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Synthesis Method of 17-Hydroxyjolkinolide B

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ABSTRACT

The invention provides a synthetic method of 17-hydroxyjolkinolide B, which comprises the following steps of: carrying out ring-forming reaction on a double bond at the C11 position of an epoxy ring by taking the Jolkinolide A, I as a raw material; brominating a methyl group at the C17 position on a lactone ring; carrying out debromination acetylation; and finally hydrolyzing acetyl to obtain the 17-hydroxyjolkinolide B, V. The invention develops a method for synthesizing 17-hydroxyjolkinolide B, V, which provides a basis for research and development of euphorbide drugs. The successful synthesis of 17- hydroxy-euphorbide B (17-hydroxyjolkinolide B, V) has provided a new direction for the research of anticancer drugs due to its further structural modification. The successful conversion of Jolkinolide A, I to 17-hydroxyjolkinolide B, V improves the quality of effective substances and reduces the cost of separating 17-hydroxyjolkinolide B, V from natural Euphorbia fischeriana.

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Synthesis Method of 17-Hydroxyjolkinolide B

TECHNICAL FIELD

The invention belongs to the field of medicine synthesis, and relates to a synthesis method of a natural euphorbia lactone compound 17-hydroxyjolkinolide B.

BACKGROUND

Euphorbia Fischeriana Steud, earliest recorded in the *Shennong's Herbal Classic*, is an authentic northern medicine in China. As a traditional Chinese medicinal, it has a long application history and is often used for the treatment of cancer, tuberculosis and ascites diseases based on the principle of "combating poison with poison". It is also used for anti-inflammation and deworming. Its root is steamed with jujube, which is used for advanced cancer and postoperative treatment of cancer, as well as anti-inflammation and deworming. *Euphorbia Fischeriana Steud* contains various diterpenoids, such as Jolkinolid A (JA), Jolkinolid B (JB)，17-Hydroxy-jolkinolid B (HJB). In the early stage, there were many reports on the composition analysis of *Euphorbia Fischeriana Steud*, and it was found that the diterpenoids extracted from *Euphorbia Fischeriana Steud* had good anti-tumor activity. Jolkinolid B can inhibit the metastasis of MDA-MB-231 breast cancer cells and induce the apoptosis of breast cancer MCF-7 cells, breast cancer Bcap37 cells and A549 cells. 17-hydroxyjolkinolide B can induce apoptosis of U251 cells and K562 cells. Among them, 17- hydroxy-Euphorbilactone B has the most obvious anti-tumor activity.

It has been reported in the literature that the contents of Jolkinolid B and 17-

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hydroxyjolkinolide B in natural *Euphorbia Fischeriana Steud* plants are relatively low, about 0.001% to 0.003%. The source of monomer compounds is very difficult to meet the current scientific research and development of new drugs. However, the compound has a complex structure and a plurality of chiral centers, and the total synthesis method has a long route and low yield. In this study, a semi-synthetic method was used to synthesize 17-hydroxyjolkinolide B from Jolkinolid A. It was relatively rich in content but had no significant biological activity, to supplement its natural isolation quality. This synthetic work has significant academic and application value for further research on its structural modification and the development of potential antitumor drugs.

SUMMARY

The invention aims to provide a semi-synthetic method of 17-hydroxyjolkinolide B, V, which can improve the yield of 17-hydroxyjolkinolide B, V

The invention provides a semi-synthesis method of 17-hydroxyjolkinolide B, V, which comprises the following steps:

(a)The C11-position double bond on the epoxy ring of Jolkinolid A(I) is subjected to cyclization reaction to obtain Jolkinolid B (II);

(b) bromination reaction is carried out on C17-position methyl on lactone ring of Jolkinolid B (II) to obtain a brominated intermediate (III);

(c) the brominated intermediate (III) undergoes debromination acetylation at C17 position on the lactone ring to obtain an acetylated intermediate (IV);

(d) hydrolyzing the C17 acetyl group on the lactone ring of the acetylation

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intermediate (IV) to generate the 17-hydroxyjolkinolide B (V).

The new semi-synt

hetic method of 17-hydroxyjolkinolide B, V has provided the basis for the study of terpenes in Euphorbia fischeriana.

The successful synthesis of 17-hydroxyjolkinolide B, V provides a better modifiable site for the development of anticancer drugs, and is of great significance for the development of anticancer drugs.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a semi-synthetic route of 17-hydroxyjolkinolide B, V.

Figure 2 is a preparation diagram of Jolkinolid B(II).

