. Recently, Kumaraswamy and co-workers reported the asymmetric synthesis of diospongins A and B, and their enantiomers by Ti^{IV}-BINOL-catalyzed HDA reaction between Danishefsky's diene and furfural, followed by Rh^{I}-catalyzed 1,4-addition of phenylboronic acid and stereoselective reduction of the C5 carbonyl group (diospongin numbering) using Noyori's ruthenium(II) catalyst.[3d] Very recently, More described a synthesis of (±)-diospongin A using an HDA reaction and a controlled C-glycosylation with anchimeric assistance as the key steps.[5c]

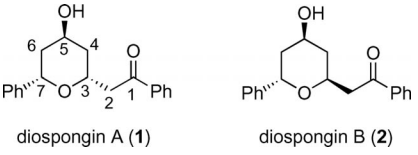

Figure 1. Structures of diospongins A (**1**) and B (**2**).

Recently, we reported that dirhodium(II) tetrakis[(*S*)-3-(benzo-fused phthalimido)-2-piperidinonate] ([Rh_2(*S*-BPTPI)$_4$]; **3**), is a highly effective Lewis acid catalyst for *endo*- and enantioselective HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes, monooxygenated dienes, and with Rawal's diene, in which enantioselectivities up to 99% *ee* have been achieved.[7] We also expanded the scope of [Rh_2(*S*-BPTPI)$_4$]-catalyzed asymmetric HDA reactions to include 4-aryl-2-silyloxy-1,3-butadienes, and we achieved the asymmetric synthesis of (–)-centrolobine, (–)-de-*O*-methylcentrolobine, and the key intermediate for (–)-calyxin L.[8] As a logical extension of our studies in this area, we now report a short, catalytic, asymmetric synthesis of diospongins A and B in which the key feature is a novel, one-pot, sequential HDA/Mukaiyama–Michael reaction process.

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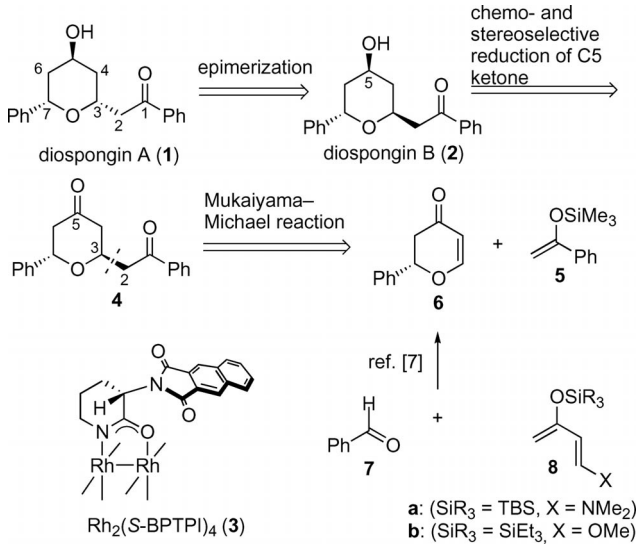
Results and Discussion

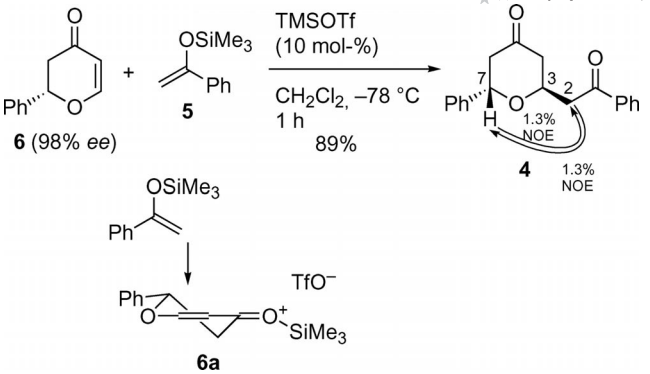
Our synthetic strategy for diospongins A and B is outlined retrosynthetically in Scheme 1. We envisioned that diospongin A (**1**) could be obtained from diospongin B (**2**) by epimerization at the C3 position, which would, in turn, be accessed through chemo- and stereoselective reduction of diketone **4** arising from Mukaiyama–Michael addition of ketone-derived silyl enol ether **5**[9] to (*S*)-dihydropyranone **6**.[10,11] Using our catalytic methodology,[7] **6** is readily prepared from benzaldehyde **7** and either Rawal's diene **8a** or Danishefsky-type diene **8b**.



