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Total synthesis of (+/−)-diospongin A via Prins reaction

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Abstract—A straightforward synthesis of (+/−)-diospongin A starting from benzaldehyde is described. A Prins cyclization reaction to control the relative configuration of the three stereogenic centers and a Mitsunobu inversion represent the key steps of the approach.

1. Introduction

Diarylheptanoids are a family of biologically active natural products isolated from Asian herbs or plants.[1–3] A well-known representative found in *Alpinia officinarum* Chinese medicinal herb is curcumin, which has various biological properties such as anticancer,[4] anti-inflammatory,[5] and anti-oxidative[6] activities (Fig. 1). The structure of diarylheptanoids is either linear or cyclic like in diarylether **1**, which was found to show antileishmanial activity.[7]

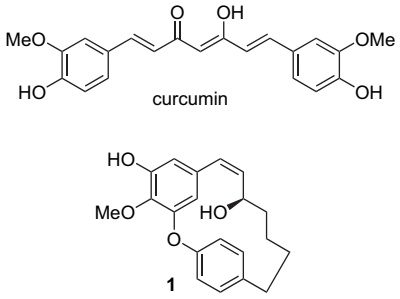

Figure 1. Linear and cyclic diarylheptanoids.

Among cyclic diarylheptanoids, some compounds present a tetrahydropyran ring in their structure. In particular, the calyxin natural products isolated from *Alpinia blepharocalyx* seeds show interesting cytotoxic activities (Fig. 2). The synthesis of several compounds of this family was reported using a strategy based on a Prins cyclization to form the core 2,4,6-*cis*-trisubstituted tetrahydropyran.[8,9] A new family of diarylheptanoids, diospongins, recently isolated from the rhizomes of *Dioscorea spongiosa* exhibit promising inhibitory activities on bone resorption and could be used for the treatment of osteoporosis, a skeletal disease.[10]

Tetrahydropyran is a very common subunit found in numerous natural products. Different strategies have already been designed to have a rapid access to these structures.[11] Among them, cyclizations of oxocarbenium ions and especially the Prins reaction have been extensively considered.[12,13] Suitable conditions are now at the disposal of organic chemists to avoid epimerization of the center directly linked to the oxygen atom, which could occur via an oxonia Cope rearrangement.[13a,14–18] Various parameters like the nature of the Lewis acid,[19–22] the solvent[23,24] or the source of heating,[25] have a profound impact on the efficiency of the reaction in terms of chemical yields and selectivities.

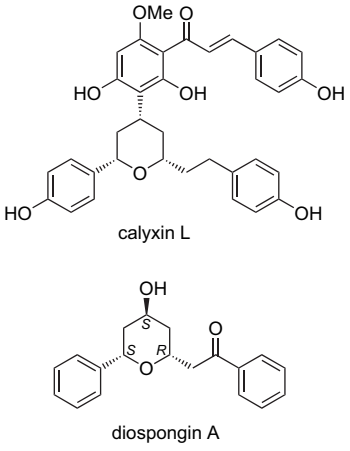

Figure 2. Tetrahydropyranyl diarylheptanoids.

Keywords: Diarylheptanoid; Tetrahydropyran; Diospongin A; Prins cyclization.
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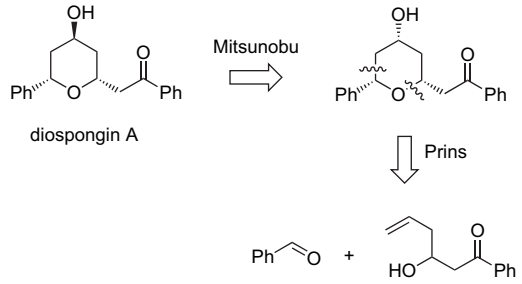
Due to the interesting antiosteoporotic activity of diospongins, syntheses of these natural products have been recently reported.[26–29] In particular, diospongin A was obtained either via a stereoselective reduction of the oxocarbenium derived from the corresponding lactol[27] or via an intramolecular oxy-Michael addition from the linear diarylheptanoid precursor obtained by cross metathesis[27,29] to form the tetrahydropyran ring. The rapid access to analogs of this biologically active natural product could lead to more active derivatives. In this purpose, the Prins reaction seemed to us a very powerful method to apply to the synthesis of diospongin A as it allows both the control of the three stereogenic centers on the tetrahydropyran ring and the rapid variation of the substrates, in particular the aldehyde counterpart and the nucleophile introduced in C4-position.

