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### REGIOSELECTIVE TRANSFER OF THE PRENYL ANION IN THE TOTAL SYNTHESIS OF (±)-SHIKONIN

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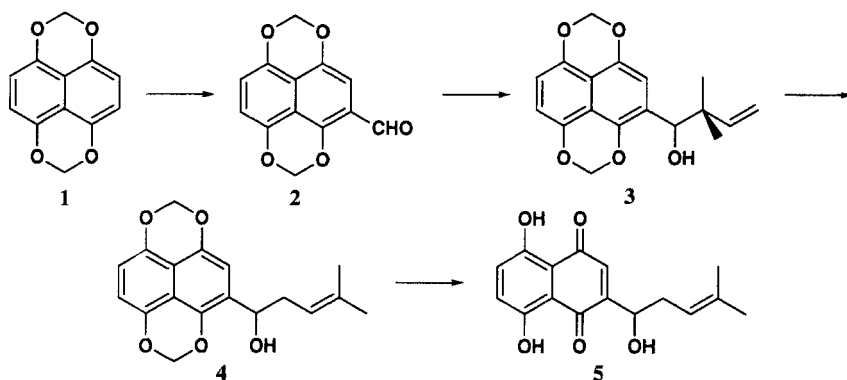
## OPPI BRIEFS

REGIOSELECTIVE TRANSFER OF THE PRENYL ANION  
IN THE TOTAL SYNTHESIS OF (±)-SHIKONINSubmitted by  
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Shikonin (**5**) exhibits a wide variety of pharmacological action, such as antibacterial,<sup>1</sup> anti-inflammatory,<sup>2</sup> antifungal<sup>3</sup> and anti-tumor activities,<sup>4</sup> etc. Several total syntheses of shikonin have been described<sup>5-10</sup> including one from 1,4,5,8-tetramethoxynaphthalene-2-carboxaldehyde by Japanese workers.<sup>11</sup> However, these methods have disadvantages, such as long and non-versatile routes, low yields, different deprotection methods and tedious purification, etc. Thus research directed toward a concise and novel route to (±)-shikonin is highly desirable. Retrosynthetic analysis indicated the most concise and efficient method for the introduction of the side-chain of (±)-shikonin to be prenylation of 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene (**2**). Apart from some exceptions,<sup>12</sup> the metal-mediated prenylation of carbonyl compounds with prenyl bromide occurred regioselectively at the  $\gamma$ -position (*e. g.* **3**). However, Hong *et al.*<sup>13</sup> reported that prenylzinc bromide reacted with aldehydes *in the presence* of hexamethylphosphoramide (HMPA) to yield the  $\alpha$ -adducts (*e. g.* **4**). We now describe a total synthesis of (±)-shikonin (*Scheme 1*) using Hong's highly regioselective and efficient method.



a)  $\text{POCl}_3$ , N-Methylformanilide, *o*-dichlorobenzene, 90-95°C, 5h; b) Zinc dust, prenyl bromide ( $\text{Me}_2\text{C}=\text{CHCH}_2\text{Br}$ ), THF, r.t., 1 h; c) THF, HMPA or *N*-MP, 130°C, 24 h; d) Lithium perchlorate, aqueous acetonitrile, electrolyzed at 3V, 24 h

Scheme 1

The addition of prenyl organometallics to 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene **2** provided varying amounts of  $\gamma$ - and  $\alpha$ -adducts (**3** and **4** respectively). While the change from the Grignard reagent (which gave the  $\gamma$ -adduct **3** exclusively) to the organocuprate (at different temperatures and in the presence of various additives) did lead to the formation of some of the  $\alpha$ -adduct, only the use of the prenylzinc bromide in the presence of hexamethylphosphoramide (HMPA) or *N*-methylpyrrolidone (*N*-MP) at 130°C led to the formation of the desired  $\alpha$ -adduct **4** as the major product in 85 and 83% yields respectively (98/2 and 97/3 ratio). Shikonin was then obtained by electrooxidative deprotection of the mixed reaction product as reported by Nicolaou *et al.*<sup>6</sup> The results suggest that the addition prenylzinc bromide to aldehyde **2** is reversible in the presence of HMPA. This is an equilibrium process in which the kinetic product **3** rearranged to the thermodynamic product **4** after prolonged heating. HMPA, an aprotic but carcinogenic solvent, may be replaced with *N*-methylpyrrolidone (*N*-MP) to give **4** in slightly lower yields.

