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# Synthesis of diospongin A

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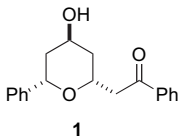
**Abstract**—A stereoselective synthesis of Diospongin A using a cross-metathesis–intramolecular Michael addition has been achieved.


## 1. Introduction

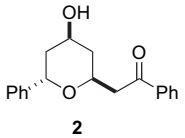
The sterocontrolled synthesis of tetrahydropyrans remains a topic of current interest due to the wide range of naturally occurring tetrahydropyrans, and the biological activity displayed by some of these compounds.

Diospongin A **1**, along with its diastereomer Diospongin B **2**, have recently been isolated from *Dioscorea spongiosa*.[1] It was further reported that Diospongin A shows anti-osteoporotic activity.[1] Sawant and Jennings have recently reported the syntheses of both isomers and rigorously confirmed the stereochemistry of the two.[2] A synthesis of diospongin has been reported by Chandrasekhar, but the data given is not in agreement with literature values.[3]

We have recently been interested in the combination of cross-metathesis[4] and intramolecular hetero-Michael addition as a route to various heterocycles.[5] The advantages of this approach are the ease with which the precursors can be assembled, the efficiency of cross-Metathesis using the Grubbs' second generation catalyst and the inherent atom-efficiency of the combination. Diospongin A **1** is an ideal candidate to extend this concept to tetrahydropyrans. The hetero-Michael addition[6] is one of a number of methods that may be used to construct tetrahydropyrans.[7]



**1**

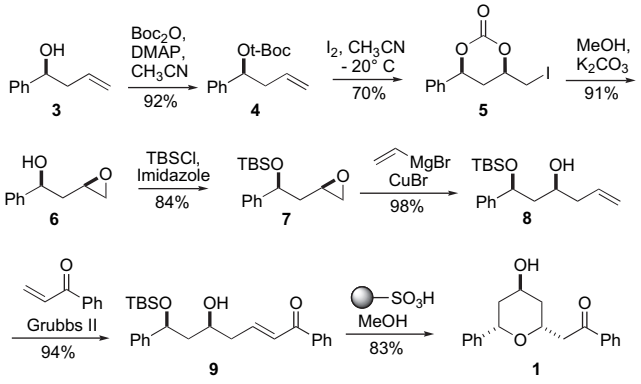


**2**

## 2. Results and discussion

To prepare the precursor for cross-metathesis, (*S*)-phenylbutenol[8] **3** was converted to the corresponding *tert*-butyl carbonate **4**.[9] Iodocyclisation proceeded as reported by Bartlett et al. and Cardillo et al., except that a reaction temperature of −20 °C was employed (Scheme 1).[10,11] Methanolysis of the resulting iodocarbonate **5** in the presence of potassium carbonate yielded the epoxy alcohol **6** as a single diastereoisomer. This compound was protected as its TBS ether **7**. Ring opening with commercially available vinyl magnesium bromide in the presence of copper(I) bromide cleanly yielded the homoallylic alcohol **8**.[12]

Homoallylic alcohol **8** underwent clean and efficient cross-metathesis with phenyl vinyl ketone using 5 mol % of the Grubbs' second generation catalyst, added gradually as a dichloromethane solution during the course of the reaction. This technique was found to be essential to obtain high yields. The cross-metathesis product **9** was found to be a single, *trans*-alkene isomer. Exposure of ketone **9** to amberlyst 15 in methanol resulted in tandem deprotection–cyclisation




**Scheme 1**. Diospongin A synthesis.

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to yield diospongin A **1** as the only product. The spectroscopic data and the optical rotation of the synthetic material {−23.9 (*c* 1, $CH_2Cl_2$); lit.: −21.2 (*c*=0.8, $CHCl_3$)} are in good agreement with those reported for the natural product. The ee of the synthetic sample was determined to be 94–95% by chiral HPLC (ODH column, 1% isopropanol in hexane at a flow rate of 1 mL/min).

## 3. Conclusion

Whether the formation of the *cis*-isomer **1** is for kinetic or thermodynamic reasons is unclear. Nevertheless, this constitutes an efficent and easily executed synthesis of tetrahydropyrans, and provides further confirmation of the structure of diospongin A **1**. Applications to other natural products in this class as well as other heterocycles, are in hand.