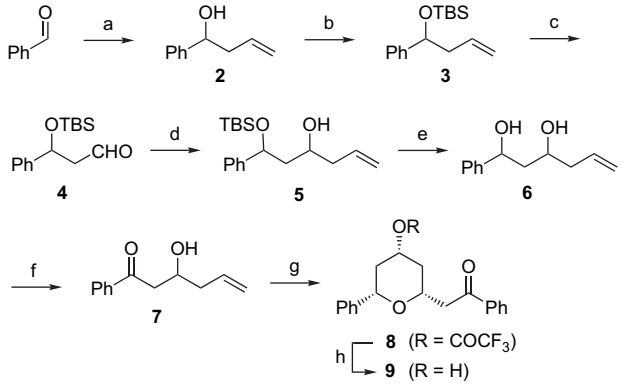
2. Results and discussion

Our strategy for the synthesis of (+/−)-diospongin A depicted on Scheme 1 is thus based on the formation of the 2,4,6-*cis*-trisubstituted tetrahydropyran ring via a Prins reaction carried out between benzaldehyde and homoallylic alcohol **7**. A final inversion step is then required to invert the C4-hydroxyl group.



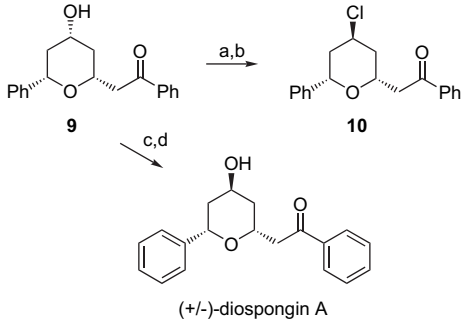
Scheme 1. Retrosynthetic analysis of diospongin A.

The homoallylic alcohol **7** was prepared from benzaldehyde in a straightforward sequence involving two allylation reactions and a selective oxidation of the benzylic alcohol **6** (Scheme 2). The TFA-promoted Prins reaction[30] between homoallylic alcohol **7** and benzaldehyde led to tetrahydropyran **8** as the sole diastereoisomers, which was directly saponified into the corresponding alcohol **9**, an epimer of diospongin A, in 83% yield over the two steps. To the best of our knowledge, this is the first example of an acid-mediated Prins cyclization using a β-hydroxyketone. The reaction proceeded in high yield and the potentially competing elimination to an enone was not observed.



Scheme 2. Reagents and conditions: (a) allylmagnesium bromide, Et_2O, 0 °C to rt, 100%; (b) TBDMSCl, imidazole, DMF, rt, 84%; (c) O_3, CH_2Cl_2, −60 °C then PPh_3, −60 °C to rt, 87%; (d) allylmagnesium bromide, Et_2O, 0 °C to rt, 92%; (e) TBAF, THF, rt, 97%; (f) MnO_2, CH_2Cl_2, reflux, 61%; (g) benzaldehyde, TFA, CH_2Cl_2, rt; (h) NaOH, MeOH, 83% (over two steps).

In order to invert in **9** the stereocenter bearing the hydroxyl group, a method described by Mukaiyama was first tested.[31] For compatibility reason with the ketone moiety, we had to slightly modify the procedure and used sodium hydride as base to assure the deprotonation of the alcohol. Instead of the expected *p*-methoxyphenylester, a nonpolar structure was isolated in 44% yield and identified as the corresponding chloride **10** (Scheme 3). This side reaction, which occurred with a total inversion of the sterocenter can be easily explained by a competitive attack of chloride ions on the activated intermediate alkoxyphosphine. The Mitsunobu reaction was next considered.[32–35] The reaction was carried out with *p*-nitrobenzoic acid and delivered the corresponding ester, which was further saponified into (+/−)-diospongin A.



Scheme 3. Reagents and conditions: (a) NaH, **7**, THF, 0 °C then diphenylphosphine chloride, 0 °C to rt; (b) 2,6-dimethylbenzoquinone, *p*-anisic acid, CH_2Cl_2, reflux (44% over two steps); (c) PPh_3, DEAD, *p*-nitrobenzoic acid, CH_2Cl_2, rt; (d) NaOH, MeOH, THF, H_2O (71%, over 2 steps).

