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History And Artificial Synthesis Method of Tanshinone llA And Its Practical Application

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Abstract:

This work presents a comprehensive review of the history, artificial synthesis, and practical application of Tanshinone IIA, a compound primarily known for its anti-inflammatory properties. Tanshinone IIA suppresses the production of L-Arginine and the activation of inducible nitric oxide synthase (INOS), making it effective in treating inflammatory conditions. The synthesis of Tanshinone IIA involves multiple steps, including monomethylation, Friedel-Crafts bromination, halogenation, allylation, radical cyclization, and catalytic reduction, with 15-naphthalenediol serving as a cost-effective starting material. The artificial synthesis method provides advantages in terms of scalability and purity compared to traditional extraction. In addition, Tanshinone IIA is now incorporated into Danyi Tablets, a modern pharmaceutical used to treat prostatitis, which is increasingly prevalent among urban males. As traditional Chinese medicine evolves, this compound offers both therapeutic and economic benefits in the medical field.

Keywords: Tanshinone llA; Artificial synthesis; Medicine.

1. Introduction

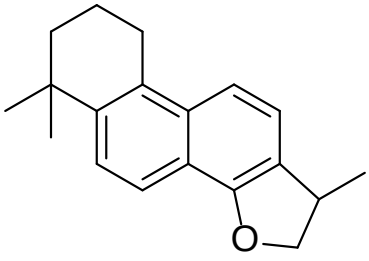

Fig.1 The structure of Tanshinone llA.

Note: Molecular weight:294.34g/mol, Melting point:Approximately 207-209℃.

History:“Shen Nong’s herb classic” is the earliest Chinese pharmacological text and is considered the foundation of Chinese herbal medicine. It details the knowledge and application of various medicinal substances known in ancient China and is revered as the “Bible of Pharmacology.” This book records a medicine named salvia miltiorrhiza and used as antiphlogistic whose main main components include Tanshinone llA. This evidence shows that Chinese

have taken this medicine to diminish inflammation for at least 2 thousand years [1].

Until 1934, The researchers from the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, first extracted Tanshinone llA from Salvia miltiorrhiza through a physical process including cutting up,dissolving, separating and purification.

Now, according to the report of National Bureau of Statistics of China among urban young males' morbidity of prostatitis is between 20% and 30%. This trend accelerates people's need for medicine that can cure prostatitis. A new medicine named Danyi Tablets substitutes Qian Lie Kang pills mainly composed of Astragalus membranaceus and Plantago asiatica. However, Qian Lie Kang pills have many side effects including stomach discomfort, anaphylaxis and damaging to liver and kidney function.

[2] predicts that prostatitis will be more and more prevalent in the later future, because young male, especially for students, always stay up late, sit for a long time without movement and even drink alcohol, which are the mainly causes of this disease. In this work, I mainly focus on the synthesis and extraction method and the practical application of Tanshinone llA.

Fig.2 Solid Tanshinone llA with a purity of 50%.

Properties: Fat-soluable: carbon carbon double bond make this compound fat-soluable as they enlarge the non-polar region area and increase their hydrophobicity,and also because fat is made up by non-polar molecules so that they stop polar molecule like water go into it.Therefore,we can uptake the compound more easily.

Oxidation resistance:Tanshinone IIA molecule contains multiple conjugated double bonds, which gives it strong electron transfer ability, effectively capturing and neutralizing free radicals reducing oxidative stress caused by free radicals[3]. Insoluable in water:The non-polar part accounts for a large proportion in Tanshinone llA,which makes it insoluabe in high polar solvent like water.

