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Efficient Total Syntheses and Structural Verification of Both Diospongins A and B via a Common δ-Lactone Intermediate

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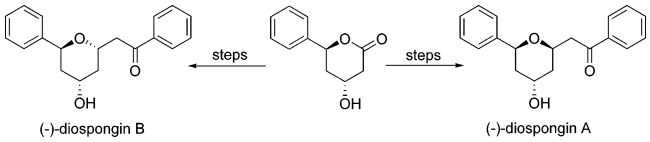

The total syntheses of the two aryl *C*-glycoside natural products diospongins A and B are described. The key reactions involved stereoselective reductions of the appropriate oxocarbenium cations that were derived from a common δ-lactone intermediate.

Osteoporosis is a skeletal disease in which bone mineral density (BMD) has been reduced and the bone microarchitecture disrupted. It is often referred to as a "silent disease" because bone loss can occur without symptoms. Osteoporosis is a major public health concern for approximately 45 million Americans, or 55% of the people 50 years of age and older. In the United States, roughly10 million individuals are estimated to already have the disease and almost 34 million more are anticipated to have low bone mass, placing them at increased risk for osteoporosis. Of the 10 million Americans estimated to have osteoporosis, 80% are female. Although more prevalent in Caucasians, significant risk has been reported in people of all ethnic backgrounds. While osteoporosis is often thought of as an elder person's disease, it can strike at any age.[1]

While some therapies that block osteoblast-mediated bone-resorption are available (i.e., Fosamax[2] and Actonel[3]), small molecule natural products with very high levels of anti-osteoporotic activity may very well be suited as alternative or additive therapeutic treatment strategies. One such natural product that has exerted potent inhibitory activities on bone resorption induced by parathyroid hormone in a bone organ culture system is (−)-diospongin B (**1**). The proposed α-C-glycoside compound **1** was isolated from the rhizomes of *Dioscorea spongiosa* via bioassay-guided fractionation and exhibited potent inhibitory activities of ^{45}Ca release at 200 μM (30.5%) and 20 μM (18.2%).[4] As shown in Figure 1, the two diospsongins [A (**2**) and B] both possess six-membered cyclic ether cores with two aromatic side chains. With these three tunable functional groups via a fairly simple molecular scaffold, a variety of analogues could be prepared with the expectation of discovering a novel and more active inhibitor of bone resorption based on the privileged α-or β-C-glycoside subunit. However, the true structure of diospongin B (vs that of diospongin A) is still unresolved.[5] Based on the disclosure report by Kadota, ^{1}H NMR data strongly supports that diospongin B possesses the α-C-glycoside subunit and diospongin A retains the β-C-glycoside.[3] Based on the anti-osteoporotic activity of **1** and uncertain configurations of both **1** and **2**, we decided to undertake the total syntheses of diospongins A and B.[3]

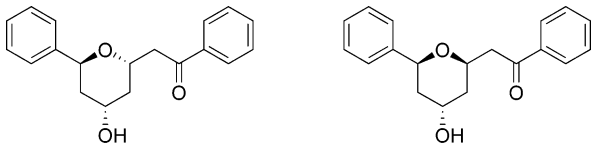

FIGURE 1. Structures of (−)-diospongins A and B.

Based on our previous reports of utilizing a δ-lactone as a precursor to β-C-glycoside subunits of natural products, we proposed that the key transformations to both targets rest with stereoselective nucleophilic additions to the appropriate oxocarbenium cations.[6] Thus, the synthesis of diospongin A can be envisioned to include a lithium enolate addition (derived from acetophenone) to the common lactone intermediate (**3**) to provide lactol **5** as highlighted in Scheme 1. Subsequent oxocarbenium formation and stereoselective reduction of the oxocarbenium intermediate **4** should provide the β-C-glycoside **2**. Likewise, a Mukaiyama-type aldol reaction of the TMS enol ether derived from acetophenone with the hydrogen-substituted oxocarbenium cation **6** should provide diospongin B (**1**). Thus, in turn, the full protected lactol **7** would readily be derived from the DIBAL reduction of the common lactone intermediate **3**.