3. Conclusion

In conclusion, we have achieved the total synthesis of (+/−)-diospongin A in 23% overall yield. A Prins reaction using an unsaturated β-hydroxyketone represents the key step to build the 2,4,6-*cis*-trisubstituted tetrahydropyran ring with a total diastereocontrol. This convergent route could allow a rapid access to diarylheptanoid analogs, in particular by variation of the aromatic aldehydes or the nucleophile used in the Prins reaction.

4. Experimental

4.1. General

^1H, ^{13}C, DEPT NMR spectra were recorded on a Brüker AM 300 MHz NMR spectrometer, which provided all necessary data for the full assignment of each compound. Chemicals shifts were reported in parts per million. High resolution mass spectrometry (HRMS) analyses were conducted using a ThermoFinigan-MAT 95 XL instrument. IR spectra were

measured on a Perkin–Elmer Spectrum One FTIR spectrometer. Melting points were measured on a B-540 Büchi apparatus. TLC analyses were performed on plates (layer thickness 0.25 mm) and were visualized with UV light, phosphomolybdic acid or *p*-anisaldehyde solution. Column chromatography was performed on silica gel (40–63 μm) using ethyl acetate (EtOAc) and hexanes as eluants. When appropriate, solvents and reagents were dried by distillation over appropriate drying agent prior to use. Diethyl ether and tetrahydrofuran were distilled from Na/benzophenone and used fresh. Dichloromethane was distilled from CaH_2.

4.1.1. 4-(*tert*-Butyldimethylsilyloxy)-4-phenylbut-1-ene (3). To a solution of 1-phenylbut-3-en-1-ol (1.48 g, 10 mmol) in 35 mL of dimethylformamide were added imidazole (1.02 g, 15 mmol) and *tert*-butyldimethylsilylchloride (1.808 g, 12 mmol) at rt. Upon completion, the reaction mixture was quenched with water (20 mL) and dichloromethane (20 mL) was added. The aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic layers were washed with an aqueous saturated ammonium chloride solution (3×40 mL), dried over $MgSO_4$ and concentrated in vacuo. A flash-chromatography (EtOAc/hexanes, 5:95 as eluent) afforded **3** as a colorless oil (2.20 g, 8.4 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.12 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 2.38 (dt, J_{AB}=13.9 Hz, J=5.3 Hz, 1H), 2.47 (dt, J_{AB}=13.9 Hz, J=7.2 Hz, 1H), 4.69 (dd, J=7.2, 5.3 Hz, 1H), 4.99–5.05 (m, 2H), 5.72–5.86 (m, 1H), 7.29–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.3, 18.6, 26.2, 45.9, 75.4, 117.2, 126.2, 127.3, 128.3, 135.6, 145.5. IR (neat) 3078, 2957, 2930, 2896, 2858, 1642, 1493, 1472, 1463, 1454, 1362, 1257, 1089, 1069, 1006, 914, 836, 776, 700 cm^{-1}; R_f=0.90 (EtOAc/hexanes, 5:95).

4.1.2. 3-(*tert*-Butyldimethylsilyloxy)-3-phenylpropanaldehyde (4). A solution of compound **3** (1.59 g, 6.05 mmol) in dichloromethane (60 mL) was cooled to −60 °C under nitrogen. Ozone was then bubbled through the solution until it became blue. The mixture was then flushed with nitrogen and triphenylphosphine (1.74 g, 6.7 mmol) was added. The solution was allowed to warm up to rt and after 3 h, methyl iodide (300 μL, 6.7 mmol) was added. After overnight stirring, the mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc/hexanes 5:95 to afford **4** as a colorless oil (1.40 g, 5.29 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.14 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 2.85–2.66 (m, 1H), 2.85 (ddd, J_{AB}=15.6 Hz, J=8.1, 2.6 Hz, 1H), 5.22 (dd, J=8.1, 4.0 Hz, 1H), 7.33–7.35 (m, 5H), 9.78–9.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.3, 18.4, 26.0 (3C), 53.3, 71.0, 126.0 (2C), 127.9, 128.8 (2C), 144.1, 201.7. IR (neat) 3078, 2957, 2930, 2896, 2858, 1642, 1493, 1472, 1463, 1454, 1362, 1257, 1089, 1069, 1006, 914, 836, 776, 700 cm^{-1}; R_f=0.30 (EtOAc/hexanes, 5:95).

