Tetrahedron Letters 51 (2010) 540–542

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple and efficient total synthesis of (±)-danshexinkun A, a bioactive diterpenoid from *Salvia miltiorrhiza*

Firouz Matloubi Moghaddam [a,*], Mahdi Moridi Farimani [a,b]

[a] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, PO Box 11155-9516, Tehran, Iran
[b] Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, PO Box 19835-389, Evin, Tehran, Iran

ARTICLE INFO

Article history:
Received 2 September 2009
Revised 17 October 2009
Accepted 20 November 2009
Available online 26 November 2009

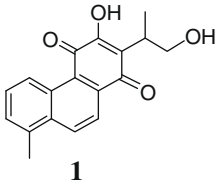
Dedicated to Professor Dr. Peter Rüedi

Keywords:
Danshexinkun A
Diterpenoid
Total synthesis
Salvia miltiorrhiza

ABSTRACT

An efficient 12-step route for the synthesis of the diterpenoid quinone (±)-danshexinkun A in 23% overall yield from the corresponding highly substituted stilbene using a photocyclization strategy is described.

Danshen, the dried root of *Salvia miltiorrhiza*, is a traditional Chinese medicine widely used for the treatment of cardiovascular diseases in China and other countries.[1] More than 50 chemical constituents of Danshen have been identified and shown to possess various biological and pharmacological activities, including improvement of microcirculation,[2] anti-blood coagulation,[3] anti-oxidant,[4] anti-myocardial ischemia,[5] anti-inflammatory,[6] and antineoplastic.[7] Previously, it was shown that the broad spectrum biological activity of Danshen was due to the presence of a number of interesting abietane diterpenoid quinones.[8,9] Nakao and Fukushima first extracted the tanshinones from Danshen in 1934.[10] A number of abietane diterpenoid quinones were subsequently isolated. Unfortunately, further investigation of the most active individual components of *S. miltiorrhiza* has been frustrated by the small amounts of some of these substances in the plant. Therefore, efficient chemical syntheses of these diterpenoids may be the best method for identifying their biological significance. Danshexinkun A **1**, isolated by Fang in 1976,[11] is one of these compounds which was isolated as (+)- and (−)-isomers in minor quantities from the same source. Later, Danheiser described a multistep total synthesis of (+)-(*S*)-danshexinkun A and concluded that the absolute configuration of the natural compound was the same as that synthesized.[12,13] Interestingly, and nearly at the same time, Ikeshiro isolated the new abietane diterpenoid (−)-danshexinkun A from *S. miltiorrhiza*,[14] which was deduced to have the (*R*) configuration.



1

According to Chen et al., (+)-danshexinkun A is an effective coronary vasodilator.[15] It also showed strong inhibitory activity against aldose reductase isolated from the eye lens of rats.[16]

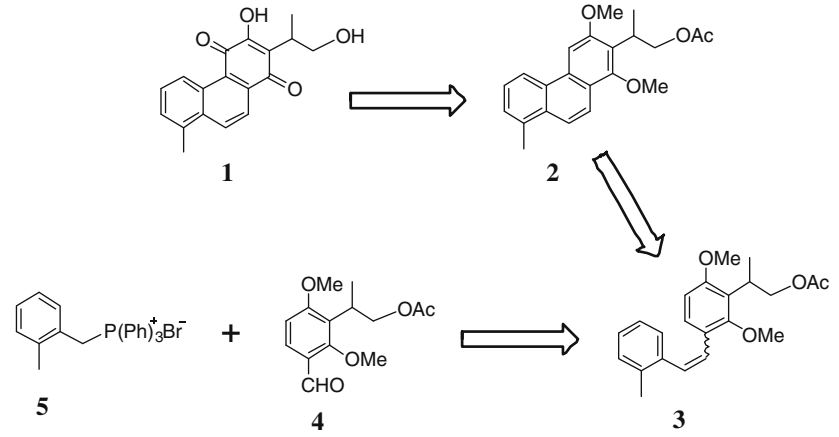
Since both the (+) and (−) enantiomers of danshexinkun A have been isolated from the same plant source, and have both shown biological activity, the racemic molecule was chosen as a synthetic target.