## EXPERIMENTAL SECTION

Reagents and solvents were obtained from commercial suppliers and used without further purification. All mps were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. NMR spectra were recorded in CDCl<sub>3</sub> on a Mercuryplus 400 spectrometer with TMS as an internal standard. Mass spectra were acquired on an HP5989B mass spectrometer. Elemental analyses were performed on a VarioEL III (Germany) analyzer.

**2-Formyl-1,8:4,5-bis(methylenedioxy)naphthalene (2).**- 1,8:4,5-bis(Methylenedioxy)naphthalene (**1**, 6.5 g, 30 mmol), prepared as described by Dallacker,<sup>14</sup> was added to a mixture of phosphoryl chloride (9.2 g, 60 mmol), *N*-methylformanilide (8.1 g, 60 mmol) and *o*-dichlorobenzene (20 mL). The mixture was heated to 90-95°C for a period of 15 min until 1,8:4,5-bis(methylenedioxy)naphthalene dissolved to give a deep red solution. After heating for 5 h, a solution of sodium acetate (38 g, 463 mmol) in 65 mL water was added to the cooled mixture. *o*-Dichlorobenzene and most of the *N*-methylaniline were distilled off with steam. The residual oil, which solidified on cooling, was broken up and washed with 6N HCl (25 mL x 2) to remove residual amine. Purification by column chromatography on silica gel (90:10 pet ether-EtOAc) gave 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene **2** as pale green crystals (5.72 g, 48% yield), mp. 190-191°C, *lit.*<sup>14</sup> mp. 191-192°C. <sup>1</sup>H NMR (400 MHz):  $\delta$  10.52 (s, 1H, ArCHO), 7.25 (s, 1H, ArH), 7.03 (d,  $J = 7.6$ , 1H, ArH), 6.95 (d,  $J = 7.6$ , 1H, ArH), 5.63 (s, 2H, OCH<sub>2</sub>O), 5.51 (s, 2H, OCH<sub>2</sub>O). <sup>13</sup>C NMR (100 MHz):  $\delta$  186.8, 150.1, 145.8, 145.1, 144.6, 118.0, 117.6, 114.9, 113.3, 110.8, 103.9, 91.99, 91.90. EIMS  $m/z$  (rel. Int.): 244 ( $M^+$ ).

**2-(1-Hydroxy-2,2-dimethyl-3-butenyl)-1,8:4,5-bis(methylenedioxy)naphthalene (3).**- 4-Bromo-2-methyl-2-butene (200 mg, 1.34 mmol) was added to a suspension of zinc dust (200 mg, 3.06 mmol) in dry THF (20 mL). After stirring at room temperature for 1 h, the solution was filtered through a Schlenk tube under nitrogen to give crude prenylzinc bromide, which was

added dropwise to a solution of 2-formyl-1,8:4,5-bis(methylenedioxy)naphthalene (24.5 mg, 0.10 mmol) THF (10 mL) at room temperature for 2 h. When the reaction was complete (TLC), a saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (5 mL) was added to the reaction mixture, followed by extraction with ethyl acetate (3 x 20 mL). The organic phase was washed with brine, dried over  $\text{MgSO}_4$ , and concentrated *in vacuo*. The residue was purified by TLC on silica gel (3:3 hexane-ether) to afford 2-(1-hydroxy-2,2-dimethyl-3-butenyl)-1,8:4,5-bis(methylenedioxy)naphthalene (**3**) as a red oil (29.5 mg, 94% yield).  $^1\text{H}$  NMR (400 MHz):  $\delta$  6.93 (s, 1H, ArH), 6.81(d,  $J = 8.4$ , 1H, ArH), 6.78 (d,  $J = 8.0$ , 1H, ArH), 5.97 (dd,  $J = 10.8, 17.2$ , 1H, C=CH), 5.51(d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.49 (d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.44 (d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.40 (d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.12 (dd,  $J = 1.2, 10.8$ , 1H,  $\text{C}=\text{CH}_{2a}$ ), 5.05 (dd,  $J = 1.2, 17.6$ , 1H,  $\text{C}=\text{CH}_{2b}$ ), 4.97 (s, 1H, CHO), 1.07 (s, 3H,  $\text{CH}_3$ ), 1.01(s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.0, 144.6, 144.6, 143.9, 141.5, 122.6, 114.8, 114.6, 114.0, 109.1, 108.9, 108.6, 91.9, 91.7, 73.4, 43.6, 24.26, 21.62. EIMS  $m/z$  (rel. Int.): 314 ( $\text{M}^+$ ).