4.1.3. 1-(*tert*-Butyldimethylsilyloxy)-1-phenylhex-5-en-3-ol (5). In a round bottom flask equipped with a reflux condenser and a dropping funnel was placed magnesium (381 mg, 15.9 mmol) and a catalytic amount of iodide. A solution of allylbromide (990 μL, 11.4 mmol) in dry ether (12 mL) was then added dropwise. The allylmagnesium bromide solution was added to a solution of aldehyde **4** (600 mg, 2.27 mmol) in dry ether (23 mL) at 0 °C. The ice bath was then removed and the reaction followed by TLC. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution and the aqueous phase extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (3×50 mL), dried with magnesium sulfate, and concentrated under reduced pressure. The 50:50 *syn*/*anti* mixture of diastereoisomers **5**, were isolated by flash-chromatography with EtOAc/hexanes 2:98 as eluent (colorless oil, 3.74 g, 25.3 mmol, 92%). *Diastereoisomer syn*: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.25 (s, 3H), −0.04 (s, 3H), 0.89 (s, 9H), 1.72–1.92 (m, 2H), 2.17–2.29 (m, 2H), 3.48 (br s, 1H), 3.83–3.90 (m, 1H), 4.87 (dd, J=9.42, 4.0 Hz, 1H), 5.04–5.10 (m, 2H), 5.82 (ddt, J=17.9, 10.7, 7.0 Hz, 1H), 7.26–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8, −4.1, 18.3, 26.1 (3C), 42.3, 46.8, 70.8, 76.7, 117.8, 126.3 (2C), 127.8, 128.6 (2C), 135.0, 145.0; IR (neat) 3088, 3065, 3032, 2956, 2930, 2888, 2858, 2721, 1728, 1604, 1494, 1472, 1463, 1455, 1406, 1362, 1307, 1290, 1257, 1217, 1097, 1028, 1005, 978, 939, 914, 838, 778, 701 cm^{-1}; R_f=0.25 (EtOAc/hexanes, 5:95). *Diastereoisomer anti*: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 3H), −0.07 (s, 3H), 0.90 (s, 9H), 1.79–1.83 (m, 2H), 2.16–2.21 (m, 2H), 3.09 (br s, 1H), 3.78–3.87 (m, 1H), 5.02–5.09 (m, 3H), 5.82 (ddt, J=14.1, 9.7, 7.2 Hz, 1H), 7.26–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.9, −4.4, 18.5, 26.1 (3C), 42.5, 46.0, 67.7, 73.7, 117.7, 126.0 (2C), 127.4, 128.5 (2C), 135.2, 144.6; IR (neat) 3088, 3065, 3032, 2956, 2930, 2888, 2858, 2721, 1728, 1604, 1494, 1472, 1463, 1455, 1406, 1362, 1307, 1290, 1257, 1217, 1097, 1028, 1005, 978, 939, 914, 838, 778, 701 cm^{-1}; R_f=0.20 (EtOAc/hexanes, 5:95).

4.1.4. 1-Phenylhex-5-en-1,3-diol (6). To a solution of alcohol **5** (798 mg, 2.9 mmol) in tetrahydrofuran (30 mL) was added a solution of TBAF (1 N in tetrahydrofuran, 4.3 mL). After 2 h stirring at rt, the reaction mixture was concentrated under reduced pressure and purified by column chromatography eluting with EtOAc/hexanes 20:80 to afford diol **6** as a 50:50 *syn*/*anti* mixture of diastereosiomers, which were not separated (colorless oil, 537 mg, 2.80 mmol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69–1.79 (m, 2H), 2.13–2.18 (m, 2H), 3.65 (br s, 2H), 3.78–3.89 (m, 1H), 4.79 (dd, J=8.1, 5.1 Hz, 1H, isomer 1), 4.92 (dd, J=8.1, 3.8 Hz, 1H, isomer 2), 5.00–5.05 (m, 2H), 5.70 (ddt, J=17.0, 9.6, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) [two diastereoisomers] δ 42.1, 42.6, 44.3, 44.8, 68.2, 71.5, 71.8, 75.1, 118.2, 118.3, 125.8 (2C), 126.0 (2C), 127.4, 127.8, 128.6 (2C), 128.7 (2C), 134.4, 134.8, 144.6, 144.8. IR (neat) 3692–3120, 3071, 3027, 2978, 2914, 1641, 1492, 1454, 1328, 1202, 1084, 1062, 996, 916, 759, 701 cm^{-1}; R_f=0.30 (EtOAc/hexanes, 30:70).

