A new synthetic method toward a key intermediate in the total synthesis of alkannin and shikonin

Xiaogang Zheng¹, Hang Hu² and Defeng Xu²

Abstract
In the present work, a new synthetic method toward a key intermediate in the total synthesis of alkannin and shikonin is developed. The key intermediate, 4-methyl-1-(naphtho[1,8-de:4,5-d’e’]bis([1,3]dioxine)-4-yl)pent-3-en-1-one (5), is synthesized via the reaction of 1,8:4,5-bis(methyleneedioxy)naphthalene-2-carboxylic acid N-methoxy-N-methylamide with prenyllithium. This synthetic approach avoids the use of N-methoxy-N,4-dimethylpent-3-enamide, which is not easy to obtain, and the toxic reagent sodium cyanide.

Keywords
alkannin, key intermediate, prenyllithium, shikonin, synthetic route

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Introduction
Alkannin (1) and shikonin (2) (Figure 1) and their derivatives are naturally occurring purple pigments found in the roots of many traditional medicinal plants of the Boraginaceae family such as Alkanna tinctoria, Lithospermum erythrorhizon, Arnebia hispidissima, and Echium lycopsis.¹ Alkannin and shikonin are enantiomers. These compounds show a wide range of significant pharmacological activities, such as antibacterial,² anti-inflammatory,³ antifungal,⁴ and antitumor.⁵–⁸ Many methodologies on their total synthesis have been described.⁹–¹² Nicolaou¹³ reported a concise and efficient total synthesis of alkannin and shikonin. However, the toxic reagent sodium cyanide (NaCN) was used in their synthetic route (Scheme 2).

Herein, we report a new procedure for the synthesis of 4-methyl-1-(naphtho[1,8-de:4,5-d’e’]bis([1,3]dioxine)-4-yl)pent-3-en-1-one (5) (Scheme 3).

Results and discussion
Compound 5 was synthesized in four steps starting from 1,8:4,5-bis(methyleneedioxy)naphthalene (3) (Scheme 3). Compound 3 was acetylated by Friedel–Crafts acylation with acetyl chloride in the presence of AlCl₃ to afford 50% conversion. The asymmetric reduction of compound 5 followed by a one-step deprotection allowed easy and efficient access to alkannin and shikonin. Kim and co-workers¹⁴ used another method to synthesize compound 5; however, the toxic reagent sodium cyanide (NaCN) was used in their synthetic route (Scheme 2).

Compound 5 was synthesized via the reaction of 1,8:4,5-bis(methyleneedioxy)naphthalene-2-carboxylic acid N-methoxy-N-methylamide with prenyllithium. This synthetic approach avoids the use of N-methoxy-N,4-dimethylpent-3-enamide, which is not easy to obtain, and the toxic reagent sodium cyanide.

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2-acetyl-1,8;4,5-bis(methylenedioxy)naphthalene (10) in 94% yield.\textsuperscript{15} Compound 10 was then oxidized by tetrabutyl ammonium permanganate in pyridine to afford 1,8;4,5-bis(methylenedioxy)naphthalene-2-carboxylic acid (11) in 88% yield.\textsuperscript{16} The synthesis of compound 11 from compound 3 was also reported in the literature via a different method;\textsuperscript{15} however, 11 was obtained in a lower yield of 45% via this method. Treatment of compound 11 with oxalyl chloride in dichloromethane afforded the corresponding acyl chloride.\textsuperscript{17} Subsequent treatment of this acyl chloride with N,O-dimethyl hydroxylamine hydrochloride in the presence of pyridine in dichloromethane afforded 1,8;4,5-bis(methylenedioxy)naphthalene-2-carboxylic acid N-methoxy-N-methylamide (12) in 79% yield.\textsuperscript{18} The addition of prenyllithium to compound 12 afforded the desired compound 5 and 3,3-dimethyl-1-(naphtho[1,8-de:4,5-d’e’]bis([1,3]dioxine)-4-yl)pent-3-en-1-one (13) in 45% and 47% yield, respectively. Compound 5 is more polar than compound 13, and they were separated by column chromatography. The formation of compound 13 may be ascribed to the fact that the prepared prenyllithium exists a mixture of isomers (Scheme 4). The selectivity for compound 5 may be improved using other allylic organometallic compounds such as prenylmagnesium bromide.

**Conclusion**

A new synthetic method toward 4-methyl-1-(naphtho[1,8-de:4,5-d’e’]bis([1,3]dioxine)-4-yl)pent-3-en-1-one (5) has been developed. Compound 5 was synthesized from compound 3 in four steps with an overall yield of 29%. This synthetic approach avoids the use of N-methoxy-N,4-dimethylpent-3-enamide, which is not easy to obtain, as well as the toxic reagent sodium cyanide.
Experimental section

Materials

Compound 3 was synthesized according to a literature method. All other chemicals were of analytical grade and were used as received.

