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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.

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 antitumor[6] 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 synthesis[8] 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, HNO_3); 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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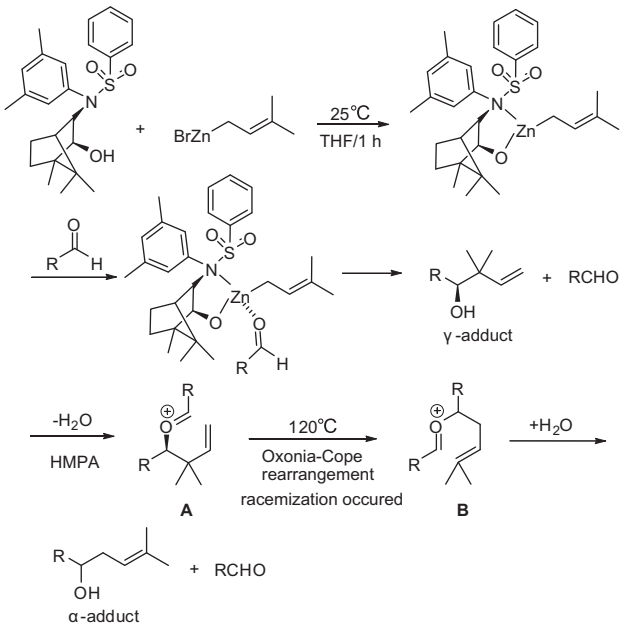
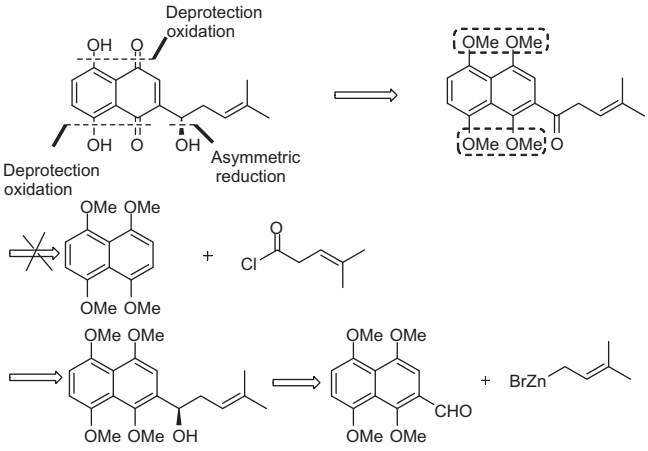
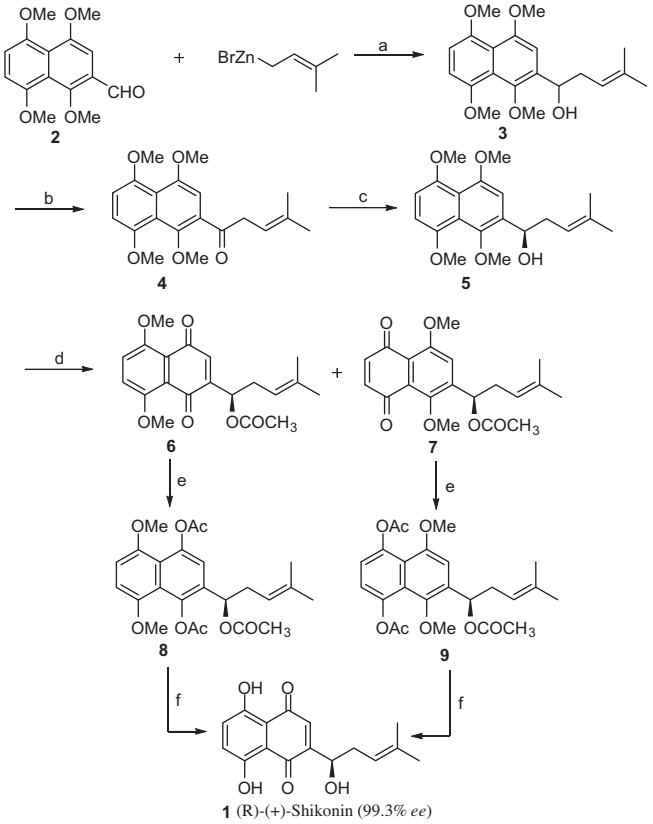


R = 2-substituted-1,4,5,8-tetramethoxynaphthalene

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.



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) $RuCl_2(PPh_3)_3$/**L-3**, *t*-BuOK/*i*-PrOH, H_2 (10 atm), 0 °C, 24 h, 99%; (d) Ac_2O, Et_3N, DMAP, dry CH_2Cl_2, rt, 20 min, then CAN, CH_2Cl_2, rt, 15 min, 25% (**6**), 67% (**7**); (e) Zn, Ac_2O, Et_3N, DMAP, 2 h, rt, 76% (**8**), 86% (**9**); (f) CAN, CH_3CN, rt, 10 min, then 1 M NaOH, 6 h, then 10% HCl, 85%.

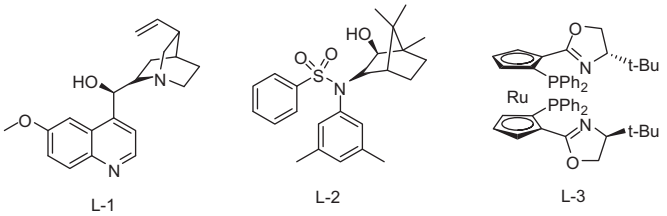


Figure 1. Ligands **1**, **2**, and **3**.

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 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