Scheme 1. Retrosynthetic analysis of diospongins A and B.

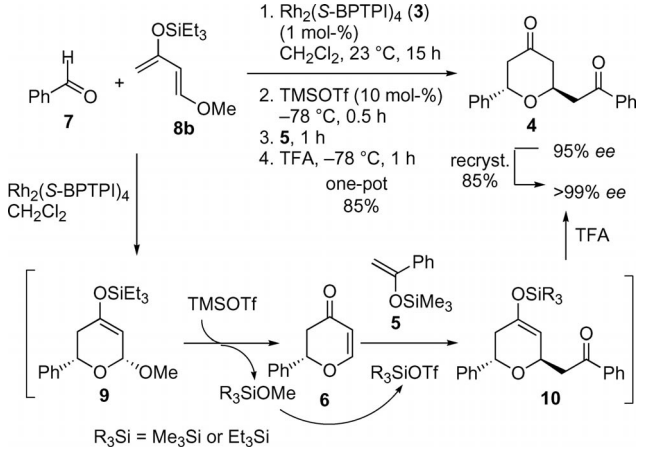
The starting (*S*)-dihydropyranone **6** (98% *ee*) was prepared by using an enantioselective HDA reaction between Rawal's diene **8a** and benzaldehyde **7** with 1 mol-% of [Rh_2(*S*-BPTPI)$_4$] (**3**), followed by treatment with acetyl chloride.[7b] The Mukaiyama–Michael addition reaction of silyl enol ether **5** to **6** in CH_2Cl_2 using 10 mol-% TMSOTf proceeded smoothly at –78 °C to completion within one hour, and gave tetrahydropyranone **4** as the sole product in 89% yield (Scheme 2). The *trans*-stereochemistry of **4** was established by an observed ^{1}H NOE correlation between C2–H and C7–H. The exclusive formation of **4** can be rationalized by an approach of silyl enol ether **5** from the top face of the half-chair conformer **6a** in which the C7 phenyl ring is oriented in the pseudoequatorial position. The use of other Lewis acids, such as [Sc(OTf)$_3$],[11a–c] $SnCl_4$, and BF_3·OEt_2 led to decomposition of the silyl enol ether, and no reaction was observed with pulverized molecular sieves (4 Å), which are an effective promoter for the Mukaiyama–Michael reaction of dihydropyranone **6** with ethyl acetate-derived silyl ketene acetal.[11d]

With optimal conditions for the Mukaiyama–Michael reaction established, attempts were then made to convert benzaldehyde (**7**) into tetrahydropyranone **4** in a one-pot, sequential process[12] (Scheme 3). After completion of the HDA reaction between Danishefsky-type diene **8b** and benzaldehyde (**7**) using 1 mol-% [Rh_2(*S*-BPTPI)$_4$] in



Scheme 2. Synthesis of *trans*-tetrahydropyranone **4**.

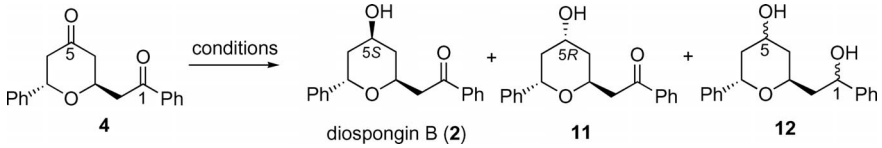
CH_2Cl_2 at room temperature, the reaction mixture was chilled to –78 °C and then treated with 10 mol-% TMSOTf. Upon addition of the latter catalyst, rapid formation of dihydropyranone **6** ensued. Gratifyingly, subsequent treatment of the reaction mixture with silyl enol ether **5** (1.2 equiv.) at –78 °C in the same reaction vessel for one hour, provided **4** in 85% yield with 95% *ee*. The reaction is presumed to proceed through silylation of the methoxy group of cycloadduct **9** by TMSOTf, followed by attack of the triflate ion on the triethylsilyl group, triggering a β-elimination to reveal the dihydropyranone **6** along with the regeneration of silyl triflate as the catalyst for the subsequent Mukaiyama–Michael reaction. It was found that Rawal's diene (**8a**) was not compatible with the present one-pot process because the dimethylamino-substituted dihydropyran formed by the HDA reaction decomposed in the presence of TMSOTf.[13] A single recrystallization of **4** (95% *ee*) from ethanol produced an optically pure sample {m.p. 73.5–74.0 °C, $[a]_D^{22}$ = –16.1 (*c* = 1.12, $CHCl_3$)}, in 85% yield.



