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Synthesis of tetrahedral diarylheptanoid *ent*-diospongin A and *epimer*-diospongin B by employing Julia–Kocienski olefination

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ABSTRACT

Total synthesis of *ent*-diospongin A and *epimer*-diospongin B has been accomplished in good yield with high optical purity. The key steps of diospongin synthesis involve Julia–Kocienski olefination, Weinreb amide formation, Grignard reaction, reduction, acetonide deprotection, Lewis acid catalyzed cyclization, and Wacker oxidation.

Diaryl heptanoids are biologically active natural products isolated from Asian herbs or plants.[1] They exhibit anti-oxidant,[2] anti-cancer,[3] and anti-inflammatory[4] pharmacological activity.[5] A new class of diaryl heptanoids diospongin A (**1**) and B (**2**) were first isolated by Kadota et al. from rhizomes of Dioscorea spongiosa.[6] According to the literature evidence, these tetrahydropyran derivatives showed potent anti-osteoporotic activity in a bone organ culture. These new derivatives possess a six-membered cyclic ether as core structure with two aromatic side chains. Diospongins gained the attention of synthetic organic chemists and various approaches have been reported in the literature (Fig. 1).[7,8]

Yadav et al. reported the synthesis of diospongin using Prins cyclization as a key reaction followed by an enzymatic resolution.[9a] Jennings and co-workers[9b] reported the stereo selective reduction of an oxocarbenium cation obtained from δ-lactone as key strategy. Olivier Piva and co-workers[9c] reported the synthesis of diospongin A (**1**) beginning with Grignard reaction of an aldehyde with an ally magnesium bromide followed by Prins cyclization of keto alcohol with benzaldehyde. Kumaraswamy and co-workers[9d] reported the enantioselective total synthesis of diospongins A, B, and their corresponding enantiomers by employing (i) catalytic asymmetric hetero-Diels–Alder reaction, (ii) diastereoselective rhodium-(I)-catalyzed 1,4-addition, and (iii) catalytic asymmetric transfer hydrogenation (CATHy) reaction.

As part of our continued efforts to develop new synthetic methodologies[10] to synthesize biologically active natural and unnatural products, herein we describe a concise total synthesis of diospongins from the easily accessible starting materials in good yield. The retro synthesis of the target molecule is illustrated in Scheme 1.

The synthesis of *ent*-diospongin A (**3**) and *epimer*-diospongin B (**4**) was initiated with sulfone **18** as the key starting material. The latter was synthesized as per the literature procedure with minor modifications.[11a] The optically pure sulfone **18** was subjected to the Julia–Kocienski olefination reaction[11a,b] with benzaldehyde **17** to selectively afford *E* olefin ester **16** in 92:8 ratio of *E*:*Z* diastereomers.

The reaction was carried out with LiHMDS as base in THF under Barbier conditions,[12] which resulted in 92% conversion with *E*:*Z* ratio of 11.5:1. Our attempts to improve the *E*:*Z* ratio further by altering the reaction conditions as well as using different bases were not successful. The crude olefin ester **16** obtained after Julia–Kocienski reaction was purified by column chromatography to remove impurities other than the diastereomers obtained to afford the pure mixture in 85% yield as pale yellow liquid which

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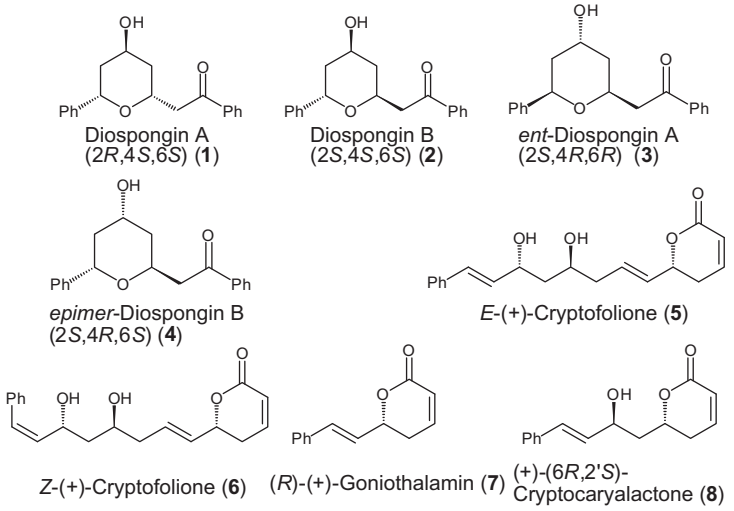
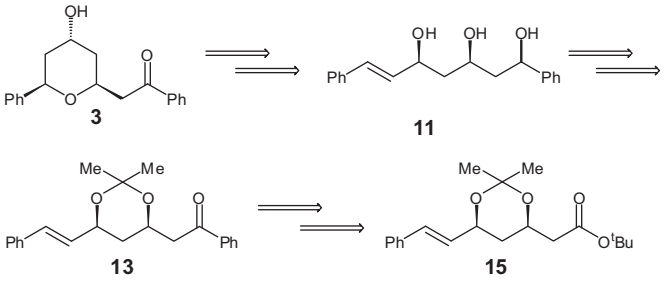


Figure 1. Biologically active natural products of diaryl heptanoids.

