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New Asymmetric Synthesis of Alkannin and Shikonin

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Abstract: A new approach for asymmetric synthesis of alkannin and shikonin is presented. The chiral centers of the targets were introduced *via* an asymmetric *C*-arylation of protected chiral glyceraldehyde in high de. The two enantiomers were prepared with the D-isopropylideneglyceraldehyde as the starting material.

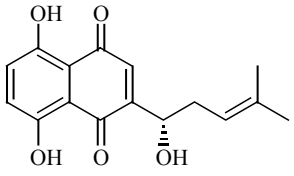
Keywords: Asymmetric synthesis, alkannin, shikonin, arylglycerols.

Alkannin **1** and shikonin **2** 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 and their derivatives have recently attracted much attention due to their omnifarious biological profiles, including anti-inflammatory[2], antibacterial[3], antifungal[4], anticancer[5], anti-HIV[6], antithrombotic[7], immunostimulatory[8], and wound healing properties[9].

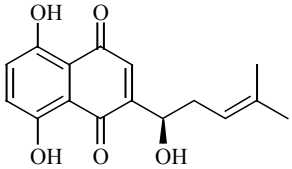
Several routes[10] were reported for asymmetric synthesis of **1** and **2**. In these reported papers, the expensive reagents, such as DIP-Cl, and Corey's oxazaborolidine were used to synthesize **1** and **2** in high e.e..

Herein we would like to report an asymmetric approach towards the title compounds. The chiral centers were established through a regiocontrolled C-arylation of D-isopropylideneglyceraldehyde. D-isopropylideneglyceraldehyde, a widely used chiral intermediate to introduce the chiral center in organic synthesis[11], can be easily prepared from mannitol.

5, 8-Dimethoxynaphthalen-1-ol **3** and D-isopropylideneglyceraldehyde **4** were prepared according to literature[12]. Treatment of **3** with EtMgBr, followed with **4**, then



1



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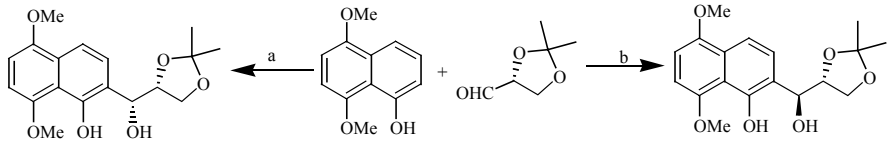
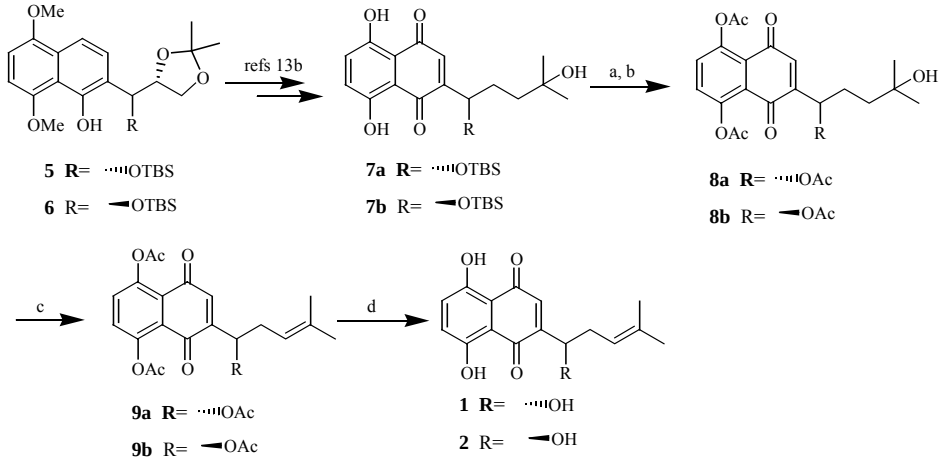
Scheme 1



5 **3** **4** **6**

Reagents and conditions: a) EtMgBr, CH_2Cl_2, 91% d.e., 70%; b) Ti(O-*i*-Pr)$_4$, toluene, 90% d.e., 65%.