Scheme 3. One-pot sequential enantioselective HDA/Mukaiyama–Michael reaction.

With the optically pure 3,7-*trans*-disubstituted tetrahydropyranone **4** on hand, the remaining portion of the asymmetric synthesis of diospongin B (**2**) required chemo- and stereoselective reduction of the two carbonyl groups of **4**. The reduction of **4** with one equivalent of $NaBH_4$ in

Table 1. Chemo- and stereoselective reduction of diketone **4**.



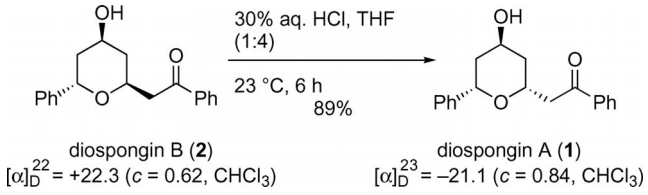
Entry	Conditions Reductant	Solvent	Temp. [°C]	Time [h]	Yield [%][a] **2/11** (ratio)[b]	**12**	**4**[c]
1	$NaBH_4$	THF/EtOH (1:1)	–20	2	81 (48:52)	8	8
2	$LiBHEt_3$	THF	–78	1	42 (34:66)	22	27
3	$LiAlH(OtBu)_3$	THF	–78	6	80 (70:30)	5	2
4	L-Selectride®	THF	–78	2	69 (>99:1)	18	11
5	K-Selectride®	THF	–78	2	86 (>99:1)	7	5

[a] Isolated yield. [b] The ratio was determined by 500 MHz ^{1}H NMR spectroscopic analysis of the crude mixture. [c] Recovered yield.

tetrahydrofuran (THF)/ethanol (1:1) at –20 °C afforded an inseparable mixture of diospongin B (**2**) and its C5 epimer **11** in a 48:52 ratio and 81% combined yield, together with 8% unreacted starting material **4** (Table 1, entry 1). In addition, 1,5-diol **12** (8%) was obtained as an inseparable mixture of diastereomers. Interestingly, 1-hydroxy 5-ketone, the formation of which may result from reduction of C1 ketone, was not detected under these reaction conditions, probably because of the low reactivity of the bulky phenyl ketone relative to the cyclic ketone. The reduction with equimolar amounts of Super Hydride® gave a 34:66 mixture of **2** and **11** in 42% yield along with 22% of **12** and 27% of **4** (Table 1, entry 2). The use of lithium tri-*tert*-butoxyaluminum hydride improved the diastereoselectivity of **2/11** to 70:30 (Table 1, entry 3). We were pleased to find that the use of L-Selectride® in THF at –78 °C gave **2** as a single diastereomer in 69% yield, along with 18% of diol **12** and 11% unreacted diketone **4** (Table 1, entry 4). Finally, K-Selectride® was found to be the optimal reducing agent, giving diospongin B (**2**) as a single diastereomer in 86% yield along with 7% of **12** and 5% of **4** (Table 1, entry 5).[14,15]

