Total Synthesis of Diospongin A via an Enzymatic Kinetic Resolution of (±)-Tetrahydropyranol Derived from Prins Cyclization

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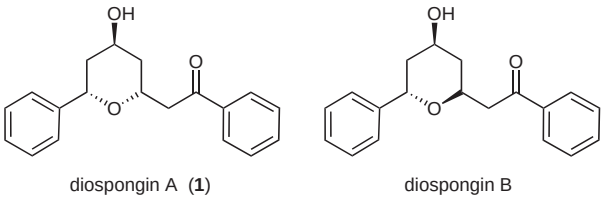
Abstract: A concise and efficient total synthesis of diospongin A is described; it utilizes Prins cyclization and enzymatic kinetic resolution as key steps. This is the first report on the synthesis of diospongin A by means of lipase-mediated transesterification of (±)-tetrahydropyranol derived from Prins cyclization.

Key words: Prins cyclization, kinetic resolution, Mitsunobu inversion, Wacker oxidation

Diospongins A and B possess a six-membered cyclic ether core with two aromatic side chains (Figure 1). Diospongins A and B were first isolated recently from the rhizomes of *Dioscorea spongiosa*.[1] They are known to exhibit potent anti-osteoporotic activity. Due to the promising biological activities of diospongins, we have been interested in the total synthesis of bioactive natural products, which contain substituted tetrahydropyran rings.

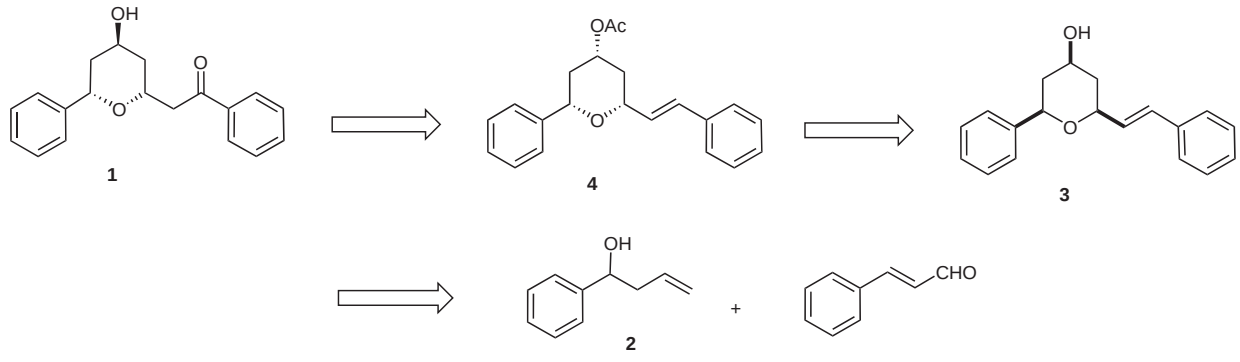
Prins cyclization[2] is one of the most simple and straightforward approaches for the construction of tetrahydropyran ring system. Surprisingly, there have been no reports on the total synthesis of diospongins using Prins cyclization. In recent years, the application of enzymes as biocatalysts has received great importance in organic synthesis. In particular, lipases are the most widely used enzymes for the regio- and enantioselective biotransformations as they are inexpensive, stable at different pH values and temperatures, and easy to recycle on immobilization of enzyme. Lipase-catalyzed reactions have been applied to solve a number of synthetic problems, one of which is the kinetic resolution of diastereomeric and enantiomeric mixtures of primary and secondary alcohols either by selective hydrolysis of the racemic esters or by transesterification of racemic alcohols.[3a] Lipases (triglycerol acylhydrolases, EC 3.1.1.3) are particularly suited for the resolution of secondary alcohols, since these enzymes exhibit enhanced stability and enantioselectivity in organic solvents while accepting a broad range of substrates. For these reasons *Porcine pancreatic* lipase (PPL), which is available as an inexpensive crude preparation, has found many practical applications.[3b] Porcine pancreatic lipase (PPL) is one of the most versatile and widely used enzymes in the resolution of esters and alcohols in both aqueous and organic media. This enhanced our interest in employing the Porcine pancreatic lipase for the kinetic resolution of (±)-tetrahydropyranol **3** derived by means of Prins cyclization.