Figure 3 is a preparation diagram of the brominated intermediate (III).

Figure 4 is a preparation diagram of the acetylated intermediate (IV).

Figure 5 is a preparation diagram of the 17-hydroxyjolkinolide B, (V).

DESCRIPTION OF THE INVENTION

The present invention will be described in detail below with reference to examples.

Example

The semi-synthetic route of 17-hydroxyjolkinolide B, V of the present invention is shown in figure 1

The invention provides a semi-synthetic method of 17-hydroxyjolkinolide B , V , which comprises the following four steps:

（a）Preparation of Jolkinolid B (II):

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Jolkinolid A (I) (170 mg, 0.5 mmol) was dissolved in dichloromethane (150.0 mL) and m-CPBA(172.0 mg, 2.0 eq) was added. After the reaction was stirred for 5 h at room temperature, 10% aqueous $Na_2S_2O_3$ solution (150 mL) was added to terminate the reaction. Extraction with ethyl acetate (3×120 mL), the ethyl acetate layer washed with saturated saline (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the crude product. The product was isolated on a silica gel column eluting with Hexane/EtOAc=8/2 (800 mL) to give Jolkinolide B, II (123.0 mg) in 73% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 4.04 (s, 1H), 3.68 (s, 1H), 2.28 (s, 1H), 2.09 (s, 3H, 17-CH_3), 2.03-1.81 (m, 2H), 1.79 (m, 1H), 1.62-1.46 (m, 4H), 1.40-1.23 (m, 2H), 1.18 (m, 1H), 0.94 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.83 (s, 3H, CH_3)。 ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 169.5, 148.4, 131.2, 85.4, 66.1, 60.9, 55.3, 53.3, 47.8, 41.3, 39.2, 39.1, 35.6, 33.5, 33.2, 22.3, 21.4, 18.1, 16.4, 9.7。MS (ESI), *m/z*: 331.2 $[M+H]^+$。

（b） Preparation of brominated intermediate (III)

Compound Jolkinolide B, II (165.0 mg, 0.50 mmol) was dissolved in carbon tetrachloride (25.0 mL) and dichloromethane (5.0 mL) to which was added NBS(445.0 mg, 5.0 eq) and AIBN(82.0 mg, 1 eq) with stirring at 70 C under reflux. After 30 h of reaction, saturated NaHCO3 solution (100 mL) was added to terminate the reaction. Extraction with ethyl acetate (120 mL×3). The ethyl acetate layer was washed with saturated saline (200 mL); Dry over anhydrous sodium sulfate. Filter and concentrating to obtain a crude product. The product was isolated on a silica gel column eluting with Hexane/EtOAc=4/1 (1200 mL) to afford Intermediate III (142.8

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mg) in 70% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 4.26 (s, 2H), 4.08 (s, 1H), 3.85 (s, 1H), 2.32 (s, 1H), 2.08-1.76 (m, 3H), 1.73-1.46 (m, 6H), 1.40-1.25 (s, 2H), 1.15 (m, 1H), 0.95 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H)。 ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 166.7, 153.2, 130.3, 85.2, 67.9, 62.1, 54.9, 53.4, 47.8, 41.2, 39.2, 39.0, 35.6, 33.5, 33.4, 21.9, 20.8, 18.4, 16.5, 15.4。MS (ESI)，*m/z*: 409.1, 411.1 $[M+H]^+$。

（c） Preparation of acetylated intermediate (IV)

Intermediate III (245.0 mg, 0.6 mmol) was dissolved in DMF(25.0 mL) and AgOAc(171.0 mg, 1.5 eq) was added, stirring them at room temperature. After reacting for 20 h, filter it, add saturated $NaHCO_3$ solution (120 mL) to the filtrate and extract with ethyl acetate (120 mL×3), wash the ethyl acetate layer with saturated salt solution (400 mL) and dry over anhydrous sodium sulfate. Filter and concentrating to obtain a crude product. The product was isolated on a silica gel column eluting with Hexane/EtOAc=3/1 (1100 mL) to afford Intermediate IV (130.4 mg) in 56% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 5.06 (d, 1H, J = 8.4 Hz), 4.92 (d, 1H, J = 8.2 Hz), 4.66 (s, 1H), 3.99 (s, 1H), 2.31 (s, 1H), 2.14 (s, 3H), 2.08-1.78 (m, 2H), 1.62-1.27 (m, 6H), 1.40-1.27 (m, 2H), 1.25 (m, 1H), 0.94 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H)。 ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 170.4, 167.4, 154.5, 128.8, 83.5, 67.4, 61.9, 55.5, 55.3, 54.9, 47.8, 41.2, 39.2, 39.1, 35.6, 33.5, 29.6, 22.7, 21.8, 21.2, 17.3, 15.5。MS (ESI) *m/z*: 389.2 $[M+H]^+$.