Scheme 2



Reagents and conditions: a) TBAF, THF, rt, 3 h, 87%; b) Ac_2O, pyridine, 0℃, 2 h, 89%; c) pyridine, $SOCl_2$, -20℃, 27%; d) 1 mol/L NaOH, then 2 mol/L HCl, 31%.

subjected to ultrasonic wave at 0℃ for 7h, furnished the *syn* addition product **5** in high diastereoisomeric excess (d.e.) of 91% and moderate yield (70%). While **3** was treated with titanium tetraisopropoxide, followed with **4**, then stirred at 0℃ for 4h, furnished the *anti* product **6** in 90% d.e. and 65% yield[13] (**Scheme 1**). The *syn*- and *anti*- diastereoisomers **5** and **6** are easily distinguished by ^{1}H NMR spectroscopy on the basis of vicinal coupling constants ($J_{1,2}$) between H-1 and H-2 of the side chain. As a general rule[13b], the spectra of the *syn* compound display $J_{1,2}$ of about 8Hz, while a $J_{1,2}$ of 4Hz for the *anti*-isomer. In this case, compound **5** displayed $J_{1,2}$ of 7.4Hz, and therefore it was syn-isomer; while $J_{1,2}$ of 4.7 Hz was observed for compound **6**, which, correspondingly, is *anti*-isomer[14].

Compound **7a** and **7b** (**Scheme 2**) were synthesized from **5** and **6** according to our previous paper[13b]. It was problematic to eliminate the hydroxyl groups of **7a** and **7b** to form the double bond because their side chains were inclined to cyclization in the acidic condition. Following procedure was applied to establish the double bond of the side chain. Deprotection of **7a** with TBAF in THF**,** followed by the acetylation with pyridine and acetic anhydride, led to triacetate **8a**. **8a** then went through a subsequent elimination with thionyl chloride and pyridine to afford **9a** in 27% yield. Finally,

alkaline hydrolysis of the acetate **9a**, followed careful acidification with hydrochloric acid, provided **1** in 31% yield. Compound **2** was prepared from **7b** in the same procedure as **1**. The structure of the synthesized title compounds **1** and **2** was determined on the basis of ^{1}H NMR, ^{13}C NMR, IR, HRMS analysis[15].

In conclusion, we have developed new asymmetric synthesis of the title compounds. In this approach, the antipode pair alkannin/shikonin was prepared from the same chiral starting material, D-isopropylideneglyceraldehyde, which was easily prepared from mannitol.

Acknowledgments

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14. a) The data of **5**: $[\alpha]_D^{20}$ -13.5 (*c* 0.05, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$, δ ppm): 1.39(s, 3H), 1.53(s, 3H), 3.10(s, 1H), 3.80(m, 3H), 3.89(m, 3H), 4.45(m, 1H), 5.15(d, 1H, *J*=7.4Hz), 6.65(d, 1H, *J*=8.4Hz), 6.69(d, 1H, *J*=8.4Hz), 7.50(d, 1H, *J*=8.6Hz), 7.72(d, 1H, *J*=8.6Hz), 9.80(s, 1H); b) The data of **6**: $[\alpha]_D^{20}$ +12.8 (*c* 0.075, $CHCl_3$); ^{1}H NMR (400MHz, $CDCl_3$, δ ppm): 1.39(s, 3H), 1.53(s, 3H), 3.10(s, 1H), 3.80(m, 3H), 3.89(m, 3H), 4.45(m, 1H), 5.25(d, 1H, *J*=4.7Hz), 6.65(d, 1H, *J*=8.4Hz), 6.69(d, 1H, *J*=8.4Hz), 7.50(d, 1H, *J*=8.6Hz), 7.72(d, 1H, *J*=8.6Hz), 9.80(s, 1H).
15. The data of **1** and **2**: $[\alpha]_D^{20}$ -150.5 (*c* 0.05, C_6H_6) for **1** ($[\alpha]_D^{20}$ -159, refs 1), $[\alpha]_D^{20}$ +135.6 (*c* 0.05, C_6H_6) for **2** ($[\alpha]_D^{20}$ +138, refs 1); IR (KBr, cm^{-1}): 3255 (broad, OH), 1608 (C=O); ^{1}H NMR (400Hz, $CDCl_3$, δ ppm): 1.63(s, 3H), 1.75(s, 3H), 2.3-2.7(m, 2H), 4.90(m, 1H), 5.18(m, 1H), 7.13(m, 3H), 12.50(s, 1H), 12.61(s, 1H); ^{13}C NMR (100MHz, $CDCl_3$, δ ppm): 18.09, 25.97, 35.67, 111.55, 112.02, 118.42, 131.85, 132.44, 132.42, 137.49, 151.43, 164.83, 165.45, 179.89, 180.69; EIMS (*m/z*): 288[M^+], 220[$C_{10}H_5O_4CHOH^+$], 69[$CH_2CH{=}C(CH_3)_2^+$]; HRMS 288.1018, calcd. for $C_{16}H_{16}O_5$, 288.0998.

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