Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Concise Synthesis of Yashabushidiol A and (±)-Diospongin A

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(Received: Dec. 26, 2011; Accepted: Jan. 2, 2012; Published Online: Jan. 16, 2012; DOI: 10.1002/jccs.201100664)

Synthesis of (±)-diospongin A has been achieved from the (2*SR*,4*RS*)-pentane-1,2,4,5-tetraol in six steps. An intermediate has also been converted into yashabushidiol A. This work features a desymmetric cyclization and reduction of a *meso*-1,7-diarylheptanoid precursor to furnish the desired *cis*-2,6-di-substituted tetrahydropyran.

Keywords: (2*SR*,4*RS*)-pentane-1,2,4,5-tetraol; Dithiane alkylation; Desulfurization; *meso*-1,7-Diarylheptanoids; Cyclization.

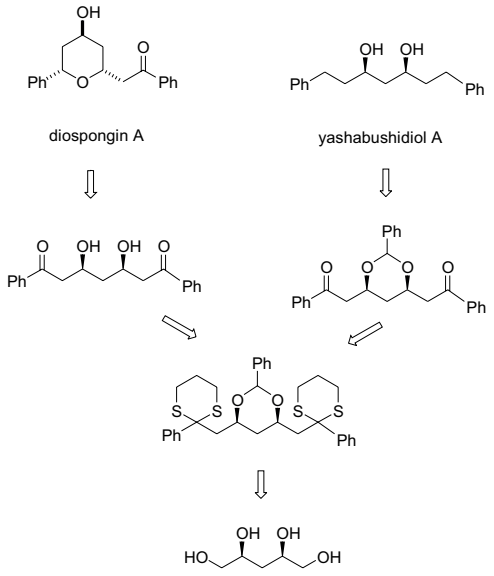
INTRODUCTION

Desymmetrization of *meso* substrates is a powerful strategy for acquiring chiral intermediates for organic synthesis. Recent examples include asymmetric ring opening of epoxide,[1] monoacylation of 2-substituted 1,3-propanediols,[2] and ring-closing metathesis that selects one of two identical double bonds.[3] Our long-standing interest in design of natural products synthesis led us to consider an approach to two 1,7-diarylheptanoids in the other context of avoiding regiochemical problems.[4]

As a metabolite in the rhizomes of *Dioscorea spongiosa,* diospongin A with anti-osteoporotic activity[5] has attracted synthetic efforts from several research groups. Routes with key reactions of cross-metathesis and intramolecular Michael addition (Cossy,[6a] Bates[6c]), ring-closing olefin metathesis (Jennings[6b]), Pd(II)-catalyzed S_N2'-type reaction (Uenishi[6d]), Prins reaction (Jadav,[6e] Piva[6f]) and tandem cross-metathesis/S_N2' reaction (Hong[6g]) have been explored.

Our synthetic design is based on of the generation of the tetrahydropyran core from a *meso* dihydroxydiketone, from which cyclic hemiacetal formation involving any pair of C=O/OH yields the same product (Scheme I). In our analysis, to establish the desired *cis*-2,6-disubstituted tetrahydro-pyran system via hydride delivery from a hydrosilane to the incipient carboxonium species would be favored by stereoelectronic effects and possibly chelation of the silicon atom with the axial hydroxyl group (Scheme II).[9] The attractiveness of this route is evident by proceeding via intermediates amenable to the elaboration of yashabushidiol A, which occurs in the male flowers of *Alnus sieboldiana* Matsum,[7] and possesses anticancer properties against certain human leukemia and melanoma cell lines. Yashabushidiol A and several cognate compounds have been synthesized.[8]

Scheme I Retrosynthetic analysis for disopongin A and yasabushidiol A



With the subgoal of our synthesis identified as dihydroxydiketone **6**. We started on its preparation from (2*SR*,4*RS*)-pentane-1,2,4,5-tetraol (**1**), which is available from D-ribose by following the procedure described for L-arabitol.[10] The synthetic process is depicted in Scheme III.

Dedicated to the memory of Professor Yung-Son Hon (1955–2011).