In this report, we wish to describe an enzymatic approach for the synthesis of diospongin A starting from cinnamaldehyde in six steps. Retrosynthetic analysis of (–)-diospongin A is depicted in Scheme 1.



diospongin A (**1**) diospongin B

Figure 1



Scheme 1

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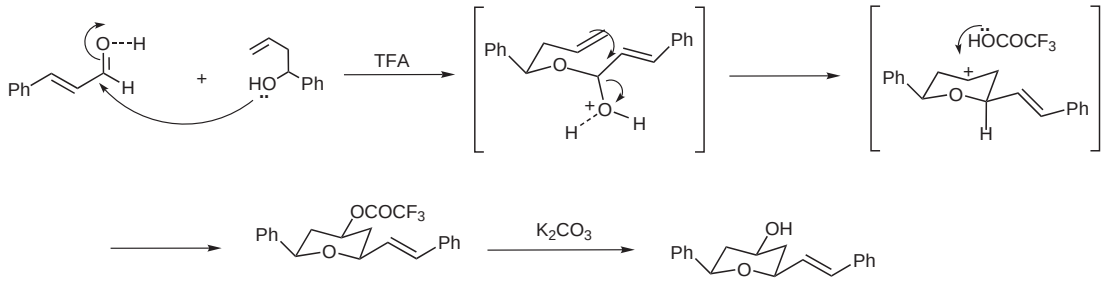
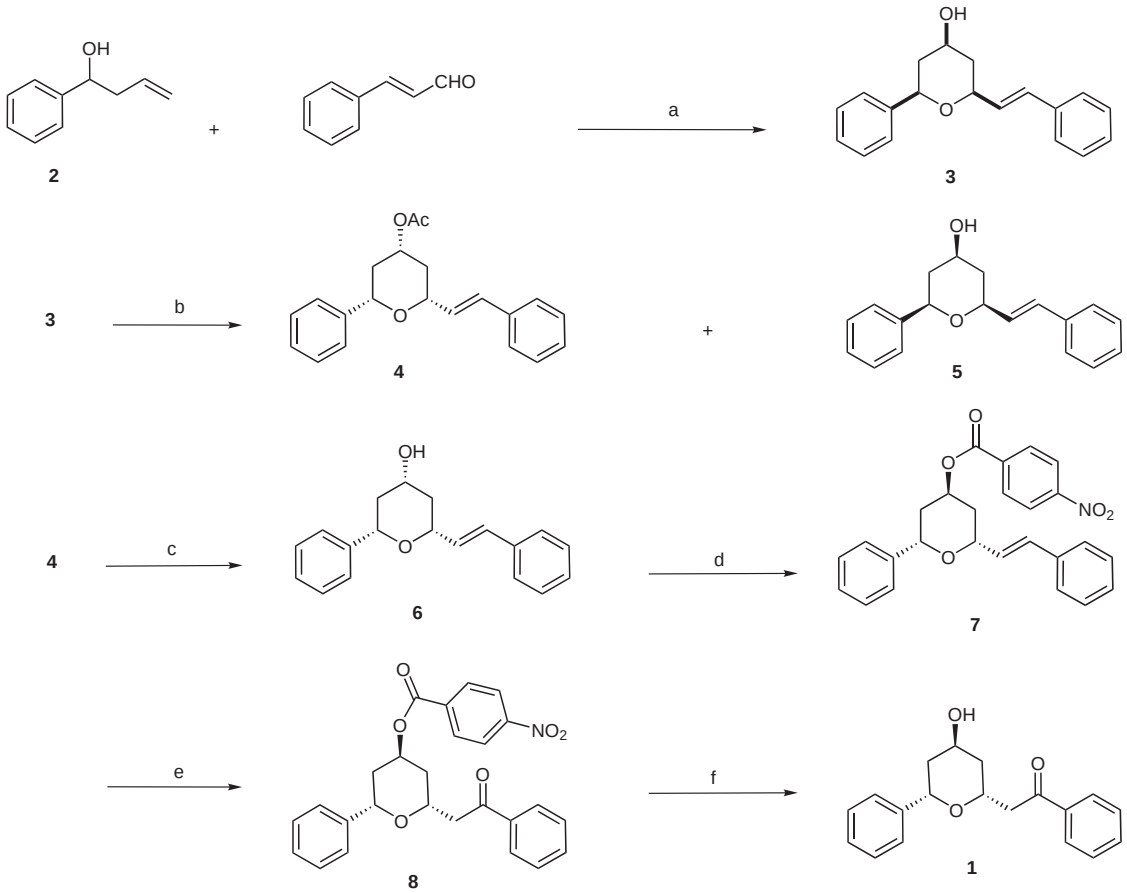


