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A novel and efficient total synthesis of shikonin

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ABSTRACT

A novel and efficient synthesis of shikonin was accomplished with excellent enantiomeric excess (99.3% ee) and high overall yield (47%) in only six steps. The synthetic strategy involved an efficient Ru(II)-catalyzed asymmetric hydrogenation employing C_2 -symmetric planar chiral ruthenocene phosphinooxazoline ligand (**L-3**), followed by the subsequent removal of the methyl protecting groups. Meanwhile, it could be preliminarily confirmed that the chiral side chain of shikonin was difficult to be constructed in one step with both stereoselectivity and α -regioselectivity.

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Introduction

In ancient times, extracts from the roots of the traditional Oriental herb *Lithospermum erythrorhizon* were used as natural purple dyes and ointments for healing wounds.¹ Shikonin (**1**), one of the major active chemical constituents from these extracts, has attracted considerable interests for its high biological activities, such as antibacterial,² antiviral,³ analgesic,⁴ angiostatic,⁵ and antitumor⁶ properties. Though existing in many species of Boraginaceae, isolation of shikonin with high optical purity from the natural resources proved unsatisfactory.

Due to the high chemical reactivity of the naphthazarin moiety and hydroxyl in the side chain, concise and efficient synthesis of **1** remains elusive, even if its molecular structure is simple apparently. Recently, we have established a total synthesis of shikonin and alkannin based on the chiral resolution of an acid intermediate,⁷ but this actually decrease the overall yield of shikonin by 50%. As a result, total asymmetric synthesis for stereoselective shikonin is more desirable.

Results and discussion

Previous synthesis⁸ of shikonin is subjected to the following problems: (1) the chiral reagents and intermediates were either expensive or difficult to obtain and the enantioselectivity is not so satisfactory; (2) most synthetic methods consist of long and non-versatile schemes with low efficiency and yield, which made it difficult for scale-up preparation; (3) most of them employed

1,4,5,8-tetramethoxy-2-naphthaldehyde (**2**) as starting material but the final deprotection procedures to reveal the moiety of naphthazarin were mostly poor-yield (20%) with harsh and costly conditions (AgO, HNO₃); the shortest synthesis was reported by Nicolaou,⁹ in which a novel protecting system (methylene protecting group) was adopted. However, the final deprotection step proceeded with electrolysis system with only half conversion of the reactant. Though the problem of low conversion was solved,¹⁰ this approach was still difficult for large scale application. Furthermore, the 'Weinreb amide' used in this route was difficult to obtain.

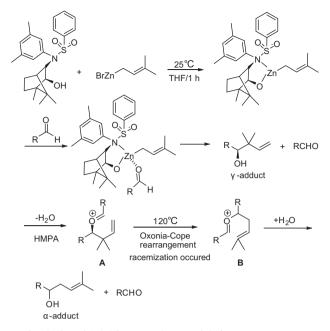
The structure of shikonin contains two parts: the naphthazarin core and the six carbon side chain with one chiral center. The naphthazarin core is susceptible to exposure to air, heat, or light. How to choose the protecting group and construct the chiral side chain are the most challenging aspects. In a word, a practical and efficient total synthesis for shikonin is supposed to overcome the following obstacles, such as (1) the starting material should be easy to obtain and suitable for large scale preparation, while the final deprotection procedures to reveal the moiety of naphthazarin should be practical; (2) the product should be prepared with high enantioselectivity (>99% ee), which is vital for drug research and development; (3) the synthetic route should be short and easy to operate with relatively high yield.

Over the past several years, our team has completed the total synthesis of protected (±)-shikonin (**3**) (Scheme 3) via a highly α -regioselective zinc-mediated addition of prenyl bromide to **2**.¹¹ Inspired by this, we considered the possibility to combine two achievements for the construction of the chiral side chain in one step, not only α -regioselectively but also stereoselectively, based on the induction of the chiral auxiliaries to the reaction system.

Aminoalcohol ligands as chiral auxiliaries were extensively used in the addition of organozinc reagents to aldehydes.¹² In an

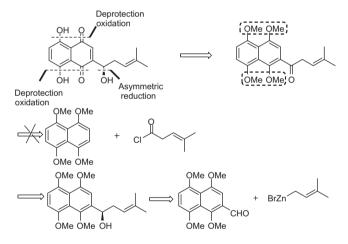
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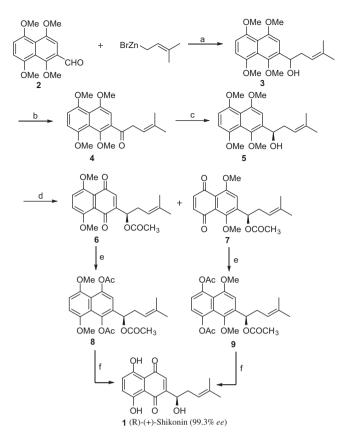
R = 2-substituted-1,4,5,8-tetramethoxynaphthalene

Scheme 1. Plausible mechanism for the production of chiral γ -adduct and its recemization to α -adduct via an Oxonia-Cope rearrangement.