The spectroscopic data (^{1}H and ^{13}C NMR, IR, and HRMS) of the synthetic material **2** were consistent with those reported for natural diospongin B (**2**). However, the sign of optical rotation of the synthetic material {$[\alpha]_D^{22}$ = +23.3 (c = 0.63, in $CHCl_3$)} was opposite to that reported for natural diospongin B {ref.[1] $[\alpha]_D^{25}$ = –23.4 (c = 0.6, in $CHCl_3$)}. Surprisingly, all of the groups who have synthesized diospongin B (**2**) have reported that synthetic (3*S*,5*S*,7*S*)-**2** is levorotatory.[2,3] This observation prompted us to conduct a study to confirm the absolute stereochemistry of diospongin B. As reported by Kadota,[1] the configuration at the C5 position of synthetic (+)-**2** was determined by the modified Mosher method[16] and unequivocally assigned as *S* (see Supporting Information). Accordingly, the absolute stereochemistry of synthetic (+)-**2** was confirmed to be (3*S*,5*S*,7*S*) as proposed by Kadota,[1] indicating that the sign of the optical rotation of natural diospongin B (**2**) is (+) and not (–) as was originally reported.[17]

Finally, we focused on the synthesis of diospongin A (**1**; Scheme 4). Exposure of **2** to 30% hydrochloric acid in THF (1:4) at room temperature for six hours provided diospongin A (**1**) in 89% yield. This reaction is presumed to proceed through a retro-Michael reaction of **2** followed by an intramolecular oxy-Michael reaction to lead to the thermodynamically more stable 3,7-*cis*-isomer **1**.[18] The synthetic material **1** was spectroscopically (^{1}H and ^{13}C NMR, and IR) identical to natural diospongin A and also had an optical rotation {$[\alpha]_D^{23}$ = –21.1 (c = 0.84, $CHCl_3$)} that was in good agreement with the value reported in literature {ref.[1] $[\alpha]_D^{25}$ = –21.2 (c = 0.8, $CHCl_3$)}.



Scheme 4. Synthesis of diospongin A (**1**) from diospongin B.

Conclusions

We have achieved a concise, asymmetric synthesis of diospongins A (4 steps, 55% overall yield) and B (3 steps, 62% overall yield) from benzaldehyde. Highlights of this synthesis include a novel, one-pot, sequential hetero-Diels–Alder/Mukaiyama–Michael reaction process for the enantioselective construction of the 2,6-*trans*-disubstituted tetrahydropyran-4-one framework, and the chemo- and stereoselective reduction of diketone **4**. The sign of the optical rotation of diospongin B was revised to be (+) on the basis of this work. Further application of this methodology to the catalytic asymmetric synthesis of other tetrahydropyran-containing natural products is in progress.

Experimental Section

General: Melting points were determined with a Büchi 535 digital melting point apparatus. IR spectra were recorded with a JASCO FT/IR-4100 spectrometer, and absorbance bands are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-ECX 400P spectrometer or a JEOL JNM-ECA 500 spectrometer.

Optical rotations were measured with a JASCO P1030 digital polarimeter at the sodium D-line (589 nm). EI-MS spectra were obtained with a JEOL JMS-FABmate spectrometer. FAB-MS spectra were obtained with a JEOL JMS-700TZ spectrometer. Analytical high performance liquid chromatography (HPLC) was performed with a JASCO PU-1580 intelligent HPLC pump and a JASCO UV-1575 intelligent UV/Vis detector (detection at 254 nm). A Chiralcel OD-H (0.46 cm × 25 cm) column, purchased from Daicel, was used. Retention times (t_R) and peak ratios were determined with a JASCO-ChromNAV analysis system. All non-aqueous reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated, stabilizer-free CH_2Cl_2 and THF were purchased from Kanto Chemical Co., Inc.