## 4. Experimental

### 4.1. General

THF was distilled from sodium/benzophenone, dichloromethane was distilled from calcium hydride and methanol was distilled from activated magnesium. Other reagents and solvents were commercial and used as received.

IR spectra were recorded on a Bio-Rad FTS 165 spectrometer either neat or as Nujol mulls using NaCl plates. $^1$H NMR spectra were recorded on a Bruker Advance DPX300 at 300 MHz with residual protic solvent as the reference. $^{13}$C spectra were recorded at the corresponding frequency on the same instrument. Chemical shifts are in parts per million and coupling constants, *J*, are in hertz. Mass spectra were recorded on a Finnigan Trace GC Ultra instrument at 70 eV with EI mode. High-resolution mass spectra were recorded on a Finnigan MAT95XP instrument, also using EI mode. Specific rotations, $[\alpha]_D$, were recorded on an Jasco P-1030 polarimeter and are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Elemental analysis was carried out at Nanyang Technological University.

**4.1.1. 3,4-Epoxy-1-*tert*-butyldimethylsiloxy-1-phenylbutane (7).** TBSCl (300 mg, 2 mmol) and imidazole (130 mg, 2 mmol) were added to a solution of the epoxide (**6**)[10–12] (160 mg, 1 mmol) in THF (10 mL). The mixture was stirred overnight. Saturated $NH_4Cl$ solution (10 mL) was added and the mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (7 g) (hexane/ethyl acetate, 90/10) to afford the silyl ether (**7**) as a colourless oil (230 mg, 84%), $R_f$=0.75 (25% ethyl acetate/hexane); $[\alpha]_D^{22}$ −42.0 (*c* 1.25, $CH_2Cl_2$); $\nu_{max}$/cm$^{-1}$ 2955, 2928, 2857, 1636, 1256, 1092, 1065; $\delta_H$ (300 MHz; $CDCl_3$) −0.13 (s, 3H, $CH_3$), 0.03 (s, 3H, $CH_3$), 0.87 (s, 9H, $3CH_3$), 1.77 (dt, 1H, *J*=14, 6, H-2), 2.06 (dt, 1H, *J*=14, 6.5, H-2), 2.44 (dd, 1H, *J*=5, 2.5, H-4), 2.70 (t, 1H, *J*=5, H-4), 2.82–2.89 (m, 1H, H-3), 4.86 (t, 1H, *J*=6.5, H-1), 7.23–7.34 (m, 5H, ArH); $\delta_C$ (75 MHz; $CDCl_3$) 144.4, 128.2, 127.3, 125.9, 73.1, 49.6, 47.0, 43.7, 25.8, 18.1, −4.7, −5.1; *m/z* 276, 261, 221, 92; HRMS Found 278.1684 ($M^+$, $C_{16}H_{26}O_2Si$ requires 278.1697).

**4.1.2. 1-(*tert*-Butyldimethylsiloxy)-1-phenylhex-5-en-3-ol (8).** Copper(I) bromide (36 mg, 0.23 mmol) was added to a solution of TBS ether (**7**) (130 mg, 0.47 mmol) in THF (4 mL). The mixture was cooled to −20 °C. Vinyl magnesium chloride (1.25 mL, 1.87 mmol, 1.6 M in THF) was added at −20 °C and the mixture was stirred for 1 h. Saturated $NH_4Cl$ solution (5 mL) was added −20 °C and the mixture was allowed to warm to room temperature and extracted twice with ethyl acetate (2×10 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product (**8**) (140 mg, 98%) was used directly in the next step; $[\alpha]_D^{22}$ −40.4 (*c* 1.25, $CH_2Cl_2$); $\nu_{max}$/cm$^{-1}$ 3435, 2955, 2930, 2897, 2886, 2857, 1641, 1257, 1083, 1063; $\delta_H$ (300 MHz; $CDCl_3$) −0.25 (s, 3H, $CH_3$), 0.04 (s, 3H, $CH_3$), 0.89 (s, 9H, $3CH_3$), 1.75 (ddd, 1H, *J*=2.5, 4.5, 14.5, H-2), 1.86 (ddd, 1H, *J*=9.9, 14.5, H-2), 2.20–2.26 (m, 2H, H-4), 3.31 (s, 1H, OH), 3.85–3.9 (m, 1H, H-3), 4.87 (dd, 1H, *J*=9, 4.5, H-1), 5.05–5.13 (m, 2H, =CH), 5.74–5.86 (m, 1H, =CH), 7.29–7.57 (m, 5H, ArH); $\delta_C$ (75 MHz; $CDCl_3$) 144.7, 134.7, 128.3, 127.5, 126.0, 117.5, 76.4, 70.5, 46.5, 42.0, 25.8, 18.0, −4.4, −5.1; *m/z* 307, 289, 249, 159; HRMS Found 307.2100 ($MH^+$, $C_{18}H_{31}O_2Si$ requires 307.2093).