Scheme 2. Retrosynthetic analysis of shikonin.

initial study, we chose L-1 (Figure 1) as the chiral auxiliary (Table 1), but the result did not show any stereoselectivity. Since the reaction conditions here were almost identical with the synthesis of (±)-shikonin except for the presence of chiral auxiliary, we wondered whether the relatively high temperature had an important influence on the stereoselectivity and may result in the racemization of the chiral product. Thus we performed the reaction at lower temperature. To our disappointment, changing the temperature from 120 to 80 °C only caused the change of ratio between α -adduct and γ -adduct, but did not show stereoselectivity (chiral α -adduct) at all (Table 1). L-2 (Fig. 1), which showed higher selectivity in some asymmetric synthesis,^{12b} was used as the chiral ligand in the subsequent reactions. However, the result was also disappointing and no stereoselectivity was observed. We doubted the amount of chiral auxiliary might be a key factor. We subsequently adjusted its amount from 0.2 to 2.0 equiv. Nevertheless, the reaction gave no stereoselectivity (Table 1). We inferred the reactions might proceed as Scheme 1. In such case, though chiral γ -adduct was



Scheme 3. Total synthesis of shikonin: (a) THF, 25 °C, 1 h, then HMPA, 120 °C, 6 h, 91%; (b) Dess–Martin periodinane, 0 °C, 15 min, 80%; (c) RuCl₂(PPh₃)₃/**L**-3, *t*-BuOK/ *i*-PrOH, H₂ (10 atm), 0 °C, 24 h, 99%; (d) Ac₂O, Et₃N, DMAP, dry CH₂Cl₂, rt, 20 min, then CAN, CH₂Cl₂, rt, 15 min, 25% (**6**), 67% (**7**); (e) Zn, Ac₂O, Et₃N, DMAP, 2 h, rt, 76% (**8**), 86% (**9**); (f) CAN, CH₃CN, rt, 10 min, then 1 M NaOH, 6 h, then 10% HCl, 85%.

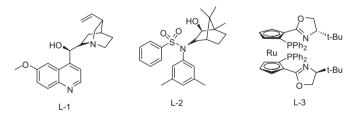


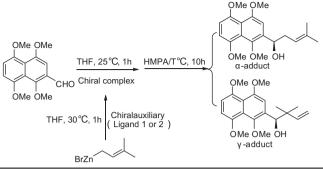
Figure 1. Ligands 1, 2, and 3.

produced, racemization occurred during the conversion of γ -adduct to α -adduct, which might suffer from the bond breakage (A–B) (Scheme 1). In order to confirm our presumption, we kept the reaction temperature at 25 °C at first to avoid the conversion of γ -adduct to α -adduct, and as a result, only chiral γ -adduct was produced by 71% ee. Then the obtained chiral γ -adduct (71% ee) was subjected to relatively high temperature (120 °C) for 10 h without the addition of HMPA, avoiding the subsequent Oxonia-Cope rearrangement. The enantiomeric excess did not change at all. Based on these results, we preliminarily deduced that it was difficult to construct the chiral side chain in one step, achieving both α -regioselectivity and stereoselectivity. Therefore, we tried to exploit other new methods.

According to the retrosynthetic analysis (Scheme 2), we designed and obtained shikonin ketone derivative as one of the key intermediates. In theory, it could be obtained by the Friedel–Crafts reaction between 1,4,5,8-tetramethoxynaphthalene and 3-pentenoyl chloride. However, it was proved to be not only uneconomic

Table 1

Synthesis of chiral shikonin by the addition of chiral auxiliaries



Ligand	T (°C)	Equivalent of the ligand	γ-adduct (%)	α-adduct (%)	ee
1	120	0.2	0	100	0
1	100	0.2	75	25	0
1	80	0.2	95	5	0
1	25	0.2	100	0	71% (R)
2	120	0.2	0	100	0
2	120	1.0	0	100	0
2	120	1.5	0	100	0
2	120	2.0	0	100	0

but also unsuccessful after extensive tests. At last, we chose 2 as a starting material, which was synthesized in good yield according to our reported procedures.¹³ Based on the convenient synthesis of protected (\pm) -shikonin (3), the shikonin ketone derivative (4) was obtained by Dess-Martin oxidation (80%) (Scheme 3). Then how to achieve the asymmetric reduction of 4 in high optical purity became an urgent problem.

