A Concise Total Synthesis of Diospongins A and B

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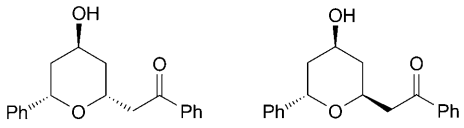
The total synthesis of the diarylheptanoids (−)-diospongin A (**1**) and B (**2**) was achieved stereoselectively *via* the δ-lactone intermediate **6**. The key reactions involved are a stereoselective reduction of β-keto ester and the *Horner–Wadsworth–Emmons* and intramolecular oxy-*Michael* reactions.

Introduction. – The 1,7-diarylheptanoids are present in a great variety of natural products which possess interesting biological [1] and pharmacological activities such as antioxidant [2], anticancer [3], and inhibitory activity on nitric oxide production [4], and anti-inflammatory [5] and antileishmanial activity [6]. (−)-Diospongin A (**1**) and B (**2**) are cyclic 1,7-diarylheptanoids which have been isolated from the rhizomes of *Dioscorea spongiosa* in 2004 *via* bioassay-guided fractionation [7]. Diospongins A and B possess a 2,6-*cis*- and 2,6-*trans*-substituted tetrahydro-2*H*-pyran ring, respectively, and these rings are assumed to be formed by an intramolecular oxy-*Michael* reaction in their biosynthesis. (−)-Diospongin B (**2**) has exerted potent inhibitory activities on bone resorption induced by parathyroid hormone in a bone-organ culture system and could be used for the treatment of osteoporosis, a skeletal disease. Due to the interesting antiosteoporotic activity of diospongins, syntheses of these natural products have been recently reported [8]. In continuation of our studies on the stereoselective synthesis of natural products [9], we report here a short and efficient total synthesis of (−)-diospongins A (**1**) and B (**2**).

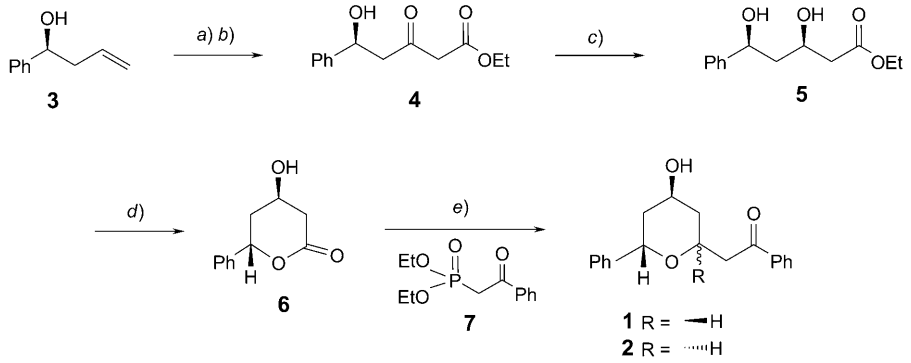


1 Diospongin A **2** Diospongin B

Results and Discussion. – The synthesis was initiated from the known chiral 1-phenylbut-3-en-1-ol (**3**), prepared from benzaldehyde by *Keck* allylation [10] with allyltributyltin in the presence of (*S*)-BINOL (=(*S*)-[1,1′-binaphthalene]-2,2′-diol) and $Ti(O^iPr)_4$ in 73% yield. The enantiomeric excess of **3** was 97% by chiral HPLC. The oxidative cleavage of the terminal olefin moiety of **3** produced the corresponding aldehyde, which without isolation was treated with ethyl diazoacetate in the presence of a catalytic amount of tin(II) chloride [11] to afford the β-keto ester **4** in 80% yield

(*Scheme 1*). The '*syn*'-selective reduction of *δ*-hydroxy-*β*-keto ester **4** was performed with catecholborane (=1,3,2-benzodioxaborol) [12] (2.2 equiv.) in dry THF at $-10°$ to afford the '*syn*'-1,3-diol **5** in 75% yield. Cyclization of ester **5** was accomplished by reacting it with a catalytic amount of TsOH (=4-methylbenzenesulfonic acid) in dry CH_2Cl_2 to afford *δ*-lactone **6** [8e] in 68% yield.