2.Artificial Synthesis Method and extraction method

2.1 Artificial Synthesis Method

2.1.1 Monomethylation:Start synthesis from 1,5-Naphthalenediol because it is cheap.

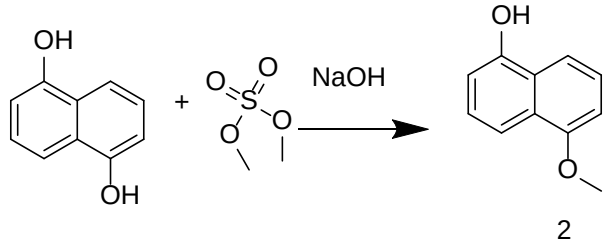

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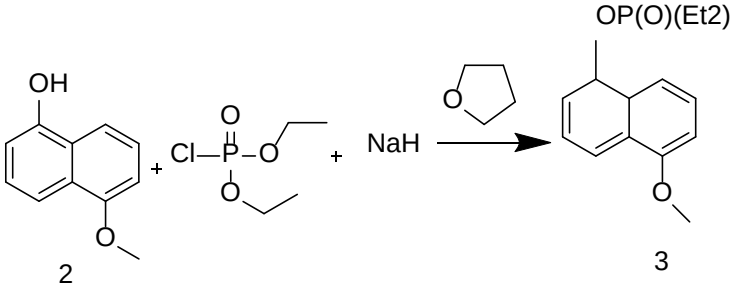
Fig.3 Monomethylation of 1,5-Naphthalenediol.

As shown in figure 3. NaOH solution makes 1,5 naphtalenediol deprotonated more easily, because deprotonated oxygen atom is negative electricity. Hydroxyl group in 1,5 naphtalenediol is nucleophilic reagent, attacking the one of the methyl groups and breaking the O-C bond. Then the methyl group forms a new C-O with the carbon atom in1,5 naphtalenediol. I named the product compound 2[4].

2.1.2 Phosphate Formation:



2 3

Fig.4 Phosphate formation of compound 2.

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As shown in figure 4. NaH, a strong base, can deprotonate the hydroxyl group and form oxygen anion working as nucleophile, which will attack compound 2 and undergo a nucleophilic substitution reaction at the phosphorus atom to form an O-P bond. I named the product compound 3.

2.1.3 Cross-coupling:

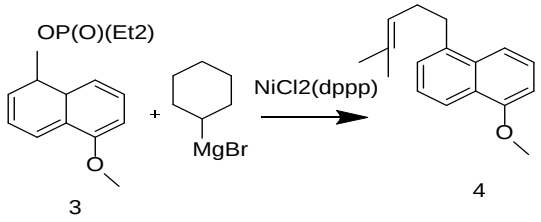

Fig.5 Cross-coupling reaction of compound3.

As shown in figure 5.iCl2(dppp) can activate the Grignard reagent and compound 3, and oxidative addtion reaction occurs between NiCl2(dppp) and Grignard reagent, forming a Ni-C bond and Ni-Br bond. The aryl group will substitute that Br .After that Ni will be reduced. I named the product compound 4.

2.1.4 Friedel-crafts annulation:

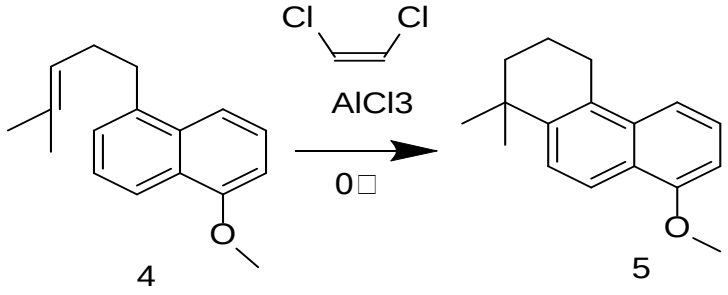

Fig.6 Friedel-crafts annulation og compound4.

As shown in figure 6. In AlCl3 environment, the oxygen atom is deprotonated. During the process,C-H bond on the aromatic ring is broken and form an aromatic radical anion, which works as a nucleophile and attacking another carbon atom on the aromatic ring that has become electrophile due to the complexation of AlCl3.During the nucleophilic substitution, the methyl group attached to the carbon atom breaks the C-C bond as a leaving group. New C-C bond forms connecting the carbon atom of the nucleophile to the attacked aromatic ring. I named the product compound 5.

2.1.5 Bromination:

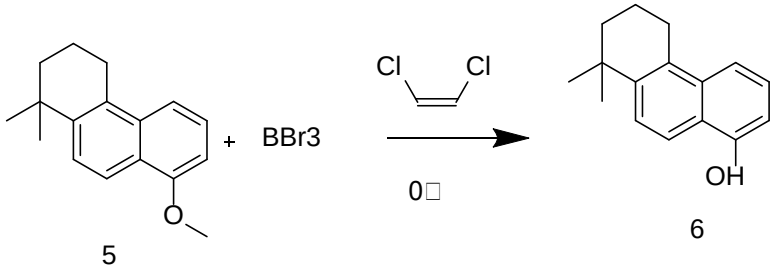

Fig.7 Bromination of compound 5.

