Chinese Chemical Letters Vol. 13, No. 6, pp 515 – 518, 2002
http://www.imm.ac.cn/journal/ccl/html

New Synthesis of (±)Shikalkin

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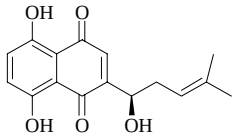
Abstract: The new synthetic route of (±)shikalkin **1** was developed. 3-(1-Hydroxy-4-methyl-3-pentenyl)-5, 8-dimethoxy-1-naphthol **8** was obtained from compound **3** in 10 steps. Then (±)shikalkin **1** was synthesized from **8** in one step with reagents AgO/HNO_3 in 1, 4-dioxane.

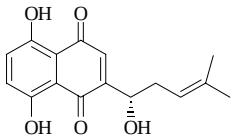
Keywords: Shikalkin, synthesis.

The naturally occurring enantiomers mixture of shikonin (**R-1**) and alkannin (**S-1**) has been named shikalkin by H.Brockmann[1]. Shikonin was first isolated as its acetate from the roots of *Lithospermum erythrorhizon* (LE) which has been used for dyeing in China, Japan, and Korea from ancient times[2]. Alkannin was found in *Alkanna tincloria*(AT) and many other type of Boraginaceous roots[1]. Shikalkin **1** and their ester derivatives showed antitumor[3], antiinflammatory[4], antibacerical[5], immunostimulating[6] activities, and can be used as raw material for cosmetics[7]. There have been many synthetic routes to shikalkin **1**, and Nicolaou[8] has reviewed the synthesis of shikalkin **1**, but those methods always involved some rigour reactions, verbose steps and very low yield. In this paper, we described our new synthetic route of the racemic shikalkin **1**. It is concise in mild-condition with better yield.

Scheme 1



R-1

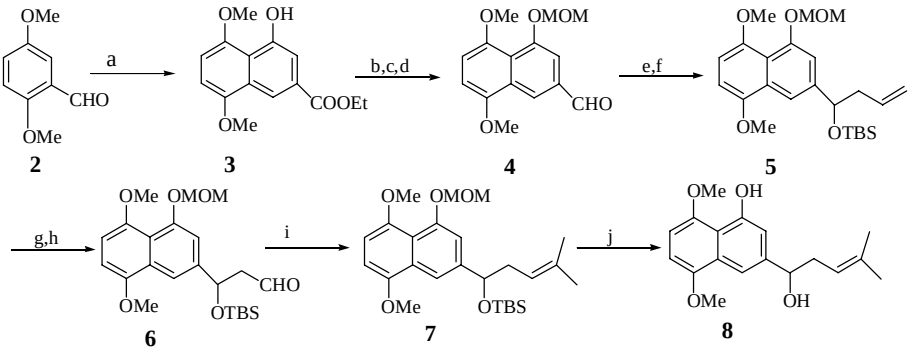


S-1

We began the synthesis of **1** from the naphthol **3**, which was prepared from 2,5-dimethoxybenzaldehyde **2** according to the literature[9]. After protecting the phenol hydroxy group with MOMCl[10], the ester group was reduced with LAH. Subsequently, the resulted hydroxy group was oxided with PDC to afford naphthoaldehyde **4**. Then, **4**

was subjected to Babier-type reaction with bromopropane/Zn[11], and protecting the hydroxy group by TBSCl[12] afforded the desired intermediate **5**. The terminal double bond of **5** was cleaved to the corresponding aldehyde **6** using a two-step protocol in very high yield, and subsequently, Wittig type[13] elongation of **7** was carried out using the ylide of 2-iodopropane. Then removal of protective group of MOM and TBS using HCl in *i*-PrOH and THF[14] gave **8** in one step (**Scheme 2**).

