Tetrahedron Letters, Vol. 33, No. 9, pp. 1149-1152, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

TOTAL SYNTHESIS OF DAN SHEN DITERPENOID QUINONES

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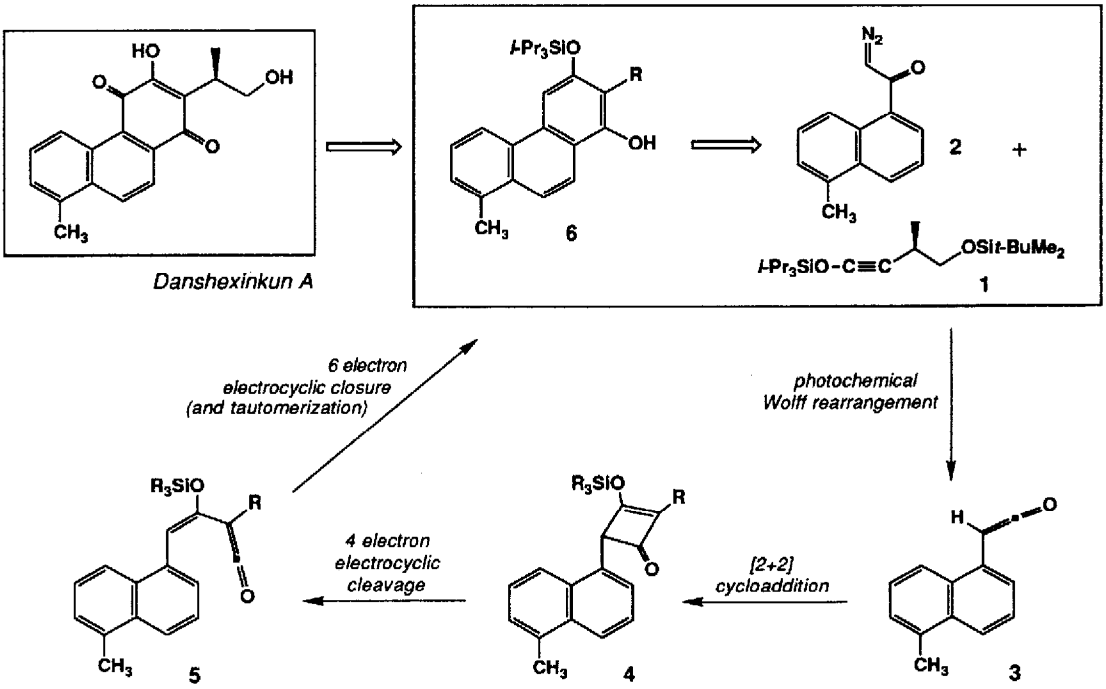
Abstract: *A photochemical aromatic annulation strategy provides efficient synthetic routes to the diterpenoid quinones (+)-danshexinkun A, danshexinkun B, danshexinkun C, (-)-dihydrotanshinone I, and tanshinone I.*

Dan Shen is regarded as one of the most important drugs in Chinese traditional medicine.[2] Obtained from the dried root of the Chinese red-rooted sage *Salvia miltiorrhiza*, today Dan Shen is used clinically for the treatment of heart disease, menstrual disorders, miscarriage, hypertension, and viral hepatitis.[2b] Dan Shen also displays antipyretic, antineoplastic, antimicrobial, and anti-inflammatory properties, and exhibits strong activity against collagen-induced platelet aggregation.[2b,3] Previously it has been shown that the broad spectrum biological activity of Dan Shen is due to a number