As shown in figure 7. The oxygen atom in compound 5 will react with boron tribromide to form a borate ester intermediate and a new B-O bond. During the process,O-H bond breaks and releases a proton. This reaction happens because BBr3 is a lewis acid with empty p orbital and the lone pair of electrons in the oxygen atom can form a new bond with boron atom. I named the product compound 6[5].

2.1.6 Halogenation:

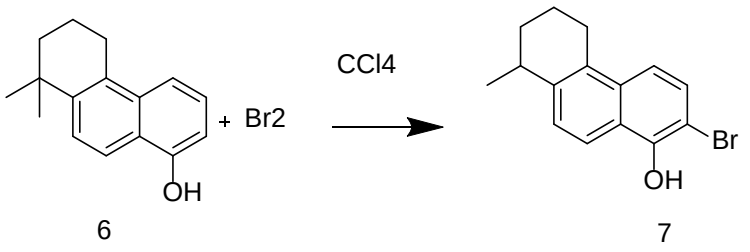

Fig8. Halogenation of compound7.

As shown in figure 8. The bromine moleculeis activated in carbon tetrachloride, forming bromine radicals with high electrophile. A hydrogen atom (C-H bond) on one of the benzene rings in compound 6 is attacked by a bromine radical, leading to the breaking of the C-H bond and the formation of a new radical. The newly formed radical then combines with another bromine atom, forming a new C-Br bond. I named the product compound 7.

2.1.7 Allylation:

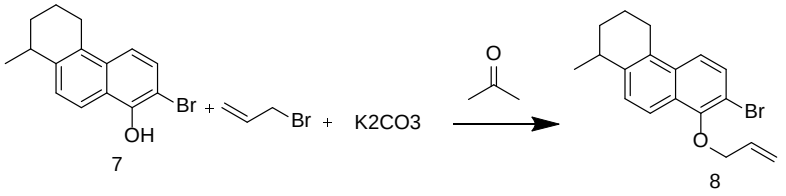

Fig9.Allylation of compound 7.

As shown in figure 9. Potassium carbonate acts as a base to deprotonate allyl bromide, forming an allyl oxide anion working as a nucleophile and attacking an electrophile carbon atom in compund 7. During the process, C-H bond in allyl bromide breaks and forms a new C-C bond with carbon atom in compound 7while bromine atom leaves. I named the product compound 8.

2.1.8 Radical Cyclization:

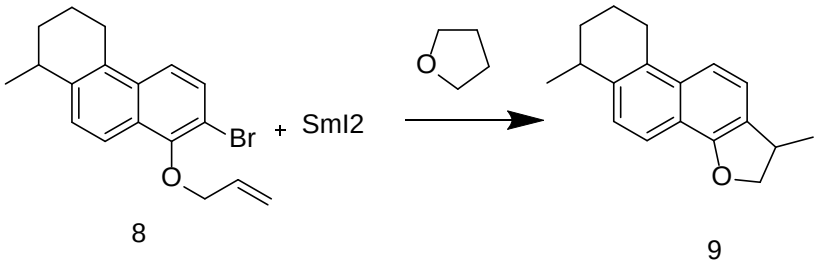

Fig10.Radical cyclization of compound 8.

As shown in figure 10. SmI2 is a strong reductant, reducing a bromine atom breaking C-Br bond and froming a carbon radical. This carbon radical will find nearset carbon atom to attack to complete the intramolecular cyclization process. I named the product compound 9.