Scheme 2

Retrosynthetic analysis of **1** illustrates that optically active tetrahydropyranol **4** could be achieved by means of an enzymatic kinetic resolution of **3**, which could easily be prepared from the Prins cyclization (Scheme 1). The synthesis of diaspongin A began with cinnamaldehyde and 1-phenylbut-3-en-1-ol (**2**), which could be easily obtained by means of Barbier allylation of benzaldehyde. Accordingly, homoallylic alcohol **2** was subjected to Prins cyclization with cinnamaldehyde to produce product **3** in 78% yield as a single diastereomer, the stereochemistry of which was determined by NOE studies as reported previously.[4] A rationale for the all-*cis* selectivity involves formation of an *E*-oxocarbenium ion via a chairlike transition state, which has an increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the nucleophile (Scheme 2).[5]

Subsequent resolution of product **3** by using Porcine pancreatic lipase and vinyl acetate in the presence of cyclohexane afforded pure acetate **4** and alcohol **5** approximately in a 1:1 ratio. The pure acetate **4** was then deprotected by using K_2CO_3 in MeOH to furnish alcohol **6** in 92% yield. The enantiomeric excess of compound **6** was 94%, which was determined by chiral HPLC.[6] Inversion of the alcohol **6** was achieved by the Mitsunobu



Scheme 3 *Reagents and conditions*: (a) cinnamaldehyde, TFA, CH_2Cl_2 then K_2CO_3, MeOH, r.t., 4 h, 78%; (b) porcine pancreatic lipase (PPL, 20%w/w), vinyl acetate, cyclohexane, r.t., 5 d, (1:1); (c) K_2CO_3 (1 equiv), MeOH, r.t., 15 min, (92%) (d) PPh_3 (1.1 equiv), DIAD (1.1 equiv), *p*-nitrobenzoic acid (1.5 equiv), dry toluene, 0 °C to r.t., 3–4 h, (90%); (e) $PdCl_2$ (0.5 equiv), CuCl (3 equiv), DMF–H_2O (1:7), 50–55 °C, O_2, 3 d, (89%); (f) K_2CO_3 (1 equiv), MeOH, r.t., 15 min (90%).

reaction[7] using diisopropylazodicaboxylate (DIAD), triphenylphosphine, and *p*-nitrobenzoic acid in toluene to afford the product **7** in 90% yield. Subsequent Wacker oxidation[8] of compound **7** using $PdCl_2$ and CuCl in DMF–H_2O afforded product **8** in 89% yield. Compound **8** was then subjected to hydrolysis using K_2CO_3 in MeOH to furnish the target molecule, diospongin A (**1**) in 90% yield (Scheme 3). The structure of the diospongin A was confirmed by comparing its spectral and physical data with the natural product isolated by Jun Yin et al.,[1] and also with previous synthetic reports.[9]

In summary, we have described a short and efficient enzymatic synthetic route for the synthesis of diospongin A. The synthesis involves direct and straightforward reactions such as the Prins cyclization, enzymatic kinetic resolution, Mitsunobu inversion, and Wacker oxidation that make it quite simple and more convenient for scaling up the products.[10]

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References and Notes

(1) Yin, J.; Kouda, K.; Tezuka, Y.; Le Tran, Q.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54.

(2) For the Prins cyclization, see for example: (a) Barry, C. S. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (b) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739. (c) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485. (d) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett.* **2005**, *7*, 2683. (e) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407. (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (h) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (i) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (j) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420. (k) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (l) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. (m) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (n) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, 885. (o) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004**, *210*, 99. (p) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem.* **2003**, 1779. (q) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Rao, N. V.; Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469.