The proposed approach for the synthesis of (±)-danshexinkun A employs photocyclization of a highly substituted stilbene as the key step. The retrosynthesis outlines the application of this strategy to the assembly of the key intermediate **2**, as a precursor to danshexinkun A. Photolysis of stilbene **3** produces the phenanthrene **2** which after deprotection and oxidation affords danshexinkun A **1**. The desired stilbene is prepared via Wittig reaction between aldehyde **4** and phosphonium salt **5** (Scheme 1).

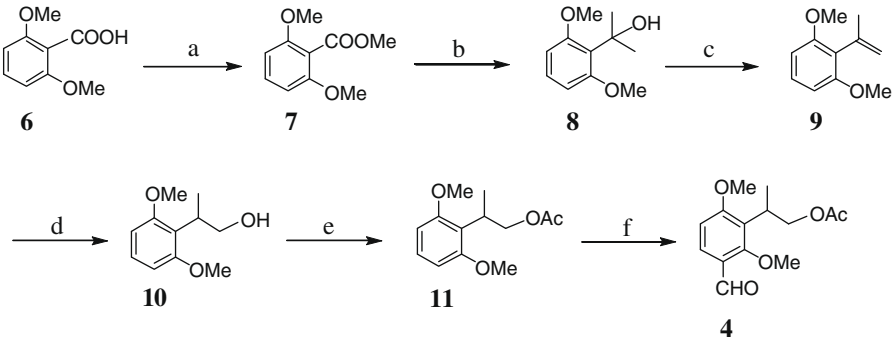
The preparation of aldehyde **4** began from 2,6-dimethoxybenzoic acid **6** and proceeded via the pathway illustrated in Scheme 2. Esterification of **6** with MeOH in the presence of concentrated sulfuric acid[17] afforded methyl ester **7** in 94% yield. Treatment of

* Corresponding author. Tel.: +98 21 66165309; fax: +98 21 66012983.
E-mail address: matloubi@sharif.edu (F.M. Moghaddam).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.093



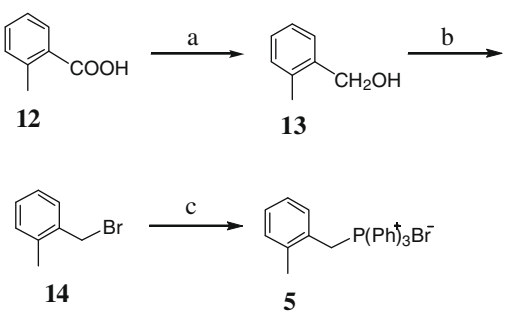
Scheme 1. Retrosynthetic analysis of (±)-danshexinkun A (**1**).



Scheme 2. Reagents and conditions: (a) MeOH, H_2SO_4 (cat), reflux, 18 h, 94%; (b) Mg, dry Et_2O, CH_3I, 93%; (c) *p*-TSA, toluene, reflux, 90%; (d) (i) $NaBH_4$, BF_3, diglyme; (ii) NaOH, H_2O_2, 80%; (e) Ac_2O, py, rt, 24 h, 95%; and (f) $TiCl_4$, Cl_2CHOMe, CH_2Cl_2, ice-acetone bath, 92%.

7 with methylmagnesium iodide provided the tertiary alcohol **8** in good yield. Alcohol **8** was dehydrated in toluene using *p*-toluenesulfonic acid to give terminal alkene **9** in 90% yield. This compound was subsequently transformed into primary alcohol **10** via a regioselective sequence of hydroboration/oxidation with in situ generated diborane. The hydroxy group of **10** was protected with acetic anhydride in pyridine to afford **11** in 95% yield. Finally, compound **11** was transformed into **4** in 92% yield via a modification of Shawe's method.[18]

Phosphonium salt **5** was prepared according to Scheme 3. Reduction of 2-methylbenzoic acid (**12**) with $LiAlH_4$ afforded alcohol **13** in 94% yield. Bromination of **13** with HBr (33%) in acetic acid provided bromide **14** in 93% yield which was subsequently reacted with triphenylphosphine to give phosphonium salt **5** in 92% yield.