Recently, with the development of novel planar chiral metallocenyl ligands and their applications in different types of asymmetric synthesis,14 the Ru(II)-catalyzed asymmetric hydrogenation of simple ketones with this ligands becomes one of the simplest ways to produce chiral alcohols. Here, one of the C₂-symmetric phosphinooxazoline ruthenocenes L-3^{14f,h} (Fig. 1) was first used by us in the Ru(II)-catalyzed asymmetric hydrogenation of 4, and 5 was obtained with almost quantitative conversion and high enantioselectivity.¹⁶ After **5** had been afforded, shikonin¹⁷ was easily achieved in excellent enantioselectivity (99.3% ee) based on our efficient and mild deprotection procedures of the methyl protecting groups^{7,15} by three chemical operations, including acetylation-oxidation, reduction-acetylation, and oxidation-hydrolysis-neutralizationtautomerization (Scheme 3).

Conclusions

In summary, based on the concise synthesis of protected (±)shikonin via a one-pot procedure of two steps, a shorter and powerful total synthesis of shikonin was described with only six steps in excellent enantiomeric excess (99.3% ee) and high yield (47%). The key step of the synthetic strategy involved an economic and efficient Ru(II)-catalyzed asymmetric hydrogenation with C2-symmetric planar chiral ruthenocene phosphinooxazoline ligand (L-3), followed by the efficient deprotection procedure of the methyl protecting groups. This research has made it possible for the concise and efficient synthesis of high enantioselective shikonin in large scale. Meanwhile, it could be preliminarily confirmed that the chiral side chain of shikonin might be difficult to construct in one step with both stereoselectivity and α -regioselectivity.

Acknowledgments

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- 16. The procedure for the asymmetric hydrogenation of 4 to obtain 5. Under an atmosphere of argon, 1 mol % of [RuCl₂(PPh₃)₃] and 0.65 mol % of chiral ligand L-3 were dissolved by heating at reflux in degassed dry 2-propanol (3 mL) for 1 h. After quickly cooling to 0 °C, a solution of 4 (0.4 mmol) in degassed dry 2propanol (2 mL) was added. Then a solution of t-BuOK in degassed dry 2propanol (0.2 M, 0.2 mL) was added to the mixture, which was stirred under a

 $\rm H_2$ atmosphere (10 atm) at 0 °C for 24 h in an autoclave. Then the above reaction mixture was concentrated under reduced pressure. The residue was determined by HPLC directly to give the percent conversion and purified by column chromatography with ethyl acetate/petrol ether (1:3) to afford pure product.

product. 17. The characterization of shikonin: HPLC (Sino-Chiral OD, no. 0A02014-C), 99.3% ee, hexane/*i*PrOH = 9:1 (Mobile phase), 0.6 ml/min (Flow rate), 516 nm (λ); HRMS: calcd for: C₁₆H₁₆O₅ 288.0998, found 288.1016; [α]²⁵_D = +237.1 (*c* 0.004, EtOH); ¹H NMR (400 MHz, CDCl₃): δ 12.58 (s, 1H, ArOH), 12.48 (s, 1H, ArOH), 7.19–7.16 (m, 3H, ArH and H_{quin}), 5.20 (dd, *J* = 8.0, 6.8 Hz, 1H, CH=C), 4.93–4.90 (m, 1H, ArCHOH), 2.39–2.32 (m, 2H, CH₂), 1.76 (s, 3H, CH₃), 1.65 (s, 3H, CH₃) ppm; ¹³C NMR (75 MHz, DMSO-*d*₆): δ 180.6 (C=O), 179.7 (C=O), 164.0 (*C*_{Ar}OH), 163.4 (*C*_{Ar}OH), 153.6 (*C*_{Ar}CH), 132.9 (*C*_{Ar}H), 131.8 (CH=C), 131.7 (*C*_{Ar}H), 131.6 (*C*_{Ar}H), 120.4 (CH=C), 111.7 (*C*_{Ar}), 111.2 (*C*_{Ar}), 66.4 (COH), 35.3 (CH₂), 25.5 (CH₃), 17.7 (CH₃) ppm.