The first order of business was the completion of the central intermediate δ-lactone **3** as highlighted in Scheme 2. Thus, attention was first focused on the introduction of the bromoacetate functionality in order to examine the stereoselective intramolecular Reformatsky lactone formation reaction sequence. With this in mind, esterification of the free secondary hydroxyl moiety resident in the known alcohol **8**[7] (derived via a Keck allylation of benzaldehyde in 92% ee as Mosher esters) with bromoacetyl bromide and pyridine provided **9** in 73% yield as shown in Scheme 2. Ensuing oxidative cleavage via the modified Johnson−Lemieux protocol of the terminal alkene moiety resident in **9** furnished the extremely labile β-bromo acetyl

(1) The facts mentioned in this manuscript were taken from the National Osteoporosis Foundation's website at: http://www.nof.org/osteoporosis/diseasefacts.htm, accessed 6/22/06.

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(5) Chandrasekhar and co-workers allege to have been the first to synthesize (−)-diospongin B. However, their NMR spectral data (both ^{1}H and ^{13}C) do not match either of the proposed (−)-diospongin structures, thus casting doubt on their claim. For more detailed information see: Chandrasekhar, S.; Shyamsunder T.; Jaya Prakash, S.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47.

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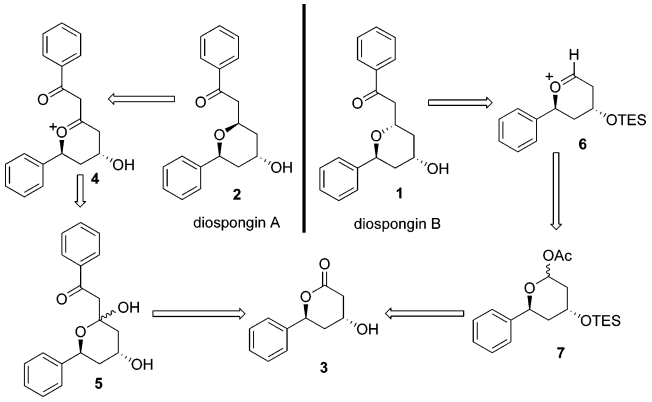
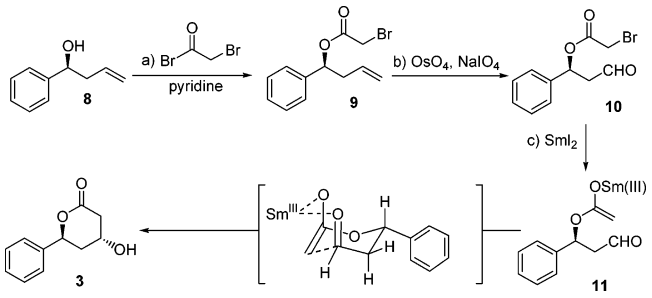
SCHEME 1. Retrosynthetic Analyses of (−)-Diospongins A and B



SCHEME 2. Synthesis of Lactone 3 via a Reformatsky Cyclization[a]

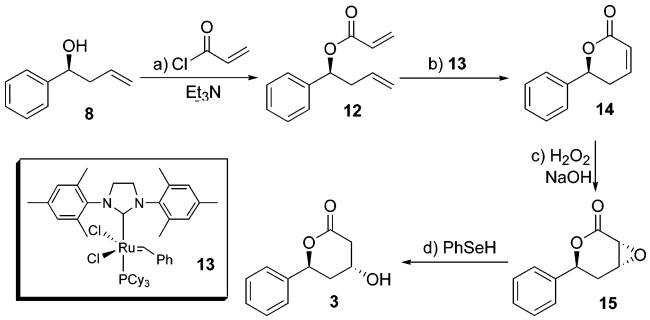


[a] Reagents and conditions: (a) bromoacetyl bromide (2.5 equiv), pyridine (2 equiv), CH_2Cl_2, 0 °C to rt, 6 h, 73%; (b) OsO_4 (0.02 equiv), $NaIO_4$ (4 equiv), dioxane/H_2O (3:1), rt, 5 h, 43%; (c) SmI_2 (3 equiv), CH_2Cl_2, 0 °C, 2 h, 32%.