2.1.9 Aromatic Nitration:

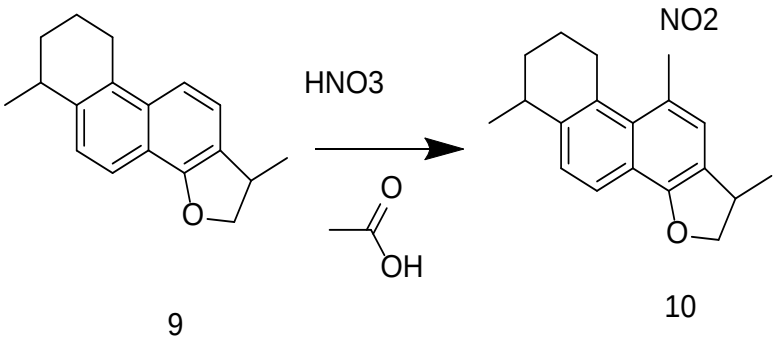

Fig11.Aromatic nitration of compound 9.

As shown in figure 11. Concentrated nitric acid forms a nitrating agent working as electrophile that can attack the aromatic ring. Then the nitrigen atom substitutes the hy-

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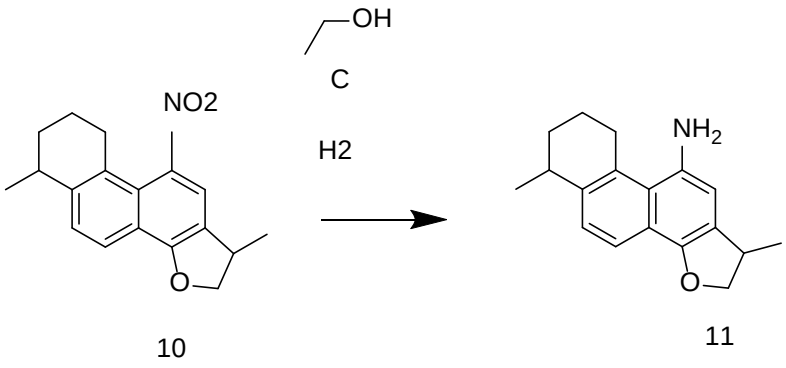
drogen atom and form C-NO2 bond. I named the product compound 10.

2.1.1 0. Catalytic reduction:

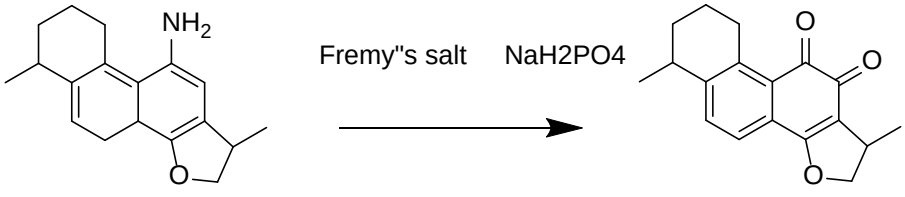


10 11

Fig12.Catalytic reduction of compound 10.

As shown in figure 12. Carbon works as reductant in this reaction, so the nitro is reduced, N-O bond breaks.N-H bon forms because hydrogen is activated and added to the nitrogen atom. The first addition can form -N(OH)OH, the second one form -NOH and the last one form -NH2.I named the product compound 11.

2.1.1 1. Oxidation with Fremy's salt:

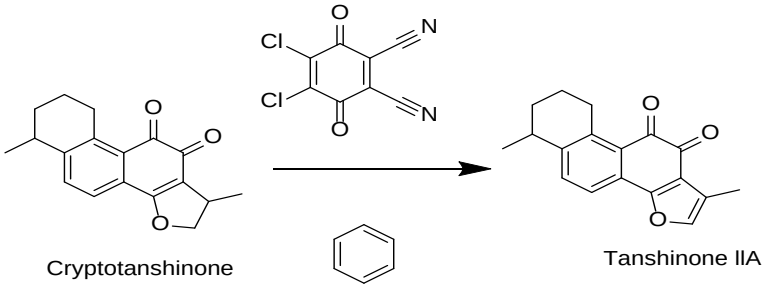


11 Cryptotanshinone

Fig13.Oxidation with Fremy's salt of compound 11.

As shown in figure 13. Fremy's salt is anoxidizing agent,-reacting with-NH2 group because this salt is a lewis acid .During this redox reaction, hydrogen atoms in the amine group is oxidized. So, oxygen atoms subsitute the hydrogen atom in amine group. Then we got Cryptotanshinone,

2.1.1 2. Oxidation with DDQ:



Cryptotanshinone Tanshinone llA

Fig14.Oxidation with DDQ of Cryptotanshinone.