(3) (a) Chojnacka, A.; Robert, O.; Wawrzeńczyka, C. *Tetrahedron: Asymmetry* **2007**, *18*, 101. (b) Morgan, B.; Oehlschlager, C. A.; Stokes, M. T. *J. Org. Chem.* **1992**, *57*, 3231.

(4) Yadav, J. S.; Reddy, B. V. S.; Mahesh Kumar, G.; Murthy Ch., V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89.

(5) (a) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960. (b) Ramesh, J.; Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2175. (c) Biermann, U.; Lutzen, A.; Metzger, J. O. *Eur. J. Org. Chem.* **2006**, 2631.

(6) The enantiomeric excess of the product **6** was determined by using the Shimadzu high-performance liquid-chromatography (HPLC) system equipped with a chiral HPLC column (Eurocel 01, 5 μm OD) and a UV detector (225 nm). A solvent system of *n*-hexane–*i*-PrOH (8:2) and a flow rate of 1.0 mL/min were used.

(7) Mitsunobu, O. *Synthesis* **1981**, 1.

(8) For a review on Wacker oxidation: Tsuji, J. *Synthesis* **1984**, 369.

(9) (a) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911. (b) Bressy, C.; Allais, F.; Cossy, J. *Synlett* **2006**, 3455. (c) Chandrasekhar, S.; Shyamsunder, T.; Jayaprakash, S.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47.

(10) **(*E*)-2-Phenyl-6-styryl-tetrahydro-2*H*-pyran-4-ol (3)**
Trifluoroacetic acid (16.3 mL) was added slowly to a solution of **2** (1.2 g, 8.0 mmol) and cinnamaldehyde (3.16 g, 24.0 mmol) in CH_2Cl_2 (50 mL) at r.t. under a nitrogen atmosphere. The reaction mixture was stirred for 3.0 h and then treated with sat. aq $NaHCO_3$ solution (40 mL) followed by Et_3N to adjust pH > 7. The organic layer was separated and then the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The solvent was removed in vacuo and the resulting crude product was treated with K_2CO_3 (2 g) in MeOH (30 mL) over 0.5 h. Then, MeOH was removed under reduced pressure and diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford product **3** as yellow liquid (1.77 g, 78%). R_f = 0.4 (SiO_2, 30% EtOAc in hexane). IR (KBr): ν = 3420, 3029, 2922, 1717, 1602, 1494, 1450, 1063, 755, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.13 (m, 10 H), 6.62 (d, *J* = 15.8 Hz, 1 H), 6.24 (dd, *J* = 15.8, 5.2 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 0.5 H), 4.44 (d, *J* = 11.3 Hz, 0.5 H), 4.17 (dd, *J* = 10.5, 4.5 Hz, 1 H), 4.11–3.92 (m, 1 H) 2.33–2.10 (m, 2 H), 1.63–1.35 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 136.7, 130.4, 129.5, 128.4, 128.3, 128.3, 127.5, 127.4, 126.4, 126.0, 125.8, 77.7, 76.3, 68.4, 42.8, 41.1. MS (EI): *m/z* = 281 [M + 1].
(2*S*,4*R*,6*R*)-2-Phenyl-6-[(*E*)-styryl]tetrahydro-2*H*-pyran-4-yl Acetate (4)
A mixture of (±)-**3** (1.5 g, 5.3 mmol) and vinyl acetate (5 mL) in cyclohexane (10 mL) was stirred with the enzyme Porcine pancreatic lipase (EC 3.1.1.3) type II (ca. 300 mg, 20% w/w) supplied by Sigma Aldrich at r.t. for 5 d. The reaction mixture was filtered through a pad of Celite. The combined filtrate and washings (EtOAc) were evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel to furnish the required enantiomerically pure acetate **4** (759 mg, 44%) and alcohol **5** (690 mg, 46%).
Compound **4**: liquid; $[a]_D^{25}$ –8.5 (*c* 1.15, $CHCl_3$). IR (KBr): ν = 3445, 3029, 2926, 2852, 1737, 1632, 1450, 1366, 1240, 1164, 1061, 1033, 968, 912, 754, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.15 (m, 10 H), 6.63 (d, *J* = 16.6 Hz, 1 H), 6.23 (dd, *J* = 6.0, 16.6 Hz, 1 H), 5.26–5.03 (m, 1 H), 4.53 (dd, *J* = 1.5, 11.3 Hz, 1 H), 4.26 (dd, *J* = 6.0, 11.3 Hz, 1 H), 2.35–2.14 (m, 2 H), 2.04 (s, 3 H), 1.73–1.50 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 142.0, 141.8, 137.0, 130.9, 129.5, 128.8, 128.6, 127.9, 126.8, 126.2, 126.1, 78.0, 77.8, 70.9, 70.7, 39.6, 39.3, 37.6, 21.5. MS (EI): *m/z* = 345 [M + 23].
Compound **5**: liquid; $[a]_D^{25}$ +4.5 (*c* 0.35, $CHCl_3$).
(2*S*,4*R*,6*R*,*E*)-2-Phenyl-6-styryltetrahydro-2*H*-pyran-4-ol (6)
Compound **4** (500 mg, 1.5 mmol) was dissolved in MeOH (10 mL) and stirred with K_2CO_3 (214 mg, 1.5 mmol) for 15

