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A Simple Synthesis of dl-Shikonin

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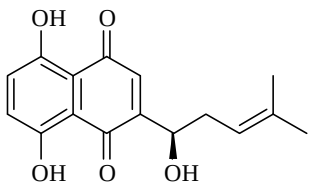
Abstract: A new facile route for the synthesis of dl-shikonin is presented. Reformatsky reaction assisted cross-coupling of 1, 4, 5, 8-tetramethoxynaphthalene-2-carbaldehyde and ethyl-bromoacetate was employed for introduction of the side chain of dl-shikonin.

Keywords: Synthesis, dl-shikonin, Reformatsky reaction.

Shikonin, **1**, Alkannin, **2**, and their derivatives, are naturally occurring dyes in the roots of many traditional medicinal plants of the Boraginaceae family (mainly in the genus of *Alkanna,lithospermum*)[1]. These compounds bear considerable promise as drugs because not only of their anti-inflammatory, antibacterial, antifungal, immunostimulating acivti- ties[2], but also of antitumor activity, especially strong inhibition of DNA topoisomerase I[3]. Since both compound **1** and **2** showed similar bioactivities, dl-shikonin may also be active.



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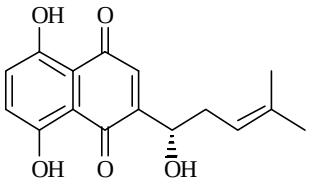

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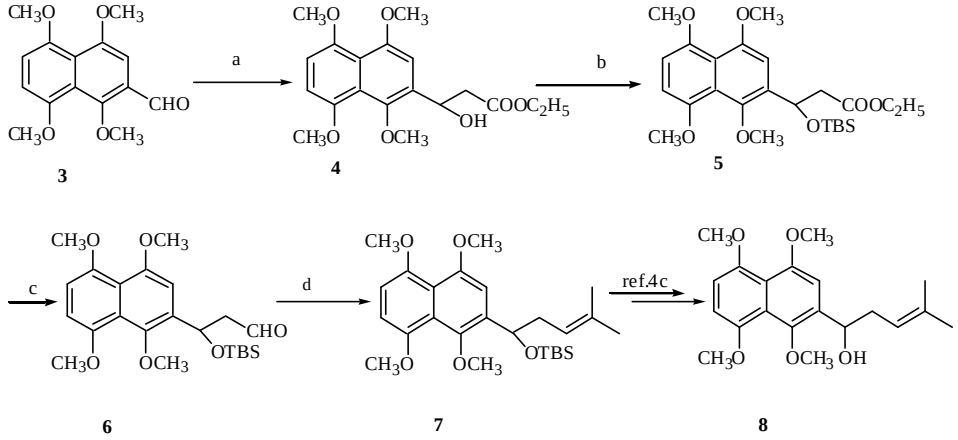
Sevaral synthetic methods for dl-shikonin have been reported in the literature[4]. Most of these methods are in low yield, especially the steps of construction of the side chain are long and impractical. Efficient synthesis of this apparently simple molecular remained elusive. We now report a simple synthetic route of dl-shikonin in which Reformatsky reaction was used to establish the key intermediate **4** (**scheme 1**).

The starting material **3** was prepared from 1,5-dihydroxynaphthalene in three steps[4a]. The key intermediate **4** was obtained simply by Reformatsky reaction of **3** with ethyl bromoacetate. After protection of the hydroxy group of **4** with TBSCl, compound **5** was reduced to corresponding aldehyde **6** with DIBAL-H in almost quantitive yield. Witting type elongation of the resulting aldehyde using the ylide of 2-bromopropane afforded fully protected dl-shikonin **7** (4 step from **3**, 40% total yield). After

deprotection of intermediate **7** by Braun's method[4c] the dl-shikonin was obtained. The asymmetric synthesis of **1** and **2** can also use the same strategy by asymmetric Reformatsky reaction and are in progress.

Scheme 1



Reagents and conditions: a) 1.5 eq. Zn, 1.5 eq. $BrCH_2COOC_2H_5$, Benzene, reflux 3 hr., 75%; b) 1.5 eq. TBSCl, 2 eq. imidazole, 0.2 eq. DMAP, DMF, rt., 5 hr., 95%; c) Ar_2, 1.3 eq. DIBAL-H (1.0 mol/L), -78°C, 12 hr., CH_2Cl_2 , 95%; d) 1.7 eq. *n*-BuLi, 2.0 eq. Ph_3PCHMe_2Br, Et_2O, O°C, 1.5 hr., then 1 eq. **6**, O°C→rt., 24 hr., 60%. DIBAL-H = diisobutylaluminum hydride, DMAP = 4-N, N-dimethylaminopyridine, TBSC l = ^{t}Butyldimethylsilyl chloride

References and Notes

1. R. H. Thomason, *Naturally Occurring Quinones, III, Recent Advances*, Chapman and Hall, New York, **1987**, pp.219-223.
2. V. P. Papageorgiou, A. N. Assimopoulou, E. A. Couldouros, *Angew. Chem. Int. Ed.*, **1999**, *38*, 270.
3. B. Z. Ahn., K. U. Baik., G. R. Weon, *J. Med. Chem.*, **1995**, *38*, 1044.
4. a) Y. Terada, A. Tanoue, Hatada, *et al*., *Bull. Chem. Soc. Jpn*., **1987**, *60*, 205.
   b) A. M. Moiseenkov, N. N. Balaneva, V. L. Novikov, G. B. Eluakov, *Dokl. Akad. Bauk. SSSR*, **1987**, *295*, 614.
   c) M. Braun, C. Bauer, *Liebigs Ann. Chem.*, **1991**, 1157.
   d) E. A. Couladouros, Z. F. Plyta, A. T. Strongilos, *Tetrahedron Lett*., **1997**, *38*, 7263.
   e) K. C. Nicolaou, David Hepworth, *Angew. Chem. Int. Ed*., **1998**, *37* (6), 839.
5. The data of **8**: IR (KBr, cm^{-1}): 3255 (broad, OH), 1608 (C=O); ^{1}HNMR (400Hz, $CDCl_3$, δ ppm): 1.63 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.30-2.70 (m, 3H, CH_2 and OH), 4..90 (m, 1H, –C<u>H</u>(OH)–), 5.18 (m, 1H, $(CH_3)_2$=C<u>H</u>–), 7.15 - 7.20 (m, 3H, Ar-H), 12.50 (s, 1H, Ar-OH), 12.61 (s, 1H, Ar-OH); EIMS (*m/z*) 288 [M^+], 219 [$C_{10}H_5O_4CHOH^+$], 69 [$CH_2CH=C(CH_3)_2^+$]; HRMS: Found: 288.1018. Calcd: 288.0998.

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