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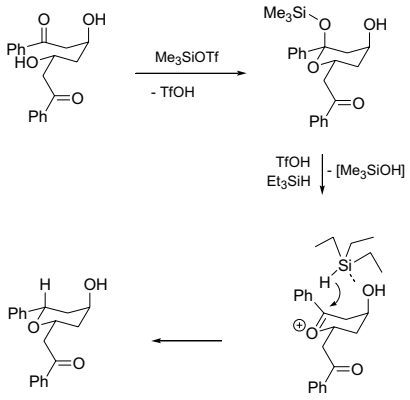
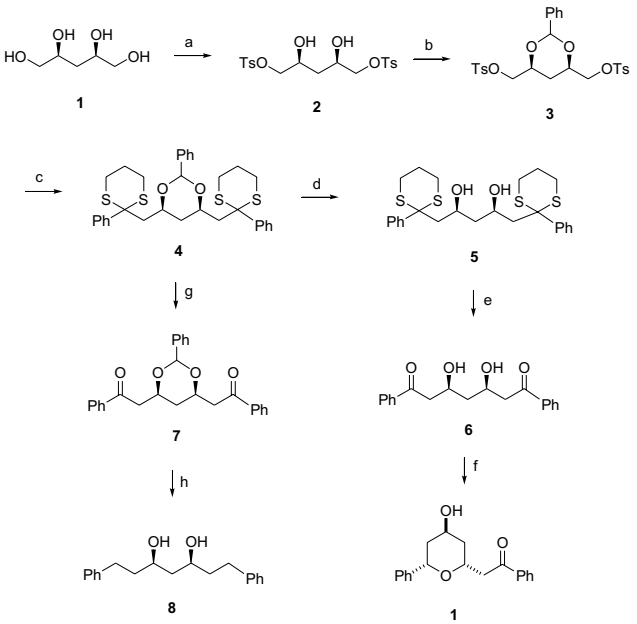
Scheme II Reductive cyclization



Scheme III



Reagents and conditions: (a) TsCl, py, DMAP, 0 °C, 36%; (b) $PhCH(OMe)_2$, CH_2Cl_2, r.t., 77%; (c) LDA, DMPU,-40 °C to 0 °C, 78%; (d) 80% HOAc, 60 °C, 74%; (e) MeCN/sat.$NaHCO_3$, I_2, 0 °C, 64%; (f) Et_3SiH, Me_3SiOTf, 0 °C, 42%; (g) HgO, $BF_3.Et_2O$, THF/H_2O, 82%; (h) H_2, $Pd(OH)_2$/C, EtOH, 35 °C, 72%.

RESULTS AND DISCUSSION

The point of departure in this work was ditosylate **2**.[11,12] The optimal conditions we found involves tosylation of **1** in pyridine at 0 °C for 12 h, but a yield of only 36% was obtained. The next step was protection[13] of the free hydroxyl groups in the form of a 2-phenyl-1,3-dioxane derivative. While benzylidenation with benzaldehyde was inefficient, transacetalization with benzaldehyde dimethyl acetal proved satisfactory, **3** was produced in 77% yield.

Next, two benzal units were introduced to complete the required chain length by way of dithiane alkylation. Thus, exposure of 2-lithio-2-phenyl-1,3-dithiane that was generated in THF at -40 °C to **3** afforded the desired product **4** (78% yield). Raising the reaction temperature to 0 °C ensured complete conversion of the mono-dithianated tosylate to **4**. Desulfurization[14] of **4** was performed with red HgO and BF_3 etherate in 15% aq. THF (Yield 82%).

It is evident that intermediates **4**, **5**, and **7** can be readily converted into yashabushidiol A (**8**). We arbitrarily chose **7** to complete the conversion and found the combined debenzylidenation and reduction[13] proceed better with the $Pd(OH)_2$/C catalyst than the more common Pd/C; yashabushidiol A was obtained in 72% yield.

Finally, the debenzylidenation[13] and desulfurization[14] were achieved in 74% and 64% yields, respectively. The key transformation was the treament of **6** with Me_3SiOTf, then Et_3SiH, in a salt-ice bath for 15 minutes, thereby affording the target molecule (±)-diospongin A in 42% yield.

In summary, a consolidated synthetic route to (±)-diospongin A and yashabushidiol A from the (2*SR*,4*RS*)-pentane-1,2,4,5-tetraol (**1**) has been developed, featuring formation of a *cis*-disubstituted tetrahydropyran and desymmetric cyclization followed by reduction of a *meso*-1,7-diarylheptanoid.