min at r.t. Then, MeOH was removed under reduced pressure and H_2O (15 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude was purified by column chromatography on silica gel to furnish desired product **6** as yellow liquid (399 mg, 92%). R_f = 0.4 (SiO_2, 30% EtOAc in hexane); $[a]_D^{25}$ –5.2 (*c* 0.35, $CHCl_3$, 94% ee). IR (KBr): ν = 3420, 3029, 2922, 1717, 1602, 1494, 1450, 1063, 755, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.15 (m, 10 H), 6.62 (d, *J* = 15.8 Hz, 1 H), 6.24 (dd, *J* = 5.2, 15.8 Hz, 1 H), 4.44 (dd, *J* = 2.2, 12.0 Hz, 1 H), 4.17 (dd, *J* = 4.5, 10.5 Hz, 1 H), 4.11–3.92 (m, 1 H), 2.31–2.11 (m, 2 H), 1.62–1.39 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.8, 136.7, 130.4, 129.5, 128.4, 128.3, 128.3, 127.5, 127.4, 126.4, 126.0, 125.8, 77.7, 76.3, 68.4, 42.8, 41.1. MS (EI): *m/z* = 281 [M + 1].

(2*S*,4*S*,6*R*)-2-Phenyl-6-[(*E*)-styryl]tetrahydro-2*H*-pyran-4-yl-4-nitrobenzoate (7)

To a solution of compound **6** (300 mg, 1.0 mmol) in dry toluene, cooled to 0–5 °C, PPh_3 (308 mg, 1.1 mmol), *p*-nitrobenzoic acid (268 mg, 1.5 mmol), and DIAD (238, 1.1 mmol) were added under inert conditions and kept stirring for 3 h at r.t. After the completion of reaction toluene was removed under vacuum and the resulting crude was subjected to column chromatography that afforded the product **7** as white solid (416 mg, 90%). R_f = 0.8 (SiO_2, 20% EtOAc in hexane); mp149–151 °C(unknown); $[a]_D^{25}$ –21.5 (*c* 1.0, $CHCl_3$). IR (KBr): ν = 3029, 2956, 2922, 2856, 1722, 1604, 1526, 1494, 1450, 1344, 1273, 1107, 1056, 1017, 965, 872, 750, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.39–8.27 (m, 4 H), 7.43–7.16 (m, 10 H), 6.67 (d, *J* = 15.8 Hz, 1 H), 6.25 (dd, *J* = 5.2, 15.8 Hz, 1 H), 5.66–5.59 (m, 1 H), 4.93 (d, *J* = 9.8 Hz, 1 H), 4.65 (dd, *J* = 5.2, 11.3 Hz, 1 H), 2.33–2.13 (m, 2 H), 2.07–1.88 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 150.6, 141.6, 136.5, 135.7, 130.7, 129.3, 128.4, 128.4, 127.7, 127.6, 126.4, 125.9, 125.7, 123.6, 74.5, 73.3, 69.7, 37.1, 35.5. MS (EI): *m/z* = 452 [M + 23].

