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# Facile and efficient total synthesis of (±)-cryptotanshinone and tanshinone IIA

Ying-Yan Jiang, Qian Li, Wei Lu* and Jun-Chao Cai*

*Shanghai Institute of Materia Medica, SIBS, Chinese Academy of Sciences, 294 Taiyuan Road, Shanghai 200031, China*

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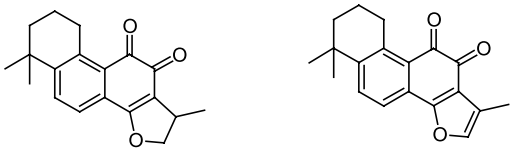
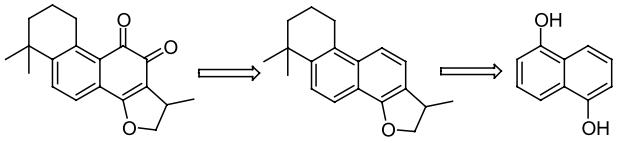
**Abstract**—A concise synthesis of (±)-cryptotanshinone and tanshinone IIA from readily available 1,5-naphthalenediol is described in which the key step is the radical cyclization process promoted by $SmI_2$ to make a furan ring. 

Danshen, the rhizome of *Salvia miltiorrhiza* Bunge, is an ancient drug in Chinese traditional medicine.[1] People use it widely to treat a range of ailments such as heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis.[2] Danshen attracts considerable attention for its broad spectrum of biological activities. Nakao and Fukushima first extracted the tanshinones from Danshen in 1934.[3] After some confusion, extensive studies showed that the tanshinones comprised four compounds named tanshinone I, IIA, IIB and cryptotanshinone.[4] A number of abietane diterpenoid quinones were subsequently isolated. Many exhibit antibacterial, antidermatophytic, antioxidant, anti-inflammatory, antineoplastic, and antiplatelet aggregation activities (Scheme 1).[5–13]



cryptotanshinone tanshinone IIA

**Scheme 1.**



**9**

**Scheme 2.**

There have been many synthetic studies of the tanshinones for their broad spectrum biological activities. In 1968, Baillie and Thomson first reported the total synthesis of cryptotanshinone and tanshinone IIA.[14] Kakisawa also finished a synthesis the same year.[15] They both used a stepwise cyclization approach. Kakisawa synthesized tanshinone I, IIA and cryptotanshinone by a Diels–Alder reaction between benzofuranoquinone and suitable dienes,[16] an efficient method to build the framework. Lee and Snyder used an ultrasound-promoted D–A cycloaddition in the absence of solvent to give tanshinone IIA, nortanshinone, and tanshindiol B.[17] In 1995, Danheiser and co-workers described the application of a photochemical aromatic strategy to the total synthesis of several diterpenoid quinones.[18]

In our program of large-scale screening for cdc25 protein phosphatases inhibitors, we found that cryptotanshinone and tanshinone IIA were moderate inhibitors of cdc25 protein phosphatases. Cdc25 is a potential target for anticancer therapy as it is overexpressed in a number of tumor cells.[19] Specific cdc25 inhibitors may afford a valuable approach in antitumor treatment. The inhibitor activity of cryptotanshinone and tanshinone IIA attracted our interest and we considered promoting their activity by modifying the structures. However, the former synthetic routes have the disadvantages of lack of availability of the starting material or harsh reactions. We needed to develop a convergent strategy to build the tanshinone structures using simple starting materials and reactions.

* Corresponding author. Tel.: 86-21-64311833; fax: 86-21-64370269; e-mail: luwei@mail.shcnc.ac.cn

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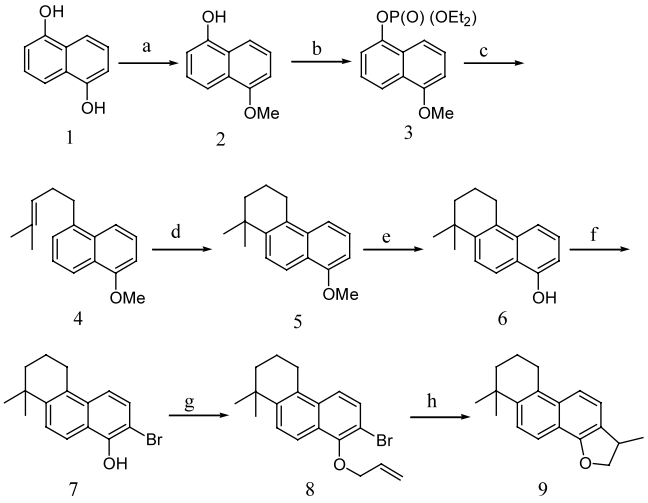
Cryptotanshinone and tanshinone IIA are both tetracyclic compounds, as shown in Scheme 2. We suggested that compound **9** might serve as a suitable precursor to cryptotanshinone and tanshinone IIA. From the structure we found that the B and C rings could be obtained from a naphthalene ring, so we planned to start the synthesis from 1,5-naphthalenediol, which is a cheap accessible intermediate. The naphthalene ring of 1,5-naphthalenediol constructs the B and C rings of tanshinones directly. Ring A could be built up via introduction of an alkyl side chain in the 5-position of 1,5-naphthalenediol, followed by intramolecular Friedel–Crafts annulation.[18,20] The naphthofuran (ring D) was expediently constructed at ambient temperature from an arene bromide with *ortho O*-substituents containing double bonds via a radical cyclization process promoted by $SmI_2$.[21]