Scheme 1

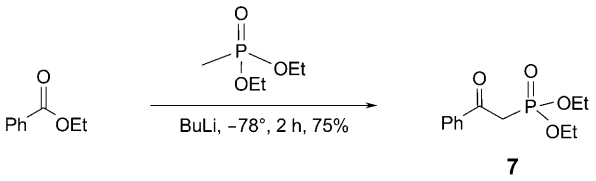


a) 1. OsO_4 (0.1M in toluene), 4-methylmorpholine 4-oxide (NMO), acetone/H_2O 4:1, overnight; 2. $NaIO_4$, CH_2Cl_2, sat. $NaHCO_3$ soln., 4 h; 85%. *b*) anh. $SnCl_2$ (cat.), $N_2CHCOOEt$, CH_2Cl_2, 0° to r.t., 40 min; 80%. *c*) Catecholborane, dry THF, $-10°$, 5 h; 75%. *d*) TsOH, CH_2Cl_2, $-78°$, 30 min; 68%. *e*) 1. DIBAL-H, dry CH_2Cl_2, $-78°$, 30 min; 2. **7**, $Ba(OH)_2 \cdot 8\,H_2O$, THF/H_2O 4:1, r.t., 5 h; 81%.

Next, the reduction of lactone **6** with DIBAL-H (=diisobutylaluminium hydride) [13] and treatment with *Horner*'s phosphonate **7** [14] and BuLi as base was performed as recently reported [9j], but the reaction was found to be sluggish, and the products could not be isolated in pure form. However, the reduction of lactone **6** with DIBAL-H [13] and treatment with *Horner*'s phosphonate **7** [14][1]) and $Ba(OH)_2 \cdot 8\,H_2O$ as base [15] in THF/H_2O 4:1 afforded a 4:6 diastereomer mixture of 2,6-*cis*/*trans* isomers, **1** and **2**, *i.e.*, (−)-diospongin A and (−)-diospongin B in an overall yield of 60%, achieving *Wittig–Horner* and intramolecular oxy-*Michael* reactions in one-pot (for recent examples of the oxy-*Michael* reaction, see [16]). Diastereoisomers **1** and **2** were separated by column chromatography, and their structures were confirmed by spectral

[1]) The required *Horner*'s phosphonate **7** was synthesized from commercially available ethyl benzoate by treatment with diethyl methylphosphonate and BuLi (*Scheme 2*).

Scheme 2



data. The physical data of the synthetic materials was fully consistent with those reported for the natural products [8b].

In summary, a short synthesis of (−)-diospongins A (**1**) and B (**2**) was achieved *via* a common intermediate lactone **6** by means of *Keck* allylation, stereoselective reduction of a β-keto ester, and *Horner–Wadsworth–Emmons* and intramolecular oxy-*Michael* reactions as key steps. The application of the method to further natural products is in progress and will be reported in due course.

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Experimental Part

General. Reactions were conducted under N_2 with anh. solvents such as CH_2Cl_2 and THF. Light petroleum ether 60–80° was used. Yields refer to chromatographically and spectroscopically (^1H, ^{13}C) homogeneous material. Air-sensitive reagents were transferred by syringe or with a double-ended needle. Evaporation of solvents was performed under reduced pressure with a *Büchi* rotary evaporator. Column chromatography (CC): silica gel (60–120 mesh) supplied by *Acme Chemical Co.*, India. TLC: *Merck-60-F_{254}* silica gel plates; visualization under UV light. Optical rotations: *Jasco-DIP-370* polarimeter; at 20°. ^1H-NMR Spectra: *Varian-FT-200MHz* (*Gemini*) and *Bruker-UXNMR-FT-300MHz (Avance*) spectrometers; $CDCl_3$ solns.; chemical shifts δ in ppm rel. to Me_4Si (δ 0.0) as an internal standard; J in Hz. Mass spectra: *LC-MSD* (*Agilent Technologies*); electron impact at 70 eV; in m/z.