(3*S*,7*S*)-3-(1-Oxo-1-phenylethyl)-7-phenyltetrahydropyran-5-one (4): To a solution of dihydropyranone (*S*)-**6**[7b] (98% *ee*, 200 mg, 1.2 mmol) and silyl enol ether **5**[9] (270 mg, 1.4 mmol) in CH_2Cl_2 (5 mL), was added TMSOTf (27 mg, 0.12 mmol, 10 mol-%) at –78 °C. After stirring at –78 °C for 1 h, trifluoroacetic acid (10% in CH_2Cl_2, ca. 0.2 mL) was added and the mixture was stirred for an additional 1 h. The mixture was partitioned between EtOAc (25 mL) and saturated $NaHCO_3$ (5 mL), and the organic layer was washed with water (5 mL) and brine (2 × 5 mL), and dried with anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (silica gel; hexane/EtOAc, 3:1) gave **4** (300 mg, 89%) as a pale-yellow solid; m.p. 70.5–72.0 °C; TLC R_f = 0.20 (hexane/EtOAc, 2:1). $[\alpha]_D^{22}$ = –16.0 (*c* = 1.17, $CHCl_3$). IR: $\tilde{\nu}$ = 3061, 2906, 1720, 1681, 1597, 1449 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.49 (ddd, *J* = 1.1, 8.0, 14.9 Hz, 1 H, C4-*H*), 2.70 (ddd, *J* = 1.1, 4.0, 14.9 Hz, 1 H, C4-*H*), 2.84 (ddd, *J* = 1.1, 5.7, 14.9 Hz, 1 H, C6-*H*), 2.92 (ddd, *J* = 1.1, 5.7, 14.9 Hz, 1 H, C6-*H*), 3.14 (dd, *J* = 6.3, 16.0 Hz, 1 H, C2-*H*), 3.39 (dd, *J* = 6.3, 16.0 Hz, 1 H, C2-*H*), 4.60 (m, 1 H, C3-*H*), 5.29 (dd, *J* = 5.4, 5.4 Hz, 1 H, C7-*H*), 7.26–7.35 (m, 5 H, ArH), 7.44–7.47 (m, 2 H, ArH), 7.56–7.60 (m, 1 H, ArH), 7.91–7.93 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.5 (CH_2), 45.4 (CH_2), 46.5 (CH_2), 68.3 (CH), 74.0 (CH), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 133.1 (CH), 136.5 (C), 139.2 (C), 196.6 (C=O), 206.1 (C=O) ppm. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{18}O_3$ $[M]^+$ 294.1256; found 294.1248. $C_{19}H_{18}O_3$ (294.34): calcd. C 77.53, H 6.16; found C 77.31, H 6.23.

One-Pot Sequential HDA/Mukaiyama–Michael Reaction. Preparation of 4 from Benzaldehyde (7): To a solution of benzaldehyde (**7**; 150 mg, 1.4 mmol) and $[Rh_2(S\text{-BPTPI})_4]\cdot 3H_2O$ (**3**; 20 mg, 0.014 mmol, 1 mol-%) in CH_2Cl_2 (1.8 mL), was added a solution of Danishefsky-type diene **8b** (300 mg, 1.4 mmol) in CH_2Cl_2 (1.0 mL) at 23 °C. After stirring at this temperature for 15 h, TMSOTf (31 mg, 0.14 mmol, 10 mol-%) was added at –78 °C and the mixture was stirred for an additional 0.5 h. A solution of silyl enol ether **5** (320 mg, 1.7 mmol) in CH_2Cl_2 (0.2 mL) was added at –78 °C and, after stirring at this temperature for 1 h, TFA (10% in CH_2Cl_2, 0.2 mL) was added and the mixture was stirred for an additional 1 h. The mixture was partitioned between EtOAc (25 mL) and saturated $NaHCO_3$ (5 mL), and the organic layer was washed with water (5 mL) and brine (2 × 5 mL), and dried with anhydrous Na_2SO_4. Filtration and evaporation in vacuo, followed by column chromatography (silica gel; hexane/EtOAc, 3:1) afforded **4** (345 mg, 85%) as a pale-yellow solid. The enantiomeric excess of **4** was determined to be 95% by HPLC analysis with a Chiralcel OD-H column (hexane/*i*PrOH, 9:1; 1.0 mL/min): t_R (major) = 20.2 min for (2*S*,6*S*)-**4**; t_R (minor) = 33.2 min for (2*R*,6*R*)-**4**.

Recrystallization was performed by dissolving **4** (120 mg, 0.41 mmol, 95% *ee*) in hot EtOH (2 mL). The colorless plates formed at r.t. after standing overnight, and were collected by suction, washed with ice-cold EtOH (0.5 mL) and dried in vacuo to give optically pure **4** (100 mg, 85%); m.p. 73.5–74.0 °C. $[\alpha]_D^{22}$ = –16.1 (*c* = 1.12, $CHCl_3$). The enatiopurity of **4** was determined to be >99% *ee* by comparison of the HPLC trace with that of a racemic sample.