（d） Preparation of 17-hydroxyjolkinolide B，**V**

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Intermediate iv (194.0 mg, 0.50 mmol) was dissolved in MeOH(25.0 mL), and Na_2CO_3 solution (0.2 M, 8.0 mL) was added to react for 5 h under stirring at room temperature, then saturated NH_4Cl solution (100 mL) was added and extracted with ethyl acetate (100 mL×3). The ethyl acetate layer was washed with saturated saline (400 mL) and then dried over anhydrous sodium sulfate. Filtering and concentrating to obtain a crude product. The product was separated by silica gel column chromatography and eluted with Hexane/EtOAc=3/1 (1200 mL) to obtain 17-hydroxyjolkinolide B, V (102.0 mg) with a yield of 59%. ^{1}HNMR ($CDCl_3$, 600 MHz) δ: 4.66 (s, 2H), 4.08 (s, 1H), 4.05 (s, 1H), 2.31 (s, 1H), 2.06-1.87 (m, 2H), 1.78 (m, 1H), 1.71-1.44 (m, 6H), 1.31-1.20 (m, 2H), 1.14 (m, 1H), 0.88 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.80 (s, 3H, CH_3)。 ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 168.1, 151.0, 132.7, 85.4, 66.7, 61.5, 56.5, 55.2, 53.5, 47.8, 41.3, 39.2, 39.1, 35.6, 33.5, 33.4, 21.8, 20.8, 18.4, 15.5。MS (ESI)，*m/z*: 347.2 $[M+H]^{+\cdot}$

The method has the beneficial effects that a new semi-synthetic method of 17-hydroxyjolkinolide B, v is developed, which provides a basis for the research of terpenoids in Euphorbia fischeriana. The successful synthesis of 17-hydroxyjolkinolide B, V provides a better modifiable site for the development of anticancer drugs, which is of great significance for the development of anticancer drugs.

Although an embodiment of the present invention has been given herein, it should be understood by those skilled in the art that changes can be made to the

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embodiment herein without departing from the spirit of the present invention. The above-mentioned embodiments are only exemplary, and the embodiments herein should not be taken as limiting the scope of the claims of the present invention.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The invention relates to a synthetic method of 17-hydroxyjolkinolide B, which is characterized by comprising the following steps of:

Using Jolkinolide A, I as the starting material, a cyclization reaction was carried out on the C11 double bond on the epoxy ring to obtain Jolkinolide B, II; Jolkinolide B, (II) performing bromination reaction on the C17 methyl group of the lactone ring to obtain a brominated intermediate (III); Performing debromination acetylation reaction on the C17 position on the lactone ring of the brominated intermediate (III) to obtain an acetylated intermediate (IV); Hydrolysis of the acetylated intermediate (IV) at the C17 acetyl group on the lactone ring yielded the resulting 17-hydroxyjolkinolide B, V; The synthetic route and structure of the Jolkinolide A, Jolkinolide B (II), the brominated intermediate (III), the acetylated intermediate (IV) and the 17-hydroxyJolkinolide B (V) are shown in figure 1.

2. The semi-synthetic method of 17-hydroxyjolkinolide b (v) according to claim 1, is characterized in that:

(a) Perform cyclization reaction on a C11 double bond on an epoxy ring of that Jolkinolide A (I) to obtain Jolkinolide B (II);

(b) Carrying out bromination reaction on the methyl group at the C17 position on the lactone ring of the jolkinolide b (II) to obtain a brominated intermediate (III);

(c) Performing a debromination acetylation reaction on the C17 position on the lactone ring of the brominated intermediate (III) to obtain an acetylated intermediate (IV);

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(d) Hydrolyzing the acetyl group at the C17 position on the lactone ring of the acetylation intermediate (IV) to generate the 17-hydroxyjolkinolide B (V).

3. The semi-synthetic method of 17-hydroxyjolkinolide B (V) according to any one of claims 1 or 2, is characterized in that the epoxidation reagent for the cyclization reaction of step (a) comprises m-CPBA and the solvent comprises dichloromethane.