*Ethyl (5*S*)-5-Hydroxy-3-oxo-5-phenylpentanoate* (**4**). To anh. tin(II) chloride (0.37 g, 2 mmol) was added CH_2Cl_2 (15 ml) followed by ethyl diazoacetate (2.5 g, 22 mmol) with stirring at r.t. To this suspension were added slowly few drops of crude aldehyde (3 g, 20 mmol; from **3**) in dry CH_2Cl_2. When N_2 evolution began, the remaining soln. of crude aldehyde was added dropwise within 10 min. After N_2 evolution had stopped (30 min), the mixture was transferred to a separatory funnel with sat. NaCl soln. (30 ml) and extracted with Et_2O (2 × 20 ml). The combined org. layer was dried (Na_2SO_4), the solvent evaporated, and the residue purified by CC (silica gel): **4** (3.7 g, 80%). Yellow liquid. $[\alpha]_D^{25} = -30.2$ (c = 1.15, $CHCl_3$). IR (neat): 3487, 2982, 2926, 1739, 1648, 1451, 1314, 1030, 757, 701. ^1H-NMR ($CDCl_3$, 200 MHz): 7.47–7.18 (m, 5 H); 5.15 (dd, J = 4.4, 3.6, 1 H); 4.18 (q, J = 7.3, 2 H); 3.43 (s, 2 H); 2.96–2.87 (m, 2 H); 1.29 (t, J = 7.3, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 192.1; 168.3; 142.7; 129.6; 128.7; 126.4; 69.0; 61.2; 52.4; 49.8; 14.1. ESI-MS: 259 ($[M+Na]^+$). HR-MS: 259.1616 ($C_{13}H_{16}NaO_4^+$, $[M+Na]^+$; calc. 259.0964).

*Ethyl (3*R*,5*S*)-3,5-Dihydroxy-5-phenylpentanoate* (**5**). The soln. of **4** (2.5 g, 10 mmol) in dry THF was chilled in a MeOH/ice bath (−10°) and charged with freshly distilled catecholborane (2.48 ml, 23 mmol). After 5 h, the mixture was quenched by the addition of anh. MeOH (1 ml) and sat. aq. sodium potassium tartrate soln. (2 ml). This mixture was stirred at r.t. for 1 h, and the desired product was isolated by CC (silica gel): **5** (1.89 g, 75%). Brown liquid. $[\alpha]_D^{25} = -15.8$ (c = 0.7, $CHCl_3$). IR (neat): 3436, 2924, 2854, 1728, 1642, 1452, 1215, 1068, 760, 701. ^1H-NMR: ($CDCl_3$, 300 MHz): 7.41–7.17 (m, 5 H); 4.94 (dd, J = 6.8, 3.0, 1 H); 4.35–4.22 (m, 1 H); 4.16 (q, J = 7.5, 2 H); 3.85 (br., 1 H, OH); 3.56 (br., 1 H, OH); 1.88 (dd, J = 14.3, 3.7, 2 H); 1.75 (t, J = 2.3, 2 H); 1.28 (t, J = 7.5, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.5; 143.7; 128.4; 127.7; 125.5; 74.3; 68.5; 60.8; 44.6; 41.6; 14.0. LC/MS: 261 ($[M+Na]^+$). HR-MS: 261.1745 ($C_{13}H_{18}NaO_4^+$, $[M+Na]^+$; calc. 261.1103).

*(4*R*,6*S*)-Tetrahydro-4-hydroxy-6-phenyl-2*H*-pyran-2-one* (**6**) [8e]. To a soln. of **5** (2 g, 8.40 mmol) in anh. CH_2Cl_2 (20 ml) was added a catalytic amount of TsOH under N_2. The mixture was stirred at r.t. for 6 h, then the reaction was quenched by the addition of solid $NaHCO_3$ (0.004 g, 0.05 mmol). The mixture was filtered, the solvent of the filtrate evaporated, and the residue purified by CC (hexane/AcOEt 4 : 6): **6** (1.09 g, 68%). Colorless liquid. $[\alpha]_D^{25} = -9.4$ (c = 1.35, $CHCl_3$). IR (neat): 3416, 2924, 2854, 1726, 1455, 1249, 1044, 758, 700. ^1H-NMR ($CDCl_3$, 200 MHz): 7.48–7.18 (m, 5 H); 5.7 (dd, J = 11.3, 3.0, 1 H); 4.40 (m, 1 H); 2.82–2.65 (m, 2 H); 2.31–1.98 (m, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 170.8; 139.1; 128.6; 128.3; 125.8; 77.3; 62.5; 38.5; 38.1. LC/MS: 215 ($[M+Na]^+$). HR-MS: 215.1298 ($C_{11}H_{12}NaO_3^+$, $[M+Na]^+$; calc. 215.0684).