EXPERIMENTAL

All solvents and reagents were dried prior to use. Diisopropylamine was distilled from calcium hydride, and THF from sodium benzophenone. *n*-Butylithium in hexane was purchased from Alfa and titrated before use. Thin-layer chromatography plates were visualized by exposure to UV light and/or immersion in a phosphomolybdic acid solution followed by heating on a hot plate. Flash chromatography was carried out utilizing 200-300 mesh silica gel. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, or a deuterated solvent otherwise indicated, on the Varian Mercury-plus 600 or Bruck 400 M instrument, for ^1H NMR spectral data are reported in *ppm* relative to chloroform (δ = 7.26 ppm) or deuterium oxide (δ = 4.68 ppm) as internal standard and ^{13}C NMR data are reported in *ppm* relative to chloroform (δ = 77.0 ppm) as internal standard. High-resolution mass spectral analysis (HRMS) data were measured on the Bruker Spexll by means of the ESI technique.

(2*SR*,4*RS*)-Pentane-1,2,4,5-tetraol (1)

Prepared in the same manner as described in ref. 10.

White solid; m.p. 37 °C; IR (KBr): 3381, 2940, 1648, 1421, 1224, 1059, 1142, 921, 785, 623, 586 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 3.91-3.85 (2H, m), 3.64 (2H, dd, *J* = 12, 4 Hz), 3.50 (2H, dd, *J* = 12, 6.4 Hz), 1.75-1.68 (1H, m), 1.64-1.56 (1H, m). ^{13}C NMR (100 MHz, D_2O): δ = 69.4, 65.1, 35.5. MS (ESI): ($M+Na^+$) 159.

(2*SR*,4*RS*)-Pentane-1,2,4,5-tetraol 1,5-ditosylate (2)

A solution of **1** (534 mg, 3.93 mmol) in distilled pyridine (8.9 mL) at 0 °C was stirred with DMAP (48 mg, 0.39 mmol) and TsCl (1.646 g, 8.64 mmol). After 12 h the reaction was quenched with aq. HCl (2N, 20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic solutions were dried over anhydrous Na_2SO_4 filtered and evaporated in vacuo to afford a residue which was chromatographed (CH_2Cl_2/EtOAc 6:1) to give **2** as a colorless oil.

Yield: 627 mg (36%). IR (KBr): 3415, 2950, 1738, 1358, 1175, 1097, 969, 816, 667, 554 cm^{-1}. ^1H NMR: δ = 7.78 (4H, d, *J* = 8.4 Hz), 7.36 (4H, d, *J* = 8 Hz), 4.09 (2H, dd, *J* = 8.8, 3.6 Hz), 3.93 (4H, d, *J* = 5.2 Hz), 3.37 (2H, s), 2.46 (6H, s), 1.67-1.52 (2H, m); ^{13}C NMR: δ = 145.3, 132.2, 130, 128, 73, 68.9, 34.5, 21.6. HRMS (ESI): *m/z* ($M+NH_4^+$) calcd for $C_{19}H_{24}O_8S_2$: 462.1251; found: 462.1244.

(2*SR*,4*RS*)-Pentane-1,2,4,5-tetraol 2,4-*O*-benzylidene 1,5-ditosylate (3)

To a solution of **2** (325 mg, 0.73 mmol) and $PhCH(OMe)_2$ (197 μL, 1.31 mmol) in dry CH_2Cl_2 (8 mL) under argon was added camphorsulfonic acid (17 mg, 0.073 mmol). The mixture was stirred for 12 h at room temperature, evaporated under high vacuum, and chromatographed (CH_2Cl_2/EtOAc 3:1) to afford **3** as a white solid; m.p. 115 °C.

Yield: 287 mg (77%). IR (KBr): 1596, 1456, 1355, 1193, 1017, 986, 917, 808, 667, 554 cm^{-1}. ^1H NMR: δ = 7.76 (4H, d, *J* = 8.4 Hz), 7.32-7.27 (11H, m), 5.42 (1H, s), 4.09 (4H, d, *J* = 8 Hz), 4.03-4.01 (2H, m), 2.45 (6H, s), 1.48-1.40 (1H, m), 1.27-1.24 (1H, m); ^{13}C NMR: δ = 145, 137.1, 132.5, 129.8, 129, 128.1, 127.9, 126.1, 100.5, 73.3, 71, 28.6, 21.6. HRMS (ESI): *m/z* ($M+NH_4^+$) calcd for $C_{26}H_{28}O_8S_2$: 550.1564; found: 220.1559.