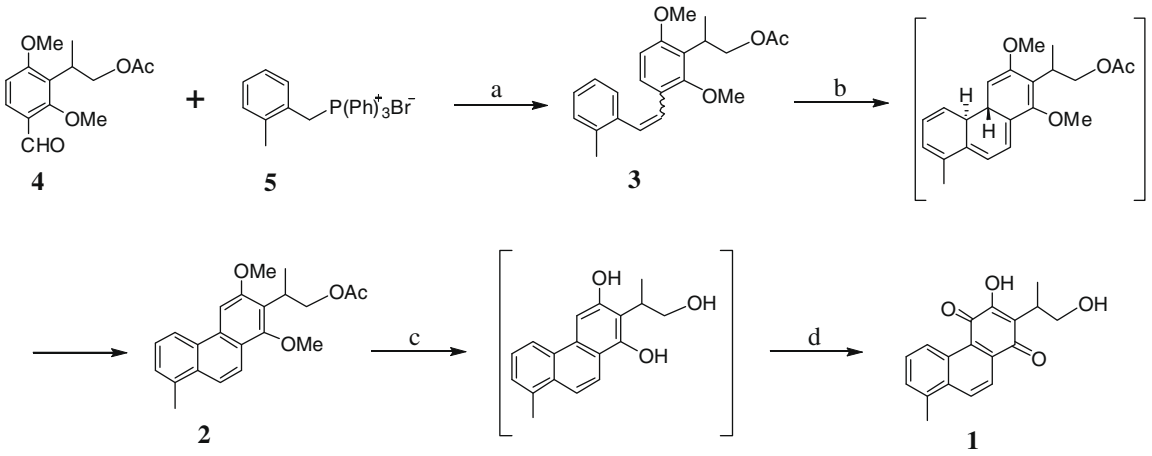
Scheme 3. Reagents and conditions: (a) $LiAlH_4$, dry Et_2O, 94%; and (b) HBr (33%), AcOH, 93%; (c) PPh_3, benzene, 96 h, rt, 92%.

The key intermediate **3** was prepared via a Wittig reaction (Scheme 4). Condensation of aldehyde **4** with the ylide generated by the treatment of phosphonium bromide **5** with *n*-butyllithium, gave stilbene **3** as a mixture of *E*/*Z* isomers (ca. 1:5) which was used in the next stage without separation. The *E*/*Z* ratio was determined from the ^1H NMR spectrum. Photochemical cyclization of stilbene **3** to give phenanthrene **2** was performed according to the method of Weber et al.[19] Thus photolysis of a dilute solution of stilbene **3** in the presence of iodine using a 450 W medium-pressure Hanovia Hg lamp led to the production of phenanthrene **2** in 73% yield via the intermediate dihydro adduct.

The final steps of the synthesis involved demethylation and subsequent oxidation of phenanthrene **2** to afford danshexinkun A. Initial efforts to deprotect **2** with BBr_3[20] led to a low yield of product, which was apparently due to the formation of a pentacyclic ring between the hydroxy groups. Attempts to demethylate with EtSH/$AlCl_3$[21] were unsatisfactory. Ultimately, **2** was deprotected using freshly prepared methylmagnesium iodide at 165 °C in the absence of solvent.[22] Exposure of the resultant crude phenol to oxygen (rt, 12 h) in an alkaline medium led to (±)-danshexinkun A in 72% yield over the two steps.