4.1.5. 3-Hydroxy-1-phenylhex-5-en-1-one (7). To a solution of 1-phenylhex-5-en-1,3-diol **6** (192 mg, 1 mmol) in CH_2Cl_2 (20 mL) was added MnO_2 (860 mg, 10 mmol). After stirring for 3 h under reflux, the reaction mixture was filtered over Celite and the residue washed with CH_2Cl_2 (100 mL). The filtrate was concentrated in vacuo and purified by flash column chromatography (EtOAc/hexanes, 15:85) to give **7** as a yellow oil (115 mg, 0.61 mmol, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (br s, 1H), 2.37 (qd, J=5.8,

1.1 Hz, 2H), 3.06 (dd, J=17.7, 8.7 Hz, 1H), 3.20 (dd, J=17.7, 3.2 Hz, 1H), 4.27–4.35 (m, 1H), 5.13–5.20 (m, 2H), 5.89 (ddt, J=17.1, 10.2, 7.1 Hz, 1H), 7.45–7.61 (m, 3H), 7.94–7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.2, 44.5, 67.5, 118.2, 128.4 (2C), 129.0 (2C), 133.8, 134.6, 137.0, 200.9. IR (neat) 3436, 3077, 2923, 1682, 1600, 1449, 1210 cm^{-1}; R_f=0.60 (EtOAc/hexanes, 30:70).

4.1.6. 2-(4-Hydroxy-6-phenyl-tetrahydropyran-2-yl)-1-phenyl-ethanone (9). Trifluoroacetic acid (1.9 mL, 24.8 mmol) was added to a solution of homoallylic alcohol **6** (115 mg, 0.60 mmol) and benzaldehyde (140 μL, 1.4 mmol) in dry CH_2Cl_2 (6 mL) under nitrogen. The reaction was followed by TLC and upon completion the reaction mixture was quenched with an aqueous saturated sodium hydrogen carbonate solution (12 mL) and the pH was adjusted to >7 by addition of triethylamine. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL) and the combined organic layers were dried over $MgSO_4$, filtered off, and concentrated under reduced pressure. The resulting crude trifluoroacetate **8** was then dissolved in MeOH (6 mL) and stirred with sodium hydroxide (150 mg, 3.75 mmol) overnight. MeOH was then removed under reduced pressure and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was then purified by flash column chromatography (EtOAc/hexanes, 40:60) to afford **9** as an orange solid (148 mg, 0.5 mmol) in 83% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (q, J=11.6 Hz, 1H), 1.51 (q, J=11.5 Hz, 1H), 1.60 (br s, 1H), 2.22 (dd, J=12.1, 4.5 Hz, 2H), 3.10 (dd, J_{AB}=16.4 Hz, J=6.4 Hz, 1H), 3.48 (dd, J_{AB}=16.4 Hz, J=6.0 Hz, 1H), 4.05 (tt, J=10.9, 4.7 Hz, 1H), 4.16–4.23 (m, 1H), 4.43 (dd, J=11.3, 1.1 Hz, 1H), 7.28–7.31 (m, 5H), 7.43–7.54 (m, 3H), 7.96–7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.2, 42.8, 45.2, 68.5, 72.9, 77.9, 126.2 (2C), 127.8, 128.6 (4C), 128.9 (2C), 133.5, 137.5, 142.1, 198.4. IR (KBr) 3402, 2947, 2914, 1683, 1449, 1063 cm^{-1}. R_f=0.30 (EtOAc/hexanes, 40:60); mp=82.4–86.8 °C; HRMS (ESI) calcd for $C_{19}H_{20}O_3Na$ (M+Na$^+$) 319.1310, found 319.1311.