As shown in figure 14.DDQ is an oxidizing agent and DDQ will be activated during the reaction.Activated DDQ will electrophilic attack on the double bond because double bond have higher electron density.The pi electrons on the double bond are transferred to DDQ and double bond breaks and forms 2 carbon radicals.These w carbon radicals combine with the radical part of DDQ to form a new C-C bond.Finally we got Tanshinone llA.

2.2 Extraction method [6]

Preparation of material: The dried roots and rhizomes of Salvia miltiorrhiza are crushed into small pieces to increase the surface area for better extraction.

Extraction: Ethanol is commonly used as a solvent for the extraction of tanshinone IIA. Methods such as maceration, ultrasound-assisted extraction (UAE), and microwave-assisted extraction (MAE) are employed.

Separation and Purification: After extraction, the liquid is filtered to separate the solid residue. Techniques such as high-speed counter-current chromatography, column

chromatography, and preparative high-performance liquid chromatography (HPLC) are used to purify the tanshinone IIA.

Concentration: The liquid extract is then concentrated by removing the solvent through evaporation or distillation, which increases the concentration of tanshinone IIA in the extract.

Drying: The concentrated extract is dried to obtain a powder form of tanshinone IIA

3. Practical application

Medical use: The major function of this compound is to diminish inflammation by preventing inflammatory mediator,a kind of molecule our body release NO when we are hurt or infection and that will cause inflammation through vasodilation process[7].For example,vasodilation process will release lots of NO when blood vessel is stimulated,which makes a tumor on our skin,but Tanshinoe ll A will suppress the activation ofINOS(an enzyme that can induce immune system)to release NO and decrease the concentration of L-Arginine.As shown in figure 15.

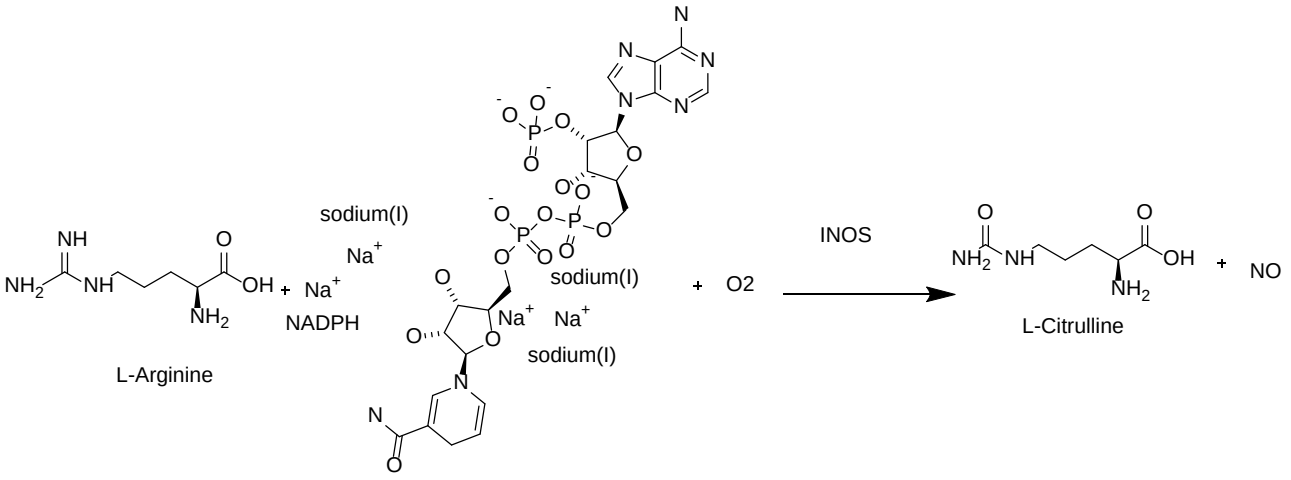


Fig15.The formula of production of NO in our body.

4. Conclusion

Based on the results and discussions presented above,the conclusions are obtained as below:

(1) It is now mainly used in medical field,but I think it will be more and more prevalent in cosmetics since it can diminish free radicals.There are some cosmetics with Tanshinone llA at the market now

(2) The artificial synthesis method needs more costs compared to extraction from herb and produces some toxic reagents,increasing environmental handling fee.

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