*Anal.* Calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_5$ : C, 68.78; H, 5.77. Found: C, 68.65; H, 5.53.

**2-(1-Hydroxy-4-methyl-3-pentenyl)1,8:4,5-bis(methylenedioxy)naphthalene (4).**- HMPA (339 mg, 1.94 mmol) was added to a mixture of crude prenylzinc bromide (29.0 mg, 0.136 mmol) and 2-(1-hydroxy- 2,2-dimethyl-3-butenyl)-1,8:4,5-bis(methylenedioxy)naphthalene (21.5 mg, 0.068 mmol) in THF (30 mL) at room temperature for 2 h. THF was distilled off and the remaining solution was heated at  $130^\circ\text{C}$  for 24 h. A saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (8 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The organic phase was washed with brine, dried over  $\text{MgSO}_4$ , and evaporated *in vacuo*. The residue was purified by TLC on silica gel to afford 2-(1-hydroxy-4-methyl-3-pentenyl)-1,8:4,5-bis(methylenedioxy)naphthalene **4** as a red oil (18.3 mg, 85% yield).  $^1\text{H}$  NMR (400 MHz):  $\delta$  7.03 (s, 1H, ArH), 6.82 (d,  $J = 8.2$ , 1H, ArH), 6.79 (d,  $J = 8.2$ , 1H, ArH), 5.55 (d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.53 (d,  $J = 5.2$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.48 (d,  $J = 2.8$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.46 (d,  $J = 2.8$ , 1H,  $\text{OCH}_2\text{O}$ ), 5.20 (t,  $J = 6.8$ , 1H, C=CH), 5.14 (dd,  $J = 8.0, 5.6$ , 1H, CHO), 2.56-2.48 (m, 2H,  $\text{CH}_2$ ), 1.72 (s, 3H,  $\text{CH}_3$ ), 1.62 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (100 MHz):  $\delta$  144.7, 144.6, 144.6, 140.6, 136.1, 125.3, 119.6, 115.1, 114.6, 109.1, 108.4, 107.0, 92.0, 91.78, 68.07, 37.13, 26.15, 18.23. EIMS  $m/z$  (rel. Int.): 314 ( $\text{M}^+$ ).

*Anal.* Calcd for  $\text{C}_{18}\text{H}_{18}\text{O}_5$ : C, 68.78; H, 5.77. Found: C, 68.43; H, 5.81.

**(±)-Shikonin (5).**- Compound **4** (94.2 mg, 0.30.0 mmol) and lithium perchlorate (4.9 g, 30.0 mmol) in 30 mL of 50% aqueous acetonitrile was introduced in an electrolytic cell with platinum foils and electrolyzed at 3V for 24 h. Removal of the solvent *in vacuo* left a liquid which was extracted with ethyl acetate. (3 x 20 mL) The organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified by column chromatography on silica gel (85:15 hexane-EtOAc) to give shikonin as a red solid (72.6 mg, 80% yield), mp.  $146\text{--}148^\circ\text{C}$ , *lit.*<sup>5</sup> mp.  $146\text{--}148^\circ\text{C}$ ,  $^1\text{H}$  NMR (400 MHz):  $\delta$  12.59 (s, 1H, ArOH), 12.49 (s, 1H, ArOH), 7.21 (d,  $J = 9.6$ , 1H, ArH), 7.19 (d,  $J = 9.6$ , 1H, ArH), 7.17 (s, 1H, Ar-H), 5.20 (dd,  $J = 8.0, 6.8$ , 1H, C=CH),

4.91 (dd,  $J = 7.2, 4.0$ , 1H, CHOH), 2.66-2.62 (m, 1H, CH<sub>2a</sub>), 2.39-2.31 (m, 1H, CH<sub>2b</sub>), 1.76 (s, 3H, CH<sub>3</sub>), 1.65 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  180.8, 180.0, 165.7, 165.1, 151.6, 137.6, 132.6, 132.5, 132.0, 118.6, 112.2, 111.7, 68.5, 35.90, 26.19, 18.32. EIMS  $m/z$  (rel. Int.): 288 (M<sup>+</sup>).

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