Recrystallization from CH_2Cl_2/*i*-Pr_2O furnished (±)-danshexinkun A as orange needles, mp 197–199 °C (lit.[12] 198–200 °C). The spectral data were identical with those of the natural product[14] and those of the Danheiser synthesis.[13]

In summary, a straightforward total synthesis of (±)-danshexinkun A **1** has been accomplished in twelve steps from commercially available 2,6-dimethoxybenzoic acid (**6**) and 2-methylbenzoic acid (**12**). This efficient route to (±)-danshexinkun A proceeded in 23% overall yield. Photocyclization of



Scheme 4. Reagents and conditions: (a) *n*-BuLi, dry THF, 0 °C, 81%; (b) *hv*, I_2 (cat), hexane, 2.5 h, 73%; (c) Mg, MeI, 165 °C, 15 min and (d) 2 N NaOH, O_2, 72% (over two steps).

highly substituted stilbene **3** was the key step. This method provides a practical approach to the preparation of (±)-danshexinkun A in high quantity for studying its biological activity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.093.

References and notes

1. Cheng, T. O. *Int. J. Cardiol.* **2006**, *113*, 437–438.
2. Chen, C. G.; Wang, Y. P. *Acta Pharm. Sinica* **2006**, *27*, 217–222.
3. Makino, T.; Wakushima, H.; Okamoto, T.; Okukubo, Y.; Saito, K.; Kano, Y. *Biol. Pharm. Bull.* **2002**, *25*, 523–525.
4. Ji, X.; Tan, B. K.; Zhu, Y. C.; Linz, W.; Zhu, Y. Z. *Life Sci.* **2003**, *73*, 1413–1426.
5. Sun, J.; Huang, S. H.; Tan, B. K.; Whiteman, M.; Zhu, Y. C.; Wu, Y. J.; Ng, Y.; Duan, W.; Zhu, Y. Z. *Life Sci.* **2005**, *76*, 2849–2860.
6. Jang, S. I.; Jeong, S. I.; Kim, K. J.; Kim, H. J.; Yu, H. H.; Park, R.; Kim, H. M.; You, Y. O. *Planta Med.* **2003**, *69*, 1057–1059.
7. Mosaddik, M. A. *Phytomedicine* **2003**, *10*, 682–685.
8. Xiao, P. G. *Modern Chinese Materia Medica*; Chemical Industry Press 1, 2002.
9. Thomson, R. H.. In *Naturally Occurring Quinones*; Chapman & Hall: London, 1987; Vol. 3.
10. Nakao, M.; Fukushima, T. J. *Pharm. Soc. Jpn.* **1934**, *54*, 154.
11. Fang, C. N.; Chang, P. L.; Hsu, T. P. *Acta Chim. Sinica* **1976**, *34*, 197.
12. Danheiser, R. L.; Casebier, D. S.; Loebach, J. L. *Tetrahedron Lett.* **1992**, *33*, 1149–1152.
13. Loebach, J. L. Ph.D. Dissertation, Massachusetts Institute of Technology, 1995.
14. Ikeshiro, Y.; Hashimoto, I.; Iwamoto, Y.; Mase, I.; Tomita, Y. *Phytochemistry* **1991**, *30*, 2791–2792.
15. Chen, C.-C.; Chen, H.-T.; Chen, Y.-P.; Hsu, H.-Y.; Hsieh, T.-C. *Taiwan Pharm. Assoc.* **1986**, *38*, 226–230.
16. Tezuka, Y.; Kasimu, R.; Basnet, P.; Namba, T.; Kadota, S. *Chem. Pharm. Bull.* **1997**, *45*, 1306–1311.
17. Thomas, M.; Varshney, U.; Bhattacharya, S. *Eur. J. Org. Chem.* **2002**, 3604–3615.
18. Shawe, T. T.; Liebeskind, L. S. *Tetrahedron* **1991**, *47*, 5643–5666.
19. Weber, W. P.; Rosen, B. I. *J. Org. Chem.* **1977**, *42*, 3463–3465.
20. Uchida, K.; Fukuda, T.; Iwao, M. *Tetrahedron* **2007**, *63*, 7178–7186.
21. Grese, T. A.; Adrian, M. D.; Philips, D. L.; Shetler, P. K.; Short, L. L.; Glasebrook, A. L.; Bryant, H. U. *J. Med. Chem.* **2001**, *44*, 2857–2860.
22. Lytollis, W.; Scannel, R. T.; Murty, V. S.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12683–12690.