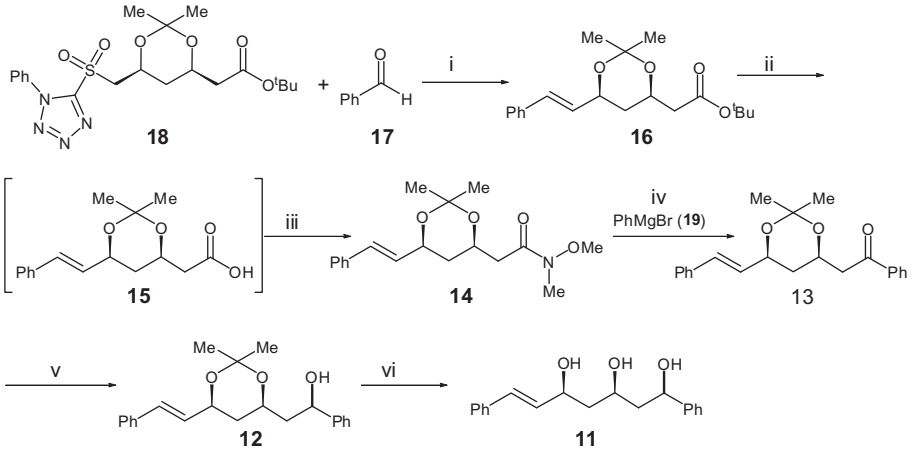


Scheme 1. Retro synthetic approach of **3**.

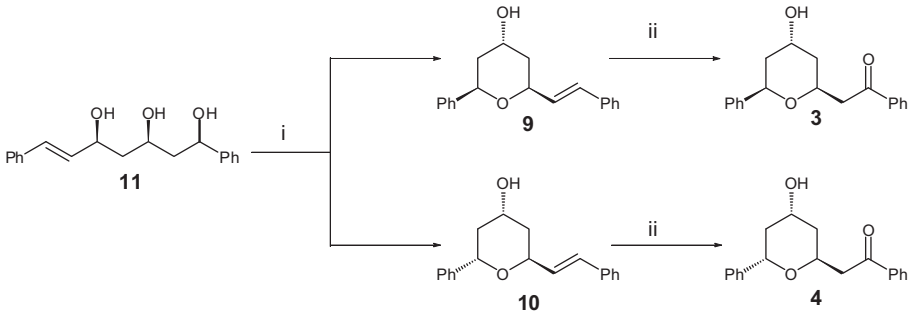
slowly solidified upon cooling to 0–10 °C over a period of 48 h as an off-white solid.

The diastereomeric mixture **16** with major *E*-isomer was subjected to ester hydrolysis using methanolic alkali. The acid **15** thus obtained due to hydrolysis of the ester was found unstable and degrading to various by products on standing. Therefore **15** was immediately converted to its corresponding Weinreb amide **14** using the reported conditions.[13] Weinreb amide **14** was treated with phenyl magnesium bromide to afford benzoyl derivative **13** in good yield. Attempts to reduce the keto carbonyl diastereoselectively either by using *anti* or *syn* selective reagents such as tetrabutylammonium triacetoxyborohydride, and diethyl methoxy borane, respectively, were unsuccessful.[14] These reactions were either found to be very sluggish or often associated with formation of several impurities. However, the reduction of **13** was carried out under Luche conditions[15] $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ to afford the secondary alcohol **12** as mixture of diastereomers (Scheme 2).

The acetonide of intermediate **12** was deprotected treating with oxalic acid in acetonitrile to afford the triol **11**. The stage is set for performing the Lewis acid catalyzed cyclization. Thus treatment of **11** with $FeCl_3$ furnished the cyclized products **9** and **10** together in 66% yield.[16] The diastereomeric mixture was successfully separated by column chromatography to furnish pure diastereomers of styryl tetrahydro pyranol derivatives **9** and **10** in 40% and 26% yields, respectively. Individually both **9** and **10** were subjected to the Wacker oxidation as per the procedure reported by Kawai et al. and Reddy et al.[17] which yielded the *ent*-diospongin A (**3**) and *epimer*-diospongin B (**4**), respectively.[18,19] The analytical results confirmed the configuration of the **3** and **4** as 2*S*,4*R*,6*R* for *ent*-diospongin A (**3**) and 2*S*,4*R*,6*S* epimer-diospongin B (**4**) (Scheme 3). The analytical data of **3** were in agreement with the reported data. The SOR obtained for **3** is $[\alpha]_D^{25} = 18.2$ (*c* 0.22, $CHCl_3$); Reported $[\alpha]_D^{27} = 19.2$ (*c* 0.26, $CHCl_3$).[17]