(−)-Diospongin A (*=1-Phenyl-2-[(2*R*,4*S*,6*S*)-tetrahydro-4-hydroxy-6-phenyl-2*H*-pyran-2-yl]ethanone*; **1**) *and (−)-Diospongin B* (*=1-Phenyl-2-[(2*S*,4*S*,6*S*)-tetrahydro-4-hydroxy-6-phenyl-2*H*-pyran-2-yl]ethanone*; **2**). To a soln. of **6** (0.1 g, 0.52 mmol) in dry CH_2Cl_2 at $-78°$ was added DIBAL-H (0.7 ml), and the mixture was stirred at $-78°$ for 30 min. Then, the reaction was quenched by slow addition of MeOH followed by sat. sodium potassium tartrate soln. The mixture was extracted with CH_2Cl_2, the combined org. layer washed with H_2O, dried (Na_2SO_4), and concentrated, and the crude lactol used without any further purification for the next reaction.

Activated $Ba(OH)_2 \cdot 8\,H_2O$ (0.32 g, 1 mmol) was added to a stirred soln. of *Horner–Wittig* reagent **7** (0.23 g, 1 mmol) in THF at 0° for 30 min, then the above crude lactol (0.1 g, 0.51 mmol) in THF/H_2O 4:1 was added, and after 5 h, the mixture was extracted with AcOEt. The combined org. layer was washed with H_2O and dried (Na_2SO_4), the solvent evaporated, and the residue purified by CC (silica gel, hexane/AcOEt 7:3): **1** and **2** as liquids.

(−)-Diospongin A (**1**): $[\alpha]_D^{25} = -21.1$ ($c = 0.8$, $CHCl_3$). IR (neat): 3443, 2921, 2853, 1678, 1512, 1450, 1286, 1215, 1058, 758, 694. ^{1}H-NMR: ($CDCl_3$, 300 MHz): 7.95 (*dd*, *J* = 7.6, 1.4, 2 H); 7.48 (*t*, *J* = 7.5, 1 H); 7.35 (*t*, *J* = 7.5, 2 H); 7.19–7.12 (*m*, 5 H); 4.87 (*dd*, *J* = 11.7, 1.9, 1 H); 4.61–4.49 (*m*, 1 H); 4.29 (*m*, 1 H); 3.32 (*dd*, *J* = 15.8, 5.3, 1 H); 2.97 (*dd*, *J* = 16.6, 7.5, 1 H); 2.31 (br., OH); 1.98–1.79 (*m*, 2 H); 1.71–1.45 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 198.4; 142.6; 137.2; 133.1; 128.5; 128.3; 128.2; 127.2; 125.7; 73.7; 69.0; 64.6; 45.1; 39.9; 38.4. LC/MS: 297.1 ($[M+1]^+$). HR-MS: 297.1475 ($C_{19}H_{21}O_3^+$, $[M+H]^+$; calc. 297.1491).

(−)-Diospongin B (**2**): $[\alpha]_D^{25} = -22.5$ ($c = 0.6$, $CHCl_3$). IR (neat): 3404, 2924, 2854, 1680, 1599, 1452, 1378, 1214, 1054, 756, 693. ^{1}H-NMR: ($CDCl_3$, 300 MHz): 7.98 (*d*, *J* = 8.2, 2 H); 7.56 (*t*, *J* = 7.4, 1 H); 7.45 (*t*, *J* = 7.9, 2 H); 7.38–7.12 (*m*, 5 H); 5.12 (*t*, *J* = 4.2, 1 H); 4.25–4.12 (*m*, 1 H); 4.03–3.89 (*m*, 1 H); 3.41 (*dd*, *J* = 15.6, 7.0, 1 H); 3.11 (*dd*, *J* = 15.7, 6.5, 1 H); 2.45 (*d*, *J* = 13.6, 1 H); 2.00 (*d*, *J* = 12.8, 1 H); 1.86 (*ddd*, *J* = 13.6, 9.8, 5.3, 1 H); 1.46 (*dd*, *J* = 9.5, 3.2, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 198.4; 140.3; 137.1; 133.1; 128.6; 128.5; 128.3; 127.1; 126.3; 72.3; 67.0; 64.2; 44.6; 40.6; 36.7. LC/MS: 297.1 ($[M+1]^+$). HR-MS: 297.1483 ($C_{19}H_{21}O_3^+$, $[M+H]^+$; calc. 297.1491).

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