4.1.7. 2-(4-Chloro-6-phenyl-tetrahydropyran-2-yl)-1-phenyl-ethanone (10). To a stirred solution of alcohol **9** (49 mg, 0.17 mmol) in dry THF (700 μL) was added sodium hydride (60% in oil, 7 mg, 0.17 mmol) at 0 °C under nitrogen. The ice bath was removed and the reaction mixture stirred at rt for 1 h. Chlorodiphenylphosphine (30 μL, 0.17 mmol) was then added at 0 °C. The resulting mixture was stirred for 1 h at rt and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 μL) and 2,6-dimethylbenzoquinone (24 mg, 0.17 mmol) and *p*-anisic acid (25 mg, 0.17 mmol) were added at once under nitrogen. The reaction was followed by TLC and quenched with water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the organic phases were dried over $MgSO_4$, filtered off, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes, 7:93) to afford **10** (23 mg, 0.07 mmol) as a white solid in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.95 (m, 2H), 2.05–2.13 (m, 2H), 2.99 (dd, J_{AB}=15.9 Hz, J=6.2 Hz, 1H), 3.33 (dd, J_{AB}=15.9 Hz, J=6.2 Hz, 1H), 4.60 (t, J=3.0 Hz, 1H), 4.64–4.70 (m, 1H), 4.92 (d, J=11.1 Hz, 1H), 7.20 (br s, 5H), 7.38 (dd, J=7.7, 7.1 Hz, 2H), 7.49 (dd, J=7.5, 7.1 Hz, 1H), 7.91 (dd, J=7.1, 1.1 Hz 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 41.1, 44.9, 56.6, 69.4, 73.9, 126.1 (2C), 127.8, 128.6 (2C), 128.7 (2C), 128.9 (2C), 133.5, 137.5, 142.1, 198.1. IR (KBr) 2958, 2908, 1586, 1255, 1057, 800 cm^{-1}. R_f=0.50 (EtOAc/hexanes, 20:80); mp=78.8–81.2 °C; HRMS (CI) calcd for $C_{19}H_{19}O_2Cl$ (M+H$^+$) 315.1152, found 315.1154.

4.1.8. (+/−)-Diospongin A. To a stirred mixture of alcohol **9** (75 mg, 0.25 mmol), triphenylphosphine (100 mg, 0.38 mmol), and *p*-nitrobenzoic acid (64 mg, 0.38 mmol) in toluene (5 mL) at rt was dropwise added diethylazodicarboxylate (60 μL, 0.38 mmol). After 5 min, the orange solution became homogenous and three new additions of reagents were necessary to obtain completion. Silica (1 g) was then added and the mixture concentrated under reduced pressure to give a solid residue, which was rapidly purified by flash column chromatography (eluant: EtOAc/hexanes, 2:98). The fractions containing the intermediate ester were collected, concentrated and, diluted in MeOH (9 mL), THF (4.5 mL), and water (4.5 mL). Sodium hydroxide (160 mg, 4 mmol) was added to the mixture, which was stirred at rt, overnight. After removal of the organic solvents, the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and after filtration, concentrated under vacuo. The crude product was purified by flash column chromatography (EtOAc/hexanes, 30:70) to yield (+/−)-diospongin A (53 mg, 0.18 mmol) as a white solid in 71% yield over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64–1.81 (m, 2H), 1.94–1.99 (m, 2H), 2.08 (br s, 1H), 3.08 (dd, J_{AB}=16.0 Hz, J=6.8 Hz, 1H), 3.43 (dd, J_{AB}=16.0 Hz, J=5.6 Hz, 1H), 4.37 (t, J=2.6 Hz, 1H), 4.62–4.70 (m, 1H), 4.94 (dd, J=11.7, 1.5 Hz, 1H), 7.23–7.31 (m, 5H), 7.45 (dd, J=7.9, 7.2 Hz, 2H), 7.48–7.56 (m, 1H), 7.99 (dd, J=8.6, 1.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.7, 40.3, 45.5, 64.9, 69.4, 74.1, 126.1 (2C), 127.5, 128.5 (2C), 128.6 (2C), 128.8 (2C), 133.4, 137.5, 143.0, 198.8. IR (KBr) 3467, 3056, 2921, 1683, 1449, 1211, 1058, 700 cm^{-1}. R_f=0.35 (EtOAc/hexanes, 40:60); mp=83.4–84.0 °C.

Acknowledgements

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