A Short and Efficient Synthesis of (–)-Diospongin A

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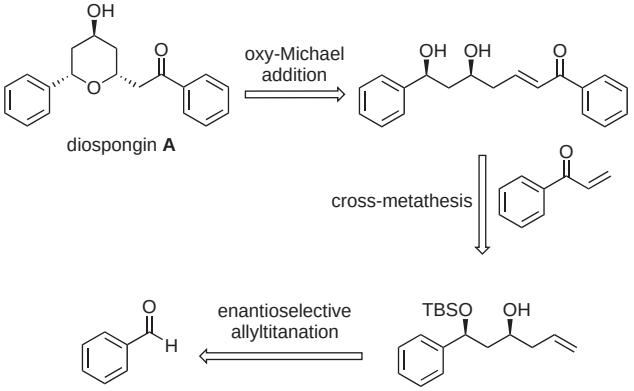
Abstract: The synthesis of (–)-diospongin A has been achieved from benzaldehyde in six steps with an overall yield of 29%.

Key words: allylations, cross-metathesis, oxy-Michael addition, natural products

1,7-Diarylheptanoids are present in a great variety of natural products which possess interesting biological properties.[1] For example, curcumin, a linear 1,7-diarylheptanoid, has antiproliferative activity against cancer cell lines and also inhibits nitric oxide formation.[2] The 1,7-diarylheptanoids **A** and **B** isolated from *Ethlingera elatior* were found to inhibit lipid peroxidation in a more potent manner than tocopherol[3] (Figure 1). Oreganin has been reported to have anti-inflammatory activity. It has also been shown that hirsutenone inhibits the activation of Nuclear Factor kappa B (NF-κB) involved in the upregulation of COX-2 and matrix metalloproteinase (MPP-Q) in human mammary epithelial cells stimulated with 2-*O*-tetradecanoylphorbol-13-acetate (TPA) which may contribute to the chemopreventive effects excited by this phytochemical.[4] Furthermore, cyclic 1,7-diarylheptanoids possess also interesting biological properties as the recent isolation of diospongins A and B from the rhizomes of *Dioscorea spongiosa* showed antiosteoporotic activity. Due to the biological activities of diospongins, they have attracted the attention of organic chemists and two syntheses have recently appeared in the literature.[5] In this paper, we would like to report a short and efficient total synthesis of (–)-diospongin A from benzaldehyde in six steps.

The synthesis of (–)-diospongin A was envisaged from benzaldehyde by using two enantioselective allyltitanations to control two of the three stereogenic centers present in the molecule, a cross-metathesis reaction and an intramolecular oxy-Michael reaction (Scheme 1).