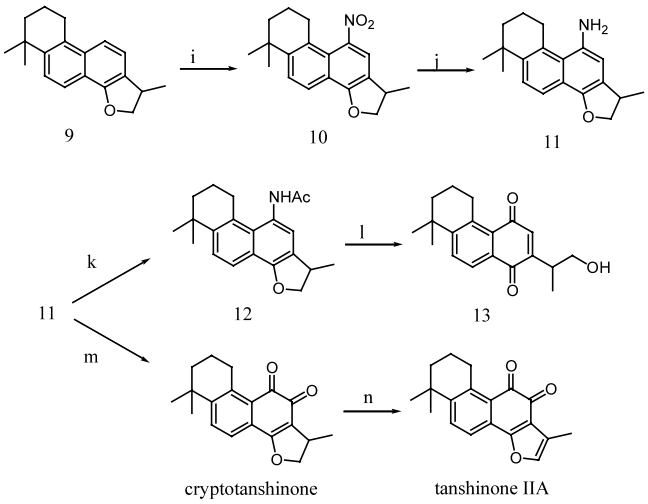
Our approach is shown in Scheme 3. 1,5-Naphthalenediol **1** was monomethylated by treatment with dimethyl sulfate in sodium hydroxide solution.[22] The resulting phenol **2** was reacted with 1.2 equiv. of sodium hydride and 1.1 equiv. of diethyl phosphorochloridate in dry THF to give aryl diethyl phosphate **3**. In the presence of $NiCl_2$(dppp),[20] compound **4** was obtained via cross-coupling of **3** with the Grignard reagent derived from 1-bromo-4-methylpent-3-ene. Cyclization of **4** to **5** proceeded in excellent yield upon exposure to aluminum chloride in dichloromethane at 0°C for 30 min.[18] Treatment of **5** with boron tribromide at 0°C provided the phenol **6** in a 95% yield.[23] Bromine diluted with carbon tetrachloride was dropped slowly into a solution of **6** in carbon tetrachloride in an ice-water bath.[22] The desired bromide **7** was treated with allyl bromide and potassium carbonate to yield compound **8** as a colorless oil.[24] Conversion of **8** into the cyclic product **9** via $SmI_2$-promoted intramolecular cyclization was executed in good yield.[21]

The next step required the introduction of an *ortho*-quinone group to compound **9** to finish the synthetic strategy. Firstly, we suggested that acylamino intermediate **12** would be oxidized by nitric acid/acetic acid to yield the target compound. Thus using mild aromatic nitration conditions **9** was smoothly converted into the nitrated derivative **10**, the nitrated compound **10** was catalytically reduced to amine **11**,[25] which was directly treated with $Ac_2O$ in pyridine to yield acylamino compound **12**. Then **12** was oxidized by nitric acid/acetic acid according to the literature method,[25] however, the furan was opened and we obtained the *p*-quinone **13** in low yield (Scheme 4). Other oxidants were tried in order to oxidize the acylamine **12** or amine **11** to the *ortho*-quinone. Finally we found that Fremy's salt could directly oxidize compound **11** to give (±)-cryptotanshinone in 50% yield as orange needles.[26] Subsequent exposure of cryptotanshinone to 2.5 equiv. of DDQ in benzene afforded tanshinone IIA in 95% yield as red crystals.[18]

In summary, we report a new synthetic method for the synthesis of cryptotanshinone and tanshinone IIA, and demonstrate a facile approach for the construction of the abietane diterpenoid quinones from Danshen.