aldehyde (**10**) (readily underwent β-elimination to provide cinnamaldehyde upon attempted purification) and set the stage for the intramolecular SmI_2-mediated Reformatsky sequence.[8] Molander reported that the treatment of a bromoacetyl moiety with SmI_2 readily allowed for the synthesis of a Sm(III) enolate, which subsequently underwent an intramolecular aldol reaction with a pendent aldehyde via a double six-membered transition state to furnish selectively a β-hydroxy lactone with exceptional diastereoselectivity.[9] On the basis of our previous successful utilization of this chemistry, it was anticipated that treatment of **10** with SmI_2 will provide the initial Sm(III) enolate intermediate (**11**) which quickly should undergo cyclization to provide lactone **3** as a single diastereomer via the proposed transition state as shown in Scheme 2. As expected, treatment of **11** with SmI_2 quickly underwent cyclization to provide lactone **3** as a single diastereomer as observed by ^1H NMR in a low 32% yield. Although the synthetic sequence delineated in Scheme 2 provided lactone **3**, we were dissatisfied with the ~15% yield over the two final synthetic operations.

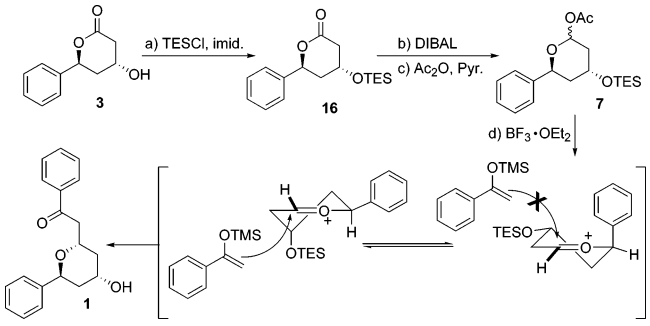
Since gram quantities of **3** were required for the completion of both **1** and **2**, we decided to investigate an alternative strategy for the synthesis of the desired β-hydroxy lactone based on our previous approach to (−)-dactylolide as described in Scheme 3.[6b] Thus, alcohol **8** was subjected to acrylate ester formation under the standard protocol (acryloyl chloride, Et_3N, DMAP)

SCHEME 3. Synthesis of Lactone 3[a]



[a] Reagents and conditions: (a) acryloyl chloride (2 equiv), DMAP (0.05 equiv), Et_3N (2.2 equiv), CH_2Cl_2, rt, 2 h, 68%; (b) **13** (0.05 equiv), CH_2Cl_2, 50 °C, 3 h, 90%; (c) H_2O_2 (3.5 equiv), NaOH (0.6 equiv), MeOH, 0 °C then rt, 4 h, then PPTS (0.05 equiv), benzene, 80 °C, 0.5 h, 85%; (d) $(PhSe)_2$ (1.5 equiv), $NaBH_4$ (3 equiv), HOAc (4 equiv), THF/EtOH (1:1), 0 °C, 1.5 h, 81%.