Scheme 2. Synthesis of **11**. Reagents and conditions: (i) 22% LiHMDS in THF, THF, −70 °C, *Y* = 85%. (ii) NaOH, MeOH, H_2O, reflux, *Y* = 82%. (iii) DCM, methoxy methyl amine HCl, diisopropyl carbodiimide, imidazole, *Y* = 70%. (iv) THF, *Y* = 85%. (v) MeOH, $NaBH_4$, $CeCl_{3.7}$, H_2O, *Y* = 91%. (vi) Oxalic acid, acetonitrile, H_2O, *Y* = 95%.



Scheme 3. Synthesis of **3** & **4**. Reagents and conditions: (i) $FeCl_3$, CH_2Cl_2, rt, 30 min, *Y* = 40.2 (**9**) and 26% (**10**). (ii) $PdCl_2$ (50 mol %) CuCl, O_2, DMF + H_2O, 50 °C, **3d** (*Y* = 45% of **3** and 38% of **4**).

In summary we have developed a concise and efficient synthesis of analogues of diospongin in good to moderate yield via a novel approach. The approach described herein utilizes easily accessible and commercially available raw materials. The application of this approach for the synthesis of substituted phenyl and hetero aryl derivatives is under progress and will be reported in due course of time.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.112.

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18. *Synthesis of 2-((2S,4R,6R)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethanone (ent-diospongin A) (**3**).* A mixture of alkene **9** (100 mg, 0.35 mmol), $PdCl_2$ (15.8 mg, 0.08 mmol), and CuCl (23.9 mg, 0.17 mmol) in DMF (3 mL) and H_2O (3 mL) was stirred at 50 °C for 3 days under an oxygen atmosphere. Evaporation of the solvent in vacuo and CC purification using 20% of EtOAc in hexanes afforded **3** (55 mg, 45%) as off-white solid. $[\alpha]_D^{25}$ +18.2 (*c* 0.22, $CHCl_3$); Reported $[\alpha]_D^{27}$ +19.2 (*c* 0.26, $CHCl_3$).[17] ^1H NMR (400 MHz, $CDCl_3$): 1.64–1.79 (m, 2H), 1.94 (d, *J* = 12.8 Hz, 2H), 3.08 (dd, *J* = 6.4, 15.6 Hz, 1H), 3.43 (dd, *J* = 6.0, 16 Hz, 1H), 4.37 (s, 1H), 4.63–4.66 (m, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 7.22–7.33 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 3H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 38.4, 40.0, 42.1, 45.1, 64.6, 69.0, 73.7, 125.7, 127.2, 128.2, 128.3, 128.5, 133.1, 137.2, 142.6 and 198.3. IR (Neat, cm^{-1}): 667, 693, 757, 976, 1058, 1216, 1378, 1682, 1732, 2853, 2925, 2956 and 3016. MS (ESI) *m/z:* 296 $[M+]^+$; HRMS (ESI): calcd for $C_{19}H_{21}O_3$, 297.1491, $[M+]^+$; found, 297.1477.
19. *Synthesis of 2-((2S,4R,6S)-4-hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethanone (epimer-diospongin B) (**4**).* The experimental procedure is the same as followed in the synthesis of compound **3**. Yield = 38%; $[\alpha]_D^{25}$ −7.66 (*c* 0.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 1.37 (d, *J* = 11.6 Hz, 1H), 1.52 (d, *J* = 12.4 Hz, 1H), 2.04–2.24 (m, 2H), 3.08 (dd, *J* = 6.8, 16.4 Hz, 1H), 3.45 (dd, *J* = 6.0, 16.4 Hz, 1H), 4.04–4.20 (m, 2H), 4.41 (d, *J* = 9.6 Hz, 1H), 7.24–7.56 (m, 8H), 7.96 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 37.5, 40.8, 42.4, 44.7, 64.6, 681, 72.4, 125.8, 126.4, 127.4, 128.1, 128.2, 128.5, 133.1, 137.1, 141.6, and 198.0 IR (Neat, cm^{-1}): 668, 698, 749, 981, 1062, 1215, 1365, 1449, 1685, 1728, 2852, and 2922. MS (ESI) *m/z:* 296 $[M+]^+$; HRMS (ESI): calcd for $C_{19}H_{21}O_3$, 297.1491, $[M+]^+$; found, 297.1496.