**Scheme 3.** *Reagents and conditions*: (a) $(CH_3)_2SO_4$, NaOH solution; 55%. (b) $ClP(O)(OEt)_2$, NaH, THF; 98%. (c) $C_6H_{11}MgBr$, cat. $NiCl_2$(dppp), $Et_2O$; 45%. (d) $AlCl_3$, $CH_2Cl_2$, 0°C, 95%. (e) $BBr_3$, $CH_2Cl_2$, 0°C; 95%. (f) $Br_2$, $CCl_4$; 90%. (g) allyl bromide, $K_2CO_3$, acetone; 95%. (h) $SmI_2$, THF; 88%.




**Scheme 4.** *Reagents and conditions*: (i) $HNO_3$, AcOH, 0°C; 87%. (j) $H_2$, Pd/C, EtOH; 99%. (k) $Ac_2O$, pyridine; 100%. (l) $HNO_3$, AcOH; 20%. (m) Fremy's salt, 0.06 M $NaH_2PO_4$; 50%. (n) DDQ, PhH, rt; 95%.

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## References


1. Duke, J. A.; Avensu, E. S. *Medicinal Plants of China*; Reference Publications: Algonac, MI, 1985; Vol. 2, p. 381.
2. *Pharmacology and Applications of Chinese Materia Medica*; Chang, H. M.; But, P., Eds.; World Scientific Publishing: Singapore, 1986; Vol. 1, pp. 255–268.
3. Nakao, M.; Fukushima, T. *J. Pharm. Soc. Jpn.* **1934**, *54*, 154.
4. (a) Takiura, K. *J. Pharm. Soc. Jpn.* **1941**, *61*, 482; (b) Takiura, K. *Chem. Pharm. Bull.* **1962**, *10*, 112.
5. Honada, G.; Koezuka, Y.; Tabata, M. *Chem. Pharm. Bull.* **1988**, *36*, 408.
6. Gao, Y. G.; Song, Y. M.; Yang, Y. Y.; Liu, W. F.; Tang, J. X. *Acta Pharm. Sinica* **1979**, *14*, 75.
7. Houlihan, C. M.; Ho, C. T.; Chang, S. S. *J. Am. Oil Chem. Soc.* **1985**, *62*, 96.
8. Gao, Y. G.; Wang, L. Z.; Tang, K. S. *Chin. J. Integrated Trad. Western Med.* **1983**, *3*, 300.
9. Wu, W. L.; Chang, W. L.; Lee, A. R.; Lin, H. C.; King, M. L. *J. Med. Sci.* **1985**, *6*, 159.
10. Onitsuka, M.; Fujiu, M.; Shinma, N.; Maruyama, H. B. *Chem. Pharm. Bull.* **1983**, *31*, 1670.
11. Lee, A. R.; Wu, W. L.; Chang, W. L.; Lin, H. C.; King, M. L. *J. Nat. Prod.* **1987**, *50*, 157.
12. Luo, H. W.; Hu, X. J.; Wang, N.; Ji, J. *Acta Pharm. Sinica* **1988**, *23*, 830.
13. Fang, C. N.; Chang, P. L.; Hsu, T. P. *Acta Chim. Sinica* **1976**, *34*, 197.
14. Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 48.
15. Kakisawa, H.; Tateishi, M.; Kusumi, T. *Tetrahedron Lett.* **1968**, *34*, 3783.
16. (a) Kakisawa, H.; Inouye, Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1327; (b) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3318.
17. (a) Lee, J.; Snyder, J. K. *J Am. Chem. Soc.* **1989**, *111*, 1522; (b) Lee, J.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 4995.
18. Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341.
19. (a) Galaktionov, K.; Lee, A. K.; Eckstein, J.; Draetta, G.; Meckler, J.; Loda, M.; Beach, D. *Science* **1995**, *269*, 1575; (b) Gasparotto, D.; Maestro, R.; Piccinin, S.; Vukosavljevic, T.; Barzan, L.; Sulfaro, S.; Boiocchi, M. *Cancer Res.* **1997**, *57*, 2366.
20. Hayashi, T.; Katsuro, Y.; Okamoto, Y.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 4449.
21. Inanaga, J.; Ujikawa, O.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 1737.
22. Hannan, R. L.; Barber, R. B.; Rapoport, H. *J.Org. Chem.* **1979**, *44*, 2153.
23. Demuynck, M.; Clercq, M. *J. Org. Chem.* **1979**, *44*, 4863.
24. Martin, S. F.; Garricon, P. J. *J. Org. Chem.* **1992**, *47*, 1513.
25. Alves, G. B. C.; Lopes, R. S. C.; Lopes, C. C. *Synthesis* **1999**, 1875.
26. Best, T. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 647.