Diospongin B (2): To a solution of diketone **4** (60 mg, 0.21 mmol, >99% *ee*) in THF (2 mL), was added a solution of K-Selectride® (1.0 M in THF, 0.21 mL, 0.21 mmol) at –78 °C. After stirring at –78 °C for 2 h, the reaction was quenched by the addition of saturated aq. $NaHCO_3$ (0.1 mL) and the mixture was partitioned between EtOAc (30 mL) and water (5 mL). The organic layer was washed with water (4 mL) and brine (2 × 4 mL), and dried with anhydrous Na_2SO_4. Filtration and evaporation in vacuo, followed by column chromatography (silica gel; toluene/EtOAc, 2:1) provided **2** (51.2 mg, 86%) as a white amorphous solid, along with **12** (5.5 mg, 7%) as a colorless amorphous solid, and diketone **4** (2.9 mg, 5%); TLC R_f = 0.36 (toluene/EtOAc, 2:1); R_f = 0.32 (hexane/EtOAc, 1:1). $[\alpha]_D^{23}$ = +23.3 (*c* = 0.63, $CHCl_3$) {ref.[1] $[\alpha]_D$ = –23.4 (*c* = 0.6, $CHCl_3$); ref.[17] $[\alpha]_D$ = +23.4 (*c* = 0.6, $CHCl_3$)}. IR: $\tilde{\nu}$ = 3406, 1686, 1598, 1495, 1450, 1052 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (ddd, *J* = 9.7, 9.7, 12.6 Hz, 1 H, C4-*H*), 1.92 (ddd, *J* = 4.0, 9.7, 13.2 Hz, 1 H, C6-*H*), 2.05 (ddd, *J* = 2.9, 5.1, 12.6 Hz, 1 H, C4-*H*), 2.51 (ddd, *J* = 4.0, 4.0, 13.2 Hz, 1 H, C6-*H*), 3.17 (dd, *J* = 6.3, 16.0 Hz, 1 H, C2-*H*), 3.45 (dd, *J* = 6.9, 16.0 Hz, 1 H, C2-*H*), 4.02 (dddd, *J* = 4.0, 5.1, 9.7, 9.7 Hz, 1 H, C5-*H*), 4.23 (dddd, *J* = 2.9, 6.3, 6.9, 9.7 Hz, 1 H, C3-*H*), 5.19 (dd, *J* = 4.0, 4.0 Hz, 1 H, C7-*H*), 7.23 (t, *J* = 6.9 Hz, 1 H, ArH), 7.32 (m, 2 H, ArH), 7.35 (m, 2 H, ArH), 7.47 (t, *J* = 7.4 Hz, 2 H, ArH), 7.58 (t, *J* = 7.4 Hz, 1 H, ArH *r*), 7.99 (d, *J* = 7.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.6 (CH_2), 40.1 (CH_2), 44.6 (CH_2), 64.1 (CH), 66.9 (CH), 72.3 (CH), 126.3 (CH), 127.0 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 133.2 (CH), 137.1 (C), 140.1 (C), 198.4 (C=O) ppm. HRMS (EI): *m*/*z* calcd. for $C_{19}H_{20}O_3$ $[M]^+$ 296.1413; found 296.1399.