**4.1.3. (*E*)-7-(*tert*-Butyldimethylsiloxy)-5-hydroxy-1,7-diphenylhept-2-en-1-one (9).** Grubbs' second generation catalyst (14 mg, 0.0165 mmol) in dichloromethane (5 mL) was added gradually to a solution of phenyl vinyl ketone (130 mg, 1 mmol) and the TBS ether (**8**) (100 mg, 0.36 mmol) in $CH_2Cl_2$ (6 mL). The mixture was heated at reflux for 3 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (7 g) (hexane/ethyl acetate, 99/1) to give enone (**9**) as a colourless oil (140 mg, 94%), $R_f$=0.16 (5% ethyl acetate/hexane); $[\alpha]_D^{29}$ −31.5 (*c* 1.0, $CH_2Cl_2$); $\nu_{max}$/cm$^{-1}$ 3428, 3065, 2955, 2930, 1645, 1612, 1083, 1063; $\delta_H$ (300 MHz; $CDCl_3$) −0.28 (s, 3H, $CH_3$), 0.01 (s, 3H, $CH_3$), 0.85 (s, 9H, $3CH_3$), 1.78 (ddd, 1H, *J*=14.5, 4, 2, H-6), 1.91 (m, 1H, H-6), 2.36–2.53 (m, 2H, H-4), 3.73 (br s, 1H, OH), 3.97–4.03 (m, 1H, H-3), 4.89 (dd, 1H, *J*=9.5, 4.0, H-1), 6.88 (d, 1H, *J*=15.5, =CH), 7.02 (dt, 1H, *J*=15.5, 8, =CH), 7.29–7.57 (m, 10H, ArH); $\delta_C$ (75 MHz; $CDCl_3$) 190.3, 145.3, 144.3, 137.7, 132.5, 128.5, 128.4, 128.3, 128.0, 127.5, 125.8, 76.2, 70.0, 46.6, 40.8, 25.7, 17.9, −4.5, −5.2; *m/z* 392, 281, 207, 115, 75; HRMS Found 392.2161 ($M^+-H_2O$, $C_{25}H_{32}O_2Si$ requires 392.2172).

**4.1.4. Diospongin A (1).** Amberlyst 15 (70 mg) was added to a solution of enone (100 mg, 0.244 mmol) in methanol (3 mL) and the mixture was stirred at room temperature for 3 h. The mixture was filtered through Celite and the volatiles were evaporated. The residue was purified by flash chromatography on silica gel (5 g) (hexane/ethyl acetate, 1/1) to afford diospongin A (**1**) as a colourless solid (60 mg, 83%) mp 102–103 °C, $R_f$=0.3 (1:1 ethyl acetate/hexane); $[\alpha]_D^{22}$ −23.9 (*c* 1.0, $CH_2Cl_2$). Found: C, 77.07; H, 6.62%. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80%; $\nu_{max}$/cm$^{-1}$ 3325, 1744, 1682, 1211, 1063; $\delta_H$ (300 MHz; $CDCl_3$)[14] 1.63–1.80 (m, 2H, H-4, 6), 1.94 (m, 1H, H-6), 1.98 (m, 1H, H-4), 3.08 (dd, 1H, *J*=16, 7, H-2), 3.42 (dd, 1H, *J*=16, 6, H-2), 4.37 (app. quin., 1H, *J*=3, H-5), 4.65 (m, 1H, H-3), 4.94 (dd, 1H, *J*=12, 2, H-7), 7.21–7.6 (m, 8H, ArH), 7.97–7.99 (m, 2H, ArH); $\delta_C$ (75 MHz; $CDCl_3$)

198.3, 142.7, 137.3, 133.1, 128.6, 128.3, 128.2, 127.3, 125.8, 73.8, 69.1, 64.7, 45.2, 40.0, 38.5.

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## Note added in proof

During the preparation of this manuscript, a related synthesis was reported by Cossy et al.[13]

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