(4*RS*,6*SR*)-2-Phenyl-4,6-bis(2-phenyl-1,3-dithian-2-yl) methyl-1,3-dioxane (4)

2-Phenyl-1,3-dithiane (528 mg, 0.27 mmol) in dry THF (4 mL) was added dropwise over 10 min into a freshly prepared LDA solution in THF (from 2.7 mmol of diisopropylamine and *n*-BuLi at -40 °C under argon, followed by DMPU (0.24 mL, 2.0 mmol)). After addition of **3** (358 mg, 0.67 mmol in THF) the mixture was stirred at 0 °C for 6 h. Quenching the reaction with satd. NH_4Cl (3 mL) was followed by warming to room temperature, washing with satd. NaCl (3 × 3 mL) and water, drying and concentrating, which gave the crude product. Purification by column chromatography (hexane/EtOAc 15:1) afforded **4** as a white solid, m.p. 53 °C.

Yield: 301 mg (78%). IR (KBr) 3057, 2906, 1594, 1486, 1277, 1028, 909, 732, 701 cm^{-1}; ^1H NMR: δ = 7.93 (4H, d, *J* = 7.6 Hz), 7.36 (4H, t, *J* = 8 Hz), 7.27-7.22 (5H, m), 7.17-7.15 (2H, m), 5.18 (1H, s), 3.84-3.80 (2H, m), 2.71-2.67 (8H, m), 2.46 (2H, dd, *J* = 14.8, 6.8 Hz), 2.05 (2H, dd, *J* = 15.2, 2.8 Hz), 1.92-1.90 (4H, m), 1.35-1.17 (2H, m). ^{13}C NMR: δ = 141.6, 138.3, 128.7, 128.5, 127.9, 127.6, 125.9, 9.2, 72.9, 57.3, 50.6, 38.3, 27.63, 27.59, 24.75. HRMS (ESI): *m/z* ($M+H^+$) calcd for $C_{32}H_{36}O_2S_4$: 581.1671; found: 581.1669.

(2*SR*,4*RS*)-1,5-Bis(2-phenyl-1,3-dithian-2-yl)pentane-2,4-diol (5)

Compound **4** (291 mg, 0.503 mmol) was dissolved in 80% acetic acid (15 mL) and warmed at 60 °C for 12 h. After neutralization with 3N NaOH, it was extracted with EtOAc (3 × 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and chromatographed (hexane/EtOAc 4:1) to yield **5** as a colorless oil.

Yield: 183 mg (74%). IR (KBr) 3445, 3056, 2905, 1594, 1484, 1099, 909, 732, 701 cm^{-1}. ^1H NMR: δ = 7.87 (4H, d, *J* = 7.6 Hz), 7.40-7.26 (6H, m), 3.91-3.86 (2H, m), 3.09 (2H, s), 2.74-2.69 (8H, m), 2.24 (2H, dd, *J* = 14.8, 7.6 Hz), 1.99-1.92 (6H, m), 1.46-1.42 (1H, m), 1.1-1.05 (1H, m); ^{13}C NMR: δ = 141.7, 128.8, 128.3, 127.3, 68.5, 57.3, 52.1, 44.2, 27.74, 27.39, 24.7. HRMS (ESI): *m/z* ($M+Na^+$) calcd for $C_{25}H_{32}O_2S_4$: 515.1177; found: 515.1167.

(3*SR*,5*RS*)-3,5-Dihydroxy-1,7-diphenylheptane-1,7-dione (6)

Compound **5** (126 mg, 0.26 mmol) was dissolved in a mixture of MeCN and satd. $NaHCO_3$ (6 mL, 1:1), kept at 0 °C, and treated with I_2 (260 mg, 1.02 mmol) for 45 min, and quenched with satd. $Na_2S_2O_3$/$NaHCO_3$ (6 mL, 1:1). The aqueous phase was extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4, and purified by column chromatography (hexane/EtOAc 2:1) to furnish **6** as a colorless oil.

Yield: 51 mg (64%). IR (KBr) 3432, 3061, 2924, 1679, 1448, 1212, 754, 691 cm^{-1}. ^1H NMR: δ = 7.97-7.95 (4H, m), 7.61-7.57 (2H, m), 7.50-7.46 (5H, m), 4.61-4.55 (2H, m), 4.03 (2H, br), 3.21-3.19 (4H, m), 1.85-1.81 (2H,

m), 1.64 (2H, br); ^{13}C NMR: δ = 200.1, 136.7, 133.6, 128.69, 128.11, 68.1, 45.3, 41.9. HRMS (ESI): *m/z* (M+Na$^+$) calcd for $C_{19}H_{24}O_4$: 335.1254; found: 335.1257.