Scheme 2

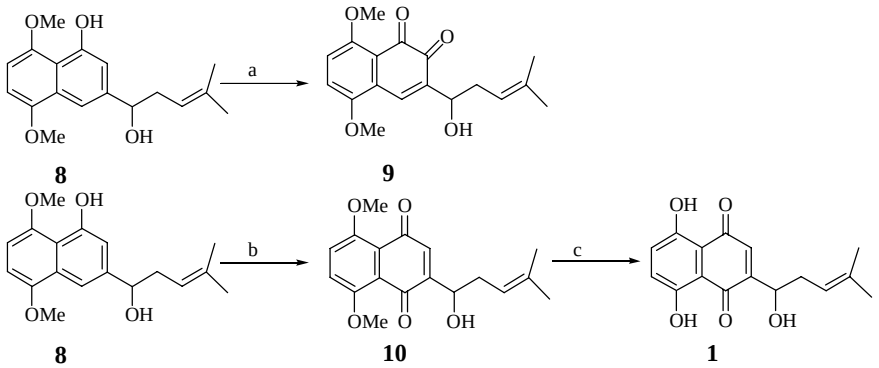


Reagents and conditions: a) I: diethyl succinate, NaH, toluene. II: $(CH_3CO)_2O$, CH_3COONa, reflux. III: CH_3COCH_3, HCl, reflux. 27% for three steps. b) CH_3OCH_2Cl, NaH, DMF, 97%. c) LAH, Et_2O, 65%. d) PDC, CH_2Cl_2, 93%. e) C_3H_5Br, Zn, THF, 69%. f) TBSCl, imidazole, DMF, 95%. g) OsO_4, $K_3[Fe(CN)_6]$, K_2CO_3, *t*-BuOH, H_2O, 99%. h) $NaIO_4$, EtOH, H_2O, 95%. i) $Ph_3PCHI(CH_3)_2$, *n*-BuLi, Et_2O, N_2, 70%. j) *i*-PrOH, THF, HCl, 95%.

Oxidation of compound **8** in the presence of catalytic amount of salcomine, almost exclusively afforded a naphthoquinone in 95% yield, which was anticipated to have *p*-quinone structure according to the literature[15]. However, the analytic data did not agree with litrature[16,17]. Moreover the chemical shift of the single quinoid proton (7.94 ppm, s)[18] and coupling constant of H-6 and H-7 (J=9.54 Hz) also proved that compound is the *o*-quinone **9**. Other oxidation agents were employed, the Fremy's salt[19] also gave *o*-quinone in 70% yield, CAN oxided to complex compounds. Alternatively the hypervalent iodine reagent[18] can get *p*-quinones **10**, but the yield is only 18%, (**Scheme 3**), and then refer the classic process[16] to the last target shikalkin **1**.

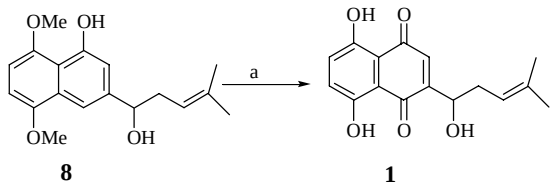
After that, we treated the compound **8** directly with AgO/HNO_3[20], unexpectedly, affording a blood-red compound, which was identified as the target shikalkin **1**[21,22], (**Scheme 4**) and the yield is 17%.

Scheme 3



Reagents and conditions: a) salcomine, O_2, 95%, or Fremy's salt, CH_3COCH_3, KH_2PO_4, 70%. b) $PhI(OCOCF_3)_2$, CH_3CN, 18%. c) AgO, HNO_3, 39%.

Scheme 4



Reagents and conditions: a) AgO, HNO_3(conc.), 1,4-dioxane, 17%.

In summary, we synthesized shikalkin **1** from naphthol **3** in ten steps**.** Now the asymmetric synthesis of shikalkin **1** is being proceeded in our research group.

Acknowledgment

We thank the National Natural Science Foundation of China [30069004] for financial supports.

References and Notes

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17. Data of compound **9**: red solid, mp: 93-95°C; EIMS (*m/z*): 316(M^+), 248, 247, 219, 189; ^{1}HNMR($CDCl_3$, 400MHz, δ ppm): 1.66 (s, 3H, CH_3C=), 1.71 (s, 3H, CH_3C=), 2.31-2.53 (m, 3H, 2H-2', OH), 3.87 (s, 3H, CH_3O-), 3.92 (s, 3H, CH_3O-), 4.63-4.66 (m, 1H, H-1'), 5.17 (m, 1H, H-3'), 7.01 (d, 1H, J=9.54 Hz), 7.16 (d, 1H, J=9.53 Hz) (2H, H-6, H-7), 7.94 (s, 1H, H-1).
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22. Data of shikalkin agreed with the literature[21] data: blood-red solid, mp: 144-145℃; IR (KBr, cm^{-1}): 3421.2, 2923.6, 1643.1, 1612.2, 1456.0, 1267.0, 1201.5, 1064.5, 854.3; ^{1}HNMR ($CDCl_3$, 400MHz, δ ppm): 1.65 (s, 3H CH_3C=), 1.76 (s, 3H, CH_3C=), 2.25-2.67 (m, 3H, 2H-2', OH), 4.90-4.97 (m, 1H, H-1'), 5.18-5.23 (m, 1H, H-3'), 7.17 (d, 1H, 1.32 Hz, H-3), 7.20 (d, 2H, 2.20 Hz, H-6, H-7), 12.50 (s), 12.60 (s). (2H, each, aromatic OH); ^{13}CNMR($CDCl_3$, 100MHz, δ ppm): 18.065, 25.929, 35.658, 68.340, 111.533, 112.010, 118.441, 129.072, 131.862, 132.378, 137.383, 151.419, 164.916, 165.531, 179.764, 180.568; EIMS (*m/z*): 288(M^+), 219, 218, 69; HREIMS (*m/z*): 288.1002 (calcd. for $C_{16}H_{16}O_5$, 288.0998).

Received 25 September, 2001