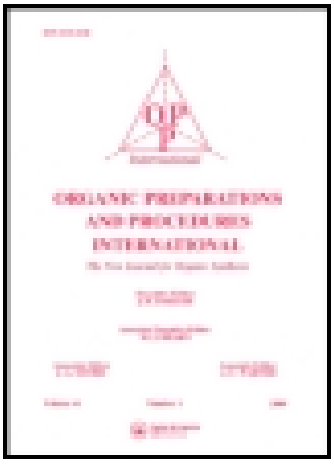

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OPPI BRIEFS

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

Submitted by (11/26/07)

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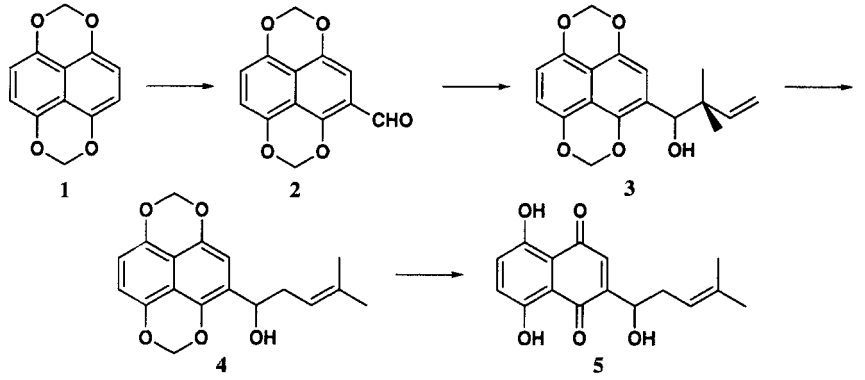
Shikonin (**5**) exhibits a wide variety of pharmacological action, such as antibacterial,[1] anti-inflammatory,[2] antifungal[3] and anti-tumor activities,[4] etc. Several total syntheses of shikonin have been described[5-10] including one from 1,4,5,8-tetramethoxynaphthalene-2-carboxaldehyde by Japanese workers.[11] 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,[12] the metal-mediated prenylation of carbonyl compounds with prenyl bromide occurred regioselectively at the γ-position (*e. g.* **3**). However, Hong *et al.*[13] reported that prenylzinc bromide reacted with aldehydes *in the presence* of hexamethylphosphoramide (HMPA) to yield the α-adducts (*e. g.* **4**). We now describe a total synthesis of (±)-shikonin (*Scheme 1*) using Hong's highly regioselective and efficient method.



1 2 3 4 5

a) $POCl_3$, N-Methylformanilide, *o*-dichlorobenzene, 90-95°C, 5h; b) Zinc dust, prenyl bromide ($Me_2C{=}CHCH_2Br$), 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 γ- and α-adducts (**3** and **4** respectively). While the change from the Grignard reagent (which gave the γ-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 α-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 α-adduct **4** as the major product in 85 and 83% yields respectively (98/2 and 97/3 ratio). Shikonin was then obtained by eletrooxidative deprotection of the mixed reaction product as reported by Nicolaou *et al.*[6] 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 $CDCl_3$ 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,[14] 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.*[14] mp. 191-192°C. ^{1}H NMR (400 MHz): δ 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_2O), 5.51 (s, 2H, OCH_2O). ^{13}C NMR (100 MHz): δ 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 NH_4Cl (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 $MgSO_4$, 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)naph-thalene (**3**) as a red oil (29.5 mg, 94% yield). ^{1}H NMR (400 MHz): δ 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, OCH_2O), 5.49 (d, *J* = 5.2, 1H, OCH_2O), 5.44 (d, *J* = 5.2, 1H, OCH_2O), 5.40 (d, *J* = 5.2, 1H, OCH_2O), 5.12 (dd, *J* = 1.2, 10.8, 1H, $C=CH_{2a}$), 5.05 (dd, *J* = 1.2, 17.6, 1H, $C=CH_{2b}$), 4.97 (s, 1H, CHOH), 1.07 (s, 3H, CH_3), 1.01(s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 (M^+).

Anal. Calcd for $C_{18}H_{18}O_5$: 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°C for 24 h. A saturated aqueous solution of NH_4Cl (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 $MgSO_4$, 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*(meth-ylenedioxy)naphthalene **4** as a red oil (18.3 mg, 85% yield). ^{1}H NMR (400 MHz): δ 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, OCH_2O), 5.53 (d, *J* = 5.2, 1H, OCH_2O), 5.48 (d, *J* = 2.8, 1H, OCH_2O), 5.46 (d, *J* = 2.8, 1H, OCH_2O), 5.20 (t, *J* = 6.8, 1H, C=CH), 5.14 (dd, *J* = 8.0, 5.6, 1H, CHOH), 2.56-2.48 (m, 2H, CH_2), 1.72 (s, 3H, CH_3), 1.62 (s, 3H, CH_3). ^{13}C NMR (100 MHz): δ 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 (M^+).

Anal. Calcd for $C_{18}H_{18}O_5$: 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 Na_2SO_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. 146-148°C, *lit.*[5] mp. 146-148°C, ^{1}H NMR (400 MHz): δ 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_{2a}), 2.39-2.31 (m, 1H, CH_{2b}), 1.76 (s, 3H, CH_3), 1.65 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 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^+).

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