(2*R*,4*S*,6*S*)-2-(2-Oxo-2-phenylethyl)-6-phenyltetrahydro-2*H*-pyran-4-yl-4-nitrobenzoate (8)

Oxygen was bubbled into a mixture of $PdCl_2$ (72 mg, 0.4 mmol), CuCl (416 mg, 2.4 mmol), DMF (7 mL), and H_2O (1 mL) at r.t. The reaction mixture was stirred at r.t. for 30 min to give a deep green mixture, and then compound **7** (350 mg, 0.8 mmol) was added. The temperature of reaction mixture was raised to 50–55 °C. The mixture was kept stirring for 3 d while maintaining the heating conditions under the atmosphere of oxygen. Then, H_2O (5 mL) was added to quench the reaction, and the resulting mixture was extracted with Et_2O (4 × 15 mL). The combined organic phases were washed with H_2O (10 mL) and brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the residue on silica gel (PE–EtOAc, 20:1) afforded **8** (323 mg, 89%) as yellow solid. R_f = 0.5 (SiO_2, 20% EtOAc in hexane); mp 167–169 °C(unknown); $[a]_D^{25}$ +31.4 (*c* 0.85, $CHCl_3$). IR (KBr): ν = 2923, 2854, 1722, 1684, 1602, 1526, 1449, 1346, 1275, 1108, 1061, 1008, 870, 784, 753 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.37–8.28 (m, 4 H), 7.97 (dd, *J* = 1.5, 6.7 Hz, 2 H), 7.61–7.35 (m, 3 H), 7.30–7.17 (m, 5 H), 5.63–5.54 (m, 1 H), 4.88 (dd, *J* = 2.2, 11.7 Hz, 1 H), 4.75–4.57 (m, 1 H), 3.46 (dd, *J* = 5.8, 16.1 Hz, 1 H), 3.04 (dd, *J* = 5.8, 16.1 Hz, 1 H), 2.23 (d, *J* = 13.9 Hz, 2 H), 2.07–1.61 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 163.8, 150.7, 141.6, 137.2, 135.7, 133.2, 130.8, 128.5, 128.3, 128.2, 127.6, 125.7, 123.6, 74.5, 69.9, 69.6, 44.7, 36.9, 35.3, 29.6. MS (EI): *m/z* 468 [M + 23].

2-[(2*R*,4*S*,6*S*)-4-Hydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl]-1-phenylethanone (1)

Compound **8** (250 mg) was dissolved in MeOH (10 mL) and stirred with K_2CO_3 (77 mg, 1 equiv) for 15 min. Then MeOH was removed under reduced pressure and H_2O (15 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers dried with Na_2SO_4, and concentrated under vacuum. The crude was purified by column chromatography on silica gel to furnish desired product, diospongin A(**1**) as colorless amorphous solid in 90% (149 mg) yield. R_f = 0.21 (SiO_2, 40% EtOAc in hexane); mp 68–70 °C(unknown); $[a]_D^{25}$ –19.8 (*c* 0.35, $CHCl_3$); lit.[9] $[a]_D^{25}$ –19.6, (*c* 0.0084, $CHCl_3$). IR (KBr): ν = 3377, 2922, 1683, 1596, 1450, 1369, 1209, 1060, 998, 914, 750, 694 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dd, *J* = 1.0, 7.5 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.33–7.17 (m, 5 H), 4.93 (dd, *J* = 2.2, 12.0 Hz, 1 H), 4.64 (dddd, *J* = 1.5, 5.2, 6.0, 11.3 Hz, 1 H), 4.39–4.34 (m, 1 H), 3.41 (dd, *J* = 5.2, 15.8 Hz, 1 H), 3.06 (dd, *J* = 7.5, 15.8 Hz, 1 H), 1.96 (d, *J* = 14.3 Hz, 2 H), 1.80–1.57 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 142.6, 137.2, 133.0, 128.5, 128.3, 128.2, 127.2, 125.8, 73.7, 69.0, 64.6, 45.1, 40.0, 38.4. MS (EI): *m/z* = 297 [M + 1].