SCHEME 4. Synthesis of 1[a]



[a] Reagents and conditions: (a) Et_3N (6 equiv), DMAP (0.09 equiv), Et_3SiCl (3 equiv), THF, rt, 6 h, 89%; (b) DIBAL (1.3 equiv), CH_2Cl_2, −78 °C, 2.5 h, 99%; (c) Ac_2O (1.8 equiv), pyridine (1.5 equiv), DMAP (1 equiv), CH_2Cl_2, 0 °C to rt, 5 h, 91%; (d) $BF_3{\cdot}OEt_2$ (2 equiv), 1-phenyl-1-trimethylsiloxyethylene (2.5 equiv), CH_2Cl_2, −78 °C, 2 h, 81%. TESCl = triethylsilyl chloride; DIBAL = diisobutylaluminum hydride; Ac = acetyl.

afforded the dienic ester **12**. Treatment of the acrylate ester **12** with Grubbs' carbene catalyst **13** readily allowed for the formation of lactenone **14** via a ring-closing olefin metathesis with a combined yield of 61% over two steps from **8**.[10,11] An ensuing stereoselective epoxidation of the corresponding lactenone intermediate **14** with basic hydroperoxide provided the epoxy-lactone **15** in 85% yield. A subsequent regioselective reduction of the oxirane resident in **15** by means of the in situ generated PhSeH afforded intermediate **3** and provided gram quantities of the coveted β-hydroxy lactone,[12] which served as the divergent point for both natural products.

With the lactone **3** readily in hand the final drive to both diospongins A and B commenced with the designed oxocarbenium chemistry via the common β-hydroxy lactone intermediate taking center stage. With this in mind, we chose to initially investigate the synthesis of the α-C-glycoside resident in the proposed structure of **1**. As delineated in Scheme 4, initial protection of the free hydroxyl moiety of **3** was accomplished

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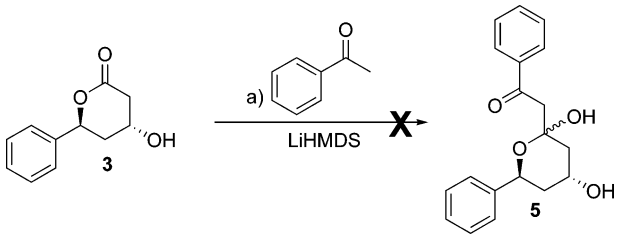
SCHEME 5. Proposed Synthesis of (−)-Diospongin A[a]



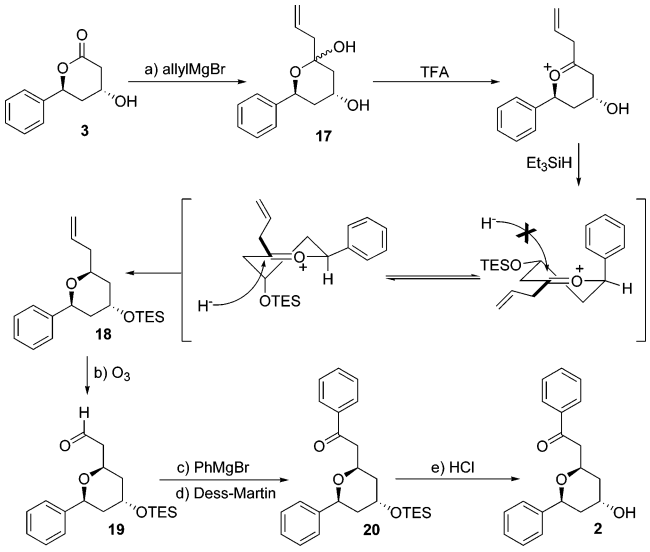
[a] Reagents and conditions: (a) LiHMDS (3.1 equiv), acetophenone (3 equiv), THF, −78 °C, 2 h.

as a TES ether under standard conditions (TESCl, Et_3N, DMAP) in 89% yield to provide **16**. Careful reduction of lactone **16** with 1.3 equiv of DIBAL readily allowed for the formation of the lactol and subsequent acetylation with Ac_2O and pyridine afforded **7**.[13] Treatment of intermediate **7** with $BF_3{\cdot}OEt_2$ presumably afforded the oxocarbenium cation. Similar to that of Woerpel's reports and our previous observations, it was predicted that the reactive conformer placed the phenyl ring at C5 in the pseudoequatorial position with the C3 hydroxyl moiety in the axial position.[6,14] This reactive conformer allowed for the stereoselective axial approach of the nucleophilic TMS enol ether (derived from acetophenone) via a chairlike transition state. Much to our delight, concomitant removal of the TES group under the reaction conditions readily proceeded to provide the coveted (−)-diospongin B (**1**) in 81% yield. The spectral data (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz), optical rotation ($[\alpha]^{rt}_D$ −22.6, *c* 0.0114, $CHCl_3$), and HRMS data of the synthetic (−)-diospongin B were in agreement with the natural sample.