4. The semi-synthetic method of 17-hydroxyjolkinolide B (V) according to any one of claims 1 or 2, is characterized in that the bromination reaction in step (b) employ a brominating agent comprising NBS, an initiator comprise AIBN and a solvent comprising carbon tetrachloride and dichloromethane.

5 The semi-synthetic method of 17-hydroxyjolkinolide B (V) according to any one of claims 1 or 2, is characterized in that the acetylation reagent employe in step (c) comprises AgOAc and that solvent comprise DMF.

6 The semi-synthetic method of 17-hydroxyjolkinolide B (V) according to any one of claims 1 or 2, is characterized in that the solvent use in that step (d) comprises MeOH, and the basic reagent comprise Na_2CO_3.

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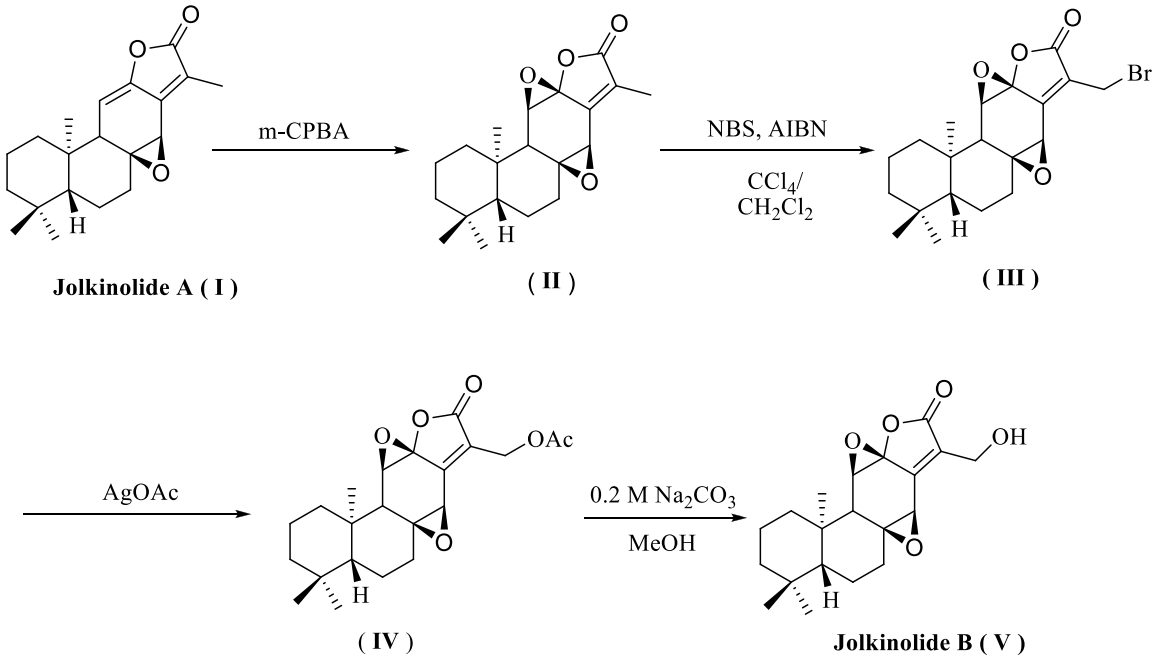
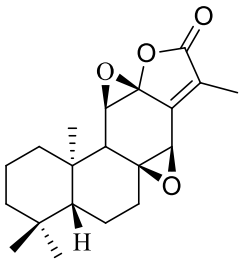
FIGURES



Jolkinolide A (I) **(II)** **(III)**

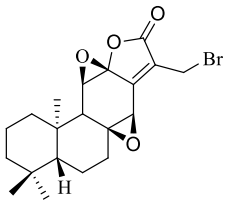
(IV) **Jolkinolide B (V)**

Figure 1



(II)

Figure 2



(III)

Figure 3

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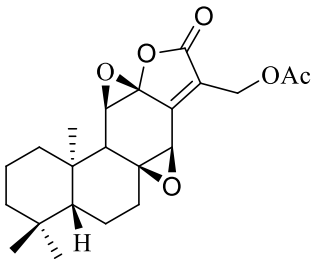
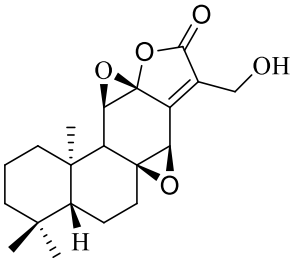


(**IV**)

Figure 4



(**V**)

Figure 5