(3*SR*,5*RS*)-3,5-*O*-Benzylidene-1,7-diphenylheptane-1,7-dione (7)

Compound **4** (55 mg, 95 μmol) and HgO (83 mg, 0.38 mmol) was dissolved in aqueous THF (2.3 mL, 15% H_2O) under argon, treated with BF_3 etherate (40 μL, 0.38 mmol) and stirred at room temperature for 1.5 h. After filtration through celite the reaction mixture was washed with EtOAc (3 × 5 mL) and chromatographed (hexane/EtOAc 6:1) to afford **7** as a white solid, m.p. 72 °C.

Yield: 31 mg (82%). IR (KBr) 3381, 3056, 2917, 1958, 1684, 1350, 1112, 753, 693 cm^{-1}. ^{1}H NMR: δ = 7.98 (4H, d, *J* = 7.2 Hz), 7.58 (2H, t, *J* = 7.2Hz), 7.49-7.45 (4H, m), 7.39-7.28 (5H, m), 5.67 (1H, s), 4.65-4.60 (2H, m), 3.50 (2H, dd, *J* = 16.4, 6.4 Hz), 3.08 (2H, dd, *J* = 16.4, 6.4 Hz), 2.06 (1H, d, *J* = 12.8 Hz), 1.61 (1H, d, *J* = 12.8 Hz); ^{13}C NMR: δ = 197.5, 138.3, 137.2, 133.4, 128.71, 128.37, 128.19, 126.1, 100.8, 73.3, 44.8, 37.1. HRMS (ESI): *m/z* (M+NH$_4^+$) calcd for $C_{26}H_{24}O_4$: 418.2013; found: 418.2018.

Yashabushidiol A (8)

Compound **7** (19 mg, 48 μmol) and 29 mg (20%) $Pd(OH)_2$/C was saturated with hydrogen in 3.5 mL of EtOH, stirred at 35 °C for 3.5 h. The mixture was filtered through celite and chromatographed (hexane/EtOAc 2:1) to afford yashabushidiol A (**8**) as a colorless oil.

Yield: 10 mg (73%). IR (KBr) 3347, 2933, 1494, 1452, 1104, 746, 699 cm^{-1}. ^{1}H NMR (600 MHz): δ = 7.29-7.25 (4H, m), 7.20-7.18 (6H, m), 3.89-3.85 (2H, m), 2.94 (2H, s), 2.78-2.74 (2H, m), 2.74-2.65 (2H, m), 1.84-1.74 (4H, m), 1.64-1.54 (2H, m); ^{13}C NMR: δ = 141.8, 128.44, 128.39, 125.9, 72.4, 43.0, 39.7, 31.6. HRMS (ESI): *m/z* (M+H$^+$) calcd for $C_{19}H_{24}O_2$: 285.1849; found: 285.1843.

(±)-Diospongin A

To the solution of **6** (16 mg, 51 μmol) in dry CH_2Cl_2 (4 mL) was added Et_3SiH (0.16 mL, 1 mmol), cooled to -18 °C, and then TMSOTf (11 μL). After 15 min, the reaction was quenched with saturated $NaHCO_3$ (1 mL) and the aqueous phase was extracted with ethyl ether (3 × 5 mL). The combined organic extract was washed with water and brine, dried over anhydrous Na_2SO_4, and purified by column chromatography (hexane/EtOAc 2:1) to yield diospongin A as a colorless oil.

Yield: 6.4 mg (42%). IR (KBr) 3407, 3061, 2922, 1679, 1212, 1060, 751, 695 cm^{-1}. ^{1}H NMR: δ = 8.0-7.98 (2H, m), 7.58-7.44 (3H, m), 7.30-7.22 (5H, m), 4.93 (2H, dd, *J* = 11.6, 2 Hz), 4.68-4.61 (1H, m), 4.38 (1H, s), 3.42 (1H, dd, *J* = 16, 5.6 Hz), 3.06 (1H, dd, *J* = 16, 6.8 Hz), 2.04-1.94 (2H, m), 1.8-1.66 (2H, m), 1.60 (1H, br), 1.55 (4H, s); ^{13}C NMR: δ = 198.2, 142.7, 137.4, 133.1, 128.5, 128.3, 128.3, 127.2, 125.8, 73.8, 69.1, 64.7, 45.2, 40.1, 38.5. HRMS (EI): *m/z* (M+H$^+$) calcd for $C_{19}H_{20}O_3$: 297.1485; found 297.1479.

ACKNOWLEDGEMENTS

We are grateful to the National Natural Science Foundation (NSFC, 20772051) and the Ministry of Education (Program "111" and NCET-05-0880), People's Republic of China, for financial support.

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