With diospongin B in hand, the final focus shifted to the completion of diospongin A via a proposed addition of the lithium enolate derived from acetophenone to lactone **3**. With this in mind and delineated in Scheme 5, treatment of lactone **3** with 1.2 equiv of the enolate anion derived from acetophenone and LiHMDS surprisingly did not provide the lactol compound **5** as a mixture of two inconsequential diastereomers. Based on this result, we decided to investigate an alternative strategy (still utilizing the oxocarbenium cation) in which the nucleophilic addition of an allyl moiety (via the Grignard reagent) to lactone **3** followed oxidative cleavage of the olefin moiety would provide a synthetic blueprint to diospongin A.

With this in mind, our attention was focused on the allyl β-C-glycoside formation followed by final elaboration of the terminal alkene functional group into the final targeted structure **2**. Thus, treatment of lactone **3** with excess allylmagnesium bromide readily afforded the lactol intermediate **17** as a mixture of two diastereomers. Immediate addition of TFA to lactol **17** seemingly provided the oxocarbenium intermediates which were subsequently reduced with Et_3SiH. Similar to that of the synthesis of diospongin B in Scheme 4 and based on the observed product, it was assumed that the more reactive conformer placed the phenyl ring at C5 in the pseudoequatorial position with the C3 hydroxyl moiety in the axial position. This reactive conformer allowed for the stereoselective axial approach of the nucleophilic hydride via a chairlike transition state. As observed in our previous synthesis of (−)-dactylolide,[6b] the free secondary hydroxyl group was concomitantly protected as a TES ether under the reductive conditions for the transformation of **17** to **18**.

SCHEME 6. Synthesis of 2[a]



[a] Reagents and conditions: (a) allylMgBr (3.1 equiv), Et_2O/THF (2:1), −78 °C, 2 h, then Et_3SiH (10 equiv), TFA (5 equiv), CH_2Cl_2, −40 °C, CH_2Cl_2, 5 h, 66%; (b) O_3, Sudan III indicator, −78 °C, CH_2Cl_2, 15 min, 95%; (c) PhMgBr (2.75 equiv), Et_2O, −78 °C to rt, 5 h, 95%; (d) Dess−Martin reagent (1.5 equiv), CH_2Cl_2, 0 °C then rt, 3 h, 96%; (e) 1% HCl, EtOH, rt, 6 h, 85%. Dess−Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxo-3-(1*H*)-one.

The overall yield of the five transformations from **3** (nucleophilic addition, oxocarbenium formation, Et_3SiH reduction of the oxocarbenium cation, active silylating reagent formation, and silylation of the free hydroxyl moiety) was a very respectable 66%. With the desired β-C-glycoside subunit **18** in hand, focus was placed on the oxidative cleavage of the terminal alkene and final addition of the phenyl substituent en route to **2**. Hence, ozonolysis of the alkene moiety in **18** was readily accomplished to provide aldehyde **19** in 95% yield. Ensuing addition of the final aromatic segment via the Grignard reagent afforded the corresponding secondary alcohol as a mixture of diastereomers, which was subsequently oxidized to the ketone intermediate **20** by means of the Dess−Martin periodinane reagent in a combined yield of 91% over the two steps from **18**.[15] Final deprotection of the TES ether with HCl in EtOH furnished diospongin A (**2**) in 85% yield. The spectral data (^{1}H NMR, 360 MHz; ^{13}C NMR, 90 MHz), optical rotation ($[\alpha]^{rt}_D$ −19.6, *c* 0.0084, $CHCl_3$), and HRMS data of the synthetic (−)-diospongin A were in accord with the natural sample. The geometries of the α-and β-C-glycoside moieties were deduced and provided further proof of the purported structures of both **1** and **2** via the NOE enhancements as shown in Figure 2.[4]