Diol 12:[19] TLC R_f = 0.22 (toluene/EtOAc, 2:1); R_f = 0.27 (hexane/EtOAc, 1:1). IR: $\tilde{\nu}$ = 3389, 2943, 1603, 1494, 1448, 1063 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (m, 0.6 H, C4-*H*), 1.45 (m, 0.4 H, C4-*H*), 1.73 (dt, *J* = 2.3, 14.3 Hz, 0.6 H, C2-H), 1.81–1.94 (m, 2.4 H, C4-*H*, C6-*H*, C2-*H*, C4-*H*, and C6-*H*), 2.03 (m, 0.4 H, C2-H), 2.13 (m, 0.6 H, C2-*H*), 2.48 (m, 0.4 H, C6-*H*), 2.53 (m, 0.6 H, C6-H), 3.77–3.81 (m, 1 H, C3-*H* and C3-*H*), 3.90–3.94 (m, 1 H, C5-*H* and C5-*H*), 4.89 (dd, *J* = 2.3, 9.2 Hz, 0.6 H, C1-*H*), 5.04 (dd, *J* = 1.7, 9.1 Hz, 0.4 H, C1-*H*), 5.22 (m, 0.4 H, C7-*H*), 5.28 (m, 0.6 H, C7-*H*), 7.21–7.43 (m, 10 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.0 (CH_2), 36.5 (CH_2), 40.3 (CH_2), 41.2 (CH_2), 44.1 (CH_2), 45.0 (CH_2), 63.6 (CH), 64.1 (CH), 67.3 (CH), 70.7 (CH), 70.8 (CH), 72.6 (CH), 73.1 (CH), 74.2 (CH), 125.5 (CH), 125.7 (CH), 126.4 (CH), 126.5 (CH), 127.30 (CH), 127.31 (CH), 127.2 (CH), 128.29 (CH), 128.31 (CH), 128.47 (CH), 128.53 (CH), 128.7 (CH), 139.7 (C), 140.2 (C), 144.1 (C), 144.6 (C) ppm. HRMS (FAB): *m*/*z* calcd. for $C_{19}H_{22}O_3Na$ $[M + Na]^+$ 321.14612; found 321.14569.

Diospongin A (1): To a solution of (+)-diospongin B (**2**; 29.6 mg, 0.1 mmol) in THF (2 mL), was added aqueous HCl (30%, 0.5 mL) at 0 °C. After stirring at 23 °C for 6 h, the reaction was quenched by addition of saturated $NaHCO_3$ (3 mL), and the mixture was extracted with EtOAc (20 mL). The organic layer was washed with water (4 mL) and brine (2 × 4 mL), and dried with anhydrous Na_2SO_4. Filtration and evaporation in vacuo, followed by column chromatography (silica gel; hexane/EtOAc, 3:1) furnished **1** (26.8 mg, 90%) as a white solid; m.p. 100–101 °C [ref.[1] m.p. 102–

103 °C]; TLC R_f = 0.43 (hexane/EtOAc, 1:1). $[\alpha]_D^{23}$ = –21.1 (c = 0.84, $CHCl_3$) [ref.[1] $[\alpha]_D^{25}$ = –21.2 (c = 0.8, $CHCl_3$)]. IR: $\tilde{\nu}$ = 3326, 1681, 1451, 1210, 1063 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.68 (ddd, J = 2.3, 11.5, 13.8 Hz, 1 H, C4-*H*), 1.76 (ddd, J = 2.9, 12.0, 14.3 Hz, 1 H, C6-*H*), 1.94–1.98 (m, 2 H, C4-*H* and C6-*H*), 3.07 (dd, J = 6.9, 16.0 Hz, 1 H, C2-*H*), 3.42 (dd, J = 5.7, 16.0 Hz, 1 H, C2-*H*), 4.37 (quint, J = 2.9 Hz, 1 H, C5-*H*), 4.65 (dddd, J = 1.7, 5.7, 6.9, 11.5 Hz, C3-*H*), 4.93 (dd, J = 1.7, 11.5 Hz, 1 H, C7-*H*), 7.21–7.32 (m, 5 H, ArH), 7.45 (t, J = 7.4 Hz, 2 H, ArH), 7.56 (t, J = 7.4 Hz, 1 H, ArH), 7.99 (dd, J = 1.1, 7.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.4 (CH_2), 40.0 (CH_2), 45.1 (CH_2), 64.6 (CH), 69.0 (CH), 73.8 (CH), 125.8 (CH), 127.2 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 133.1 (CH), 137.2 (C), 142.6 (C), 198.4 (C=O) ppm. HRMS (EI): m/z calcd. for $C_{19}H_{20}O_3$ $[M]^+$ 296.1412; found 296.1401.

Supporting Information (see also the footnote on the first page of this article): Experimental procedure for the modified Mosher analysis of **2** and copies of the ^1H and ^{13}C NMR spectra.

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[18] Kumaraswamy et al. reported that exposure of TBDPS-protected diospongin B to excess TBAF in THF furnished diospongin A.[3d]

[19] Oxidation of diol **12** with MnO_2 in CH_2Cl_2 provided diospongin B (**2**) in 95% yield with perfect chemoselectivity.

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