Scheme 1 Retrosynthesis

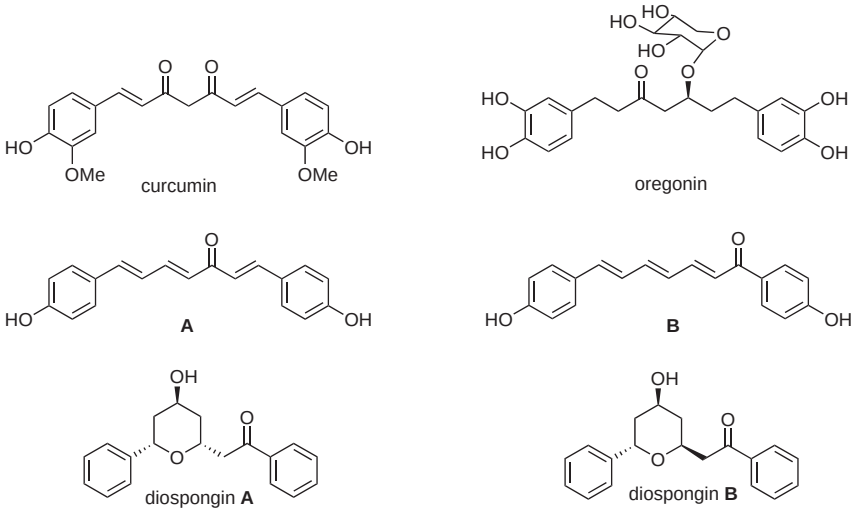


Figure 1

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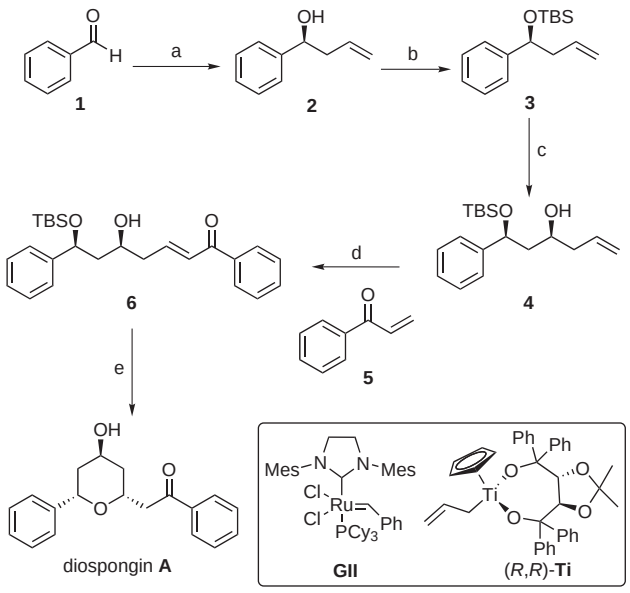
At first, benzaldehyde (**1**) was treated with the allyltitanium complex (*R*,*R*)-**Ti**[6] to afford the corresponding allylic alcohol **2** with good enantiomeric excess (ee >98%). After protection of **2** (TBSCl, imidazole, CH_2Cl_2, r.t.), compound **3** was isolated in 75% overall yield from **1**. The oxidative cleavage of the terminal olefin in **3** (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–H_2O)[7] produced the corresponding aldehyde which was directly treated with the highly face-selective complex (*R*,*R*)-**Ti** to afford the 1,3-*syn* diol **4**[8] in 87% yield (from **2**) and with a dr of 95:5. 1,3-Diol **4** was then involved in a cross-metathesis reaction (CH_2Cl_2, reflux) with the unsaturated ketone **5**[9] (3 equiv) in the presence of the second-generation Grubbs' catalyst **GII** to lead to the desired 1,7-diarylheptanoid **6**[10] in 75% yield with a *E*/*Z* ratio superior to 95:5 (Scheme 2). Finally, cleavage of the silylether and subsequent intramolecular oxy-Michael addition was successfully achieved in one pot with TBAF (1.5 equiv, THF, r.t.) to furnish (–)-diospongin A in 60% yield, whose physical data (NMR, MS, $[\alpha]_D$) matched those reported in the literature[5,11] (Scheme 2).

(–)-Diospongin A was synthesized in six steps from benzaldehyde with an overall yield of 29%. As the methodology used to synthesize (–)-diospongin A is versatile, analogues should be obtained easily for testing.



Scheme 2 *Reagents and conditions*: (a) (*R*,*R*)-**Ti**, Et_2O, –78 °C; (b) TBSCl, imidazole, CH_2Cl_2, r.t. (75%, from **1**); (c) (1) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–H_2O; (2) (*R*,*R*)-**Ti**, Et_2O, –78 °C (87%, from **3**); (d) **GII** (5% mol), **5** (3 equiv), CH_2Cl_2, reflux (75%); (e) TBAF, THF, r.t., 60%.

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(8) Spectral data for compound **4**: ^{1}H NMR (400 MHz): δ = 7.28–7.30 (m, 5 H), 5.72–5.86 (m, 1 H), 5.00–5.11 (m, 2 H), 4.80–4.90 (m, 1 H), 3.81–3.90 (m, 1 H), 3.44 (br s, 1 H, OH), 2.09–2.22 (m, 2 H), 1.67–1.97 (m, 2 H), 0.87 (s, 9 H), 0.02 (s, 3 H), –0.27 (s, 3 H). ^{13}C NMR (125 MHz): δ = 144.7 (s), 134.7 (d), 128.3 (d), 127.5 (d), 126.0 (d), 117.5 (t), 76.5 (d), 70.6 (d), 46.5 (t), 42.0 (t), 25.8 (q), 18.0 (s), –4.4 (q), –5.1 (q). IR (neat): 3500, 2931, 1256, 908, 732 cm^{-1}. MS (EI, 80 eV): *m*/*z* = 306 (1) [M$^+$], 221 (10), 181 (23), 156 (23), 104 (50), 75 (100). $[\alpha]_D^{20}$ –49.9 (*c* = 0.4, $CHCl_3$).

(9) Compound **5** was obtained from benzaldehyde in two steps: addition of vinylmagnesium bromide and oxidation by using PCC.

(10) Spectral data for compound **6**: ^{1}H NMR (400 MHz): δ = 7.13–7.82 (m, 10 H), 7.00–7.07 (dt, *J* = 7.3, 15.4 Hz, 1 H), 6.88–6.93 (d, *J* = 15.4 Hz, 1 H), 4.76–4.80 (m, 1 H), 3.98–4.08 (m, 1 H), 3.77 (br s, 1 H, OH), 2.39–2.51 (m, 2 H), 1.70–1.95 (m, 2 H), 0.87 (s, 9 H), 0.01 (s, 3 H), –0.27 (s, 3 H). ^{13}C NMR (125 MHz): δ = 190.5 (s), 145.5 (d), 144.4 (s), 137.8 (s), 132.7 (d), 128.6 (d), 128.3 (d), 128.1 (d), 127.9 (d), 127.5 (d), 126.0 (d), 76.2 (d), 70.5 (d), 46.7 (t), 40.9 (t), 25.8 (q), 18.0 (s), –4.4 (q), –5.1 (q). IR (neat): 3482, 2929, 1670, 1621, 1063, 700 cm^{-1}. MS (EI, 80 eV): *m*/*z* = 309 (5), 207 (75), 131 (70), 103 (77), 75 (100). $[\alpha]_D^{20}$ –30.1 (*c* = 0.5, $CHCl_3$).

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