In conclusion, we have provided the total syntheses of both (−)-diospongins A and B, which unequivocally have validated the structures as proposed by Kadota.[4] Based on their spectral data and in unison with ours, (−)-diospongin B possesses the α-C-glycoside subunit whereas (−)-diospongin A maintains the β-C-glycoside moiety. On the basis of the intriguing biological profile of **1** coupled with the late-stage convergence via the α-*C*-glycoside formation sequence, the synthesis of a variety of

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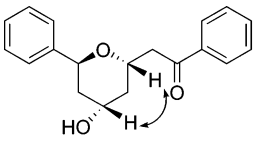
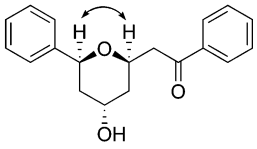


1: (-)-diospongin B



2: (-)-diospongin A

FIGURE 2. Key NOE enhancements resident in (−)-diospongins A and B.

analogues to examine the anti-osteoporotic activity of structurally diverse "diospongin B-like" compounds are currently underway and will be reported in due course.

Experimental Section

Diospongin B (1). Acetic acid 6-phenyl-4-triethylsilanyloxytetrahydropyran-2-yl ester **7** (23.7 mg, 0.71 mmol) and trimethyl(1-phenylvinyloxy)silane (37 μL, 0.1775 mmol, 2.5 equiv) were dissolved in CH_2Cl_2 (0.5 mL). Upon cooling to −78 °C, $BF_3{\cdot}OEt_2$ (18 μL, 0.142, 2 equiv) was added dropwise via syringe. On completion of the reaction as monitored by TLC, the light yellow solution was quenched with saturated solution of $NaHCO_3$ at −78 °C and reaction allowed to warm to room temperature. The mixture was extracted (30 mL × 3) with CH_2Cl_2, and the combined organic extracts were washed with brine. After drying with anhydrous sodium sulfate and evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to give 2-(4-hydroxy-6-phenyltetrahydropyran-2-yl)-1-phenylethanone (**1**) in 81% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4, 2H), 7.58 (t, J = 7.6, 1H), 7.47 (t, J = 7.9, 2H), 7.34 (m, 5H), 5.2 (t, J = 4.4, 1H), 4.23 (m, 1H), 4.03 (m, 1H), 3.45 (dd, J = 15.8, 6.9, 1H), 3.18 (dd, J = 15.8, 6.0, 1H), 2.52 (dd, J = 13.2, 1.6, 1H), 2.07 (dd, J = 12.6, 1.9, 1H), 1.92 (dd, J = 15.1, 5.4, 1H), 1.62 (d, J = 4.3, 1H), 1.5 (dd, J = 9.5, 3.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 140.3, 137.3, 133.2, 128.6, 128.5, 128.3, 126.4, 127.1, 72.3, 66.9, 64.3, 44.6, 40.2, 36.8; IR ($CHCl_3$) 3464, 1682, 1596, 1452, 1365, 1048 cm^{-1}; $[\alpha]^{25}_D$ −22.6 (c 0.0114, $CHCl_3$); R_f at 20% EtOAc/hexane 0.16; HRMS (EI) calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1416.

(2-Allyl-6-phenyltetrahydropyran-4-yloxy)triethylsilane (18). To a solution of lactone **3** (203 mg, 1.059 mmol) in 2:1 of Et_2O (10.6 mL) and THF (5.3 mL) was added allylmagnesium bromide (3.27 mL, 3.265 mmol, 3.083 equiv) at −78 °C. The reaction was stirred until the starting material was consumed. The mixture was quenched with water and extracted (30 mL × 3) with CH_2Cl_2. The organic extracts were dried with anhydrous $NaSO_4$ and concentrated under vacuum. The resultant hemiketal (263 mg, 1.1225 mmol) was dissolved in CH_2Cl_2 (11.2 mL). To the solution were added Et_3SiH (1.81 mL, 11.225 mmol, 10 equiv) and TFA (0.42 mL, 5.613 mmol, 5 equiv) in one portion at −78 °C. The temperature was allowed to warm to −40 °C, and the reaction was stirred for 0.5 h. The reaction was quenched with 10 mL of $NaHCO_3$ and extracted (20 mL × 3) with CH_2Cl_2. The organic extracts were dried with anhydrous $NaSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexanes) to give (2-allyl-6-phenyltetrahydropyran-4-yloxy)triethylsilane (**18)** in 66% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.93 (m, J = 17.3, 1H), 5.1 (dd, J = 17.3, 2.3, 2H), 4.9 (dd, J = 11.6, 2.3, 1H), 4.29 (t, J = 2.7, 1H), 4.08 (dd, J = 11.4, 2.3, 1H), 2.33 (m, 2H), 1.82 (m, 1H), 1.7 (m, 2H), 1.52(m, 1H), 1.01 (t, J = 8.2, 9H), 0.66 (q, J = 8.0, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.1, 128.2, 127.0, 125.8, 116.5, 73.5, 71.6, 65.1, 41.5, 40.7, 38.6, 6.9, 4.9. IR (neat): 2955, 2876, 2253, 1060, 9081, 735, 651 cm^{-1}; $[\alpha]^{25}_D$ −44.52 (c 0.0584, $CHCl_3$); R_f at 20% EtOAc/hexanes 0.17; HRMS (EI) calcd for $C_{20}H_{32}O_2Si$ (M^+) 332.2172, found 332.2161.

Diospongin A (2). To solution of 1-phenyl-2-(6-phenyl-4-triethylsilanyloxytetrahydropyran-2-yl)ethanone (**20**) (20 mg, 0.05 mmol) in EtOH (1 mL) was added a solution of 1% HCl in EtOH (1.25 mL). Upon completion, as determined by TLC, the reaction was quenched with $NaHCO_3$ and the aqueous residue extracted (20 mL × 3) with CH_2Cl_2. The organic residue was dried with anhydrous $MgSO_4$ and concentrated under vacuum. The crude was purified by flash column chromatography on silica gel (40% EtOAc/hexanes) to furnish desired product in 85% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.6, 1.4, 2H), 7.56 (dd, J = 7.5, 2.0, 1H), 7.46 (dd, J = 8.0, 7.3, 2H), 7.31 (m, 5H), 4.93 (dd, J = 11.8, 2.0, 1H), 4.65 (m, 1H), 4.37 (m, 1H), 3.42 (dd, J = 15.9, 5.9 1H), 3.07 (dd, J = 15.9, 6.8 1H), 1.95 (m, 2H), 1.87 (s, 1H), 1.74 (m, 1H), 1.68 (m, 1H), 1.7 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 142.7, 137.3, 133.1, 128.5, 128.3, 128.2, 127.2, 125.8, 73.8, 69.0, 64.7, 45.1, 40.0, 38.5; IR ($CDCl_3$) 3464, 1683, 1596, 1446, 1210, 911; $[\alpha]^{25}_D$ −19.6 (c 0.0084, $CHCl_3$); R_f at 40% EtOAc/hexanes 0.21; HRMS (EI) calcd for $C_{19}H_{20}O_3$ (M^+) 296.1412, found 296.1425.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds. In addition, ^{1}H NMR spectral data for the previously reported compounds are also accessible. This material is available free of charge via the Internet at http://pubs.acs.org.

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