2-Acetyl-1,8:4,5-bis(methylenedioxy)naphthalene (10)

A mixture of 1,8:4,5-bis(methylenedioxy)naphthalene (3) (2.16 g, 10.0 mmol) and anhydrous aluminum chloride (2.70 g, 20.2 mmol) in chloroform (50 mL) was added dropwise to acetyl chloride (0.9 g, 12.6 mmol), and the resulting mixture was stirred at room temperature for 3 h. When the reaction was complete, the mixture was poured into ice-water (30 g), 10% hydrochloric acid (30 mL) was added, and the mixture was filtered. The residue was recrystallized from petroleum ether to give compound 10 as light yellow crystals (2.42 g, 94%). M.p. 168–170 °C. 1H NMR (400 MHz, CDCl3): δ 7.35 (s, 1H, ArH), 6.98 (d, 1H, J = 8.0 Hz, ArH), 6.92 (d, 1H, J = 8.0 Hz, ArH), 5.63 (s, 2H, −OCH2O−), 5.50 (s, 2H, −OCH2O−), and 2.73 (s, 3H, −CH3). 13C NMR (100 MHz, CDCl3): δ 202.3, 144.1, 142.8, 142.4, 141.7, 121.5, 120.6, 114.8, 106.6, 104.3, 101.5, 91.7, and 26.8. HRMS (EI): m/z [M + H]+ calcd for C14H11O5: 259.0606; found: 259.0594.

1,8:4,5-Bis(methylenedioxy)naphthalene-2-carboxylic acid (11)

Tetrabutylammonium permanganate (6.8 g, 18.9 mmol) was added to a solution of compound 10 (2.16 g, 10.0 mmol) in pyridine (60 mL) and the mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. The reaction mixture was poured into 15% hydrochloric acid (250 mL) containing sodium hydrogen sulfite (5.0 g, 48.1 mmol) and extracted with chloroform (100 mL × 4). The chloroform solution was washed with 10% hydrochloric acid (100 mL × 2), and brine (70 mL × 2), dried over anhydrous sodium sulfate, and concentrated. The crude product was chromatographed on silica gel to give compound 11 as yellow crystals (2.14 g, 88%). M.p. 258–260 °C (lit. m.p. 258–261 °C). 1H NMR (400 MHz, CDCl3): δ 7.47 (s, 1H, ArH), 7.02–7.00 (m, 2H, ArH), 5.68 (s, 2H, −OCH2O−), and 5.53 (s, 2H, −OCH2O−).

1,8:4,5-Bis(methylenedioxy)naphthalene-2-carboxylic acid N-Methoxy-N-methylamide (12)

To a solution of compound 11 (1.24 g, 4.61 mmol) and N,N-dimethylformamide (two drops) in dichloromethane (10 mL) cooled in an ice-bath, oxalyl chloride was added dropwise (0.85 g, 10.0 mmol) over 10 min. The mixture was stirred at 0 °C for 30 min, and then allowed to warm to 20 °C for 3 h. The solvent and excess oxalyl chloride were
removed in vacuo to give the corresponding acyl chloride. The acyl chloride in dichloromethane (10 mL) was cooled in an ice-bath and added dropwise to a mixture of N,N-dimethylhydroxylamine hydrochloride (0.9 g, 9.3 mmol) and pyridine (0.8 g, 10.1 mmol) in dichloromethane (15 mL) and stirred at 0 °C for 2 h under a nitrogen atmosphere. The reaction mixture was poured into ice-water (30 g) and extracted with dichloromethane (100 mL × 2). The dichloromethane solution was washed with 5% hydrochloric acid (30 mL × 2), and water (30 mL × 2), dried over anhydrous sodium sulfate, and concentrated. The crude product was chromatographed on silica gel to give the compound 12 as white crystals (1.07 g, 79%). M.p. 124–126 °C. 1H NMR (400 MHz, CDCl3): δ 6.89 (s, 1H, ArH), 6.85 (s, 2H, ArH), 5.53 (s, 2H, –OCH2O–), 3.60 (s, 3H, –NCH3), and 3.36 (s, 3H, –OCH3). 13C NMR (100 MHz, CDCl3): δ 169.5, 143.8, 142.6, 142.3, 141.5, 120.9, 120.4, 111.2, 106.0, 104.3, 102.9, 91.6, 91.2, 63.7, and 33.4. HRMS (EI): m/z [M + H]⁺ calcld for C18H17O5: 313.1076; found: 313.1082; m/z [M + H]⁺ calcd for C18H16O5: 312.1076; found: 312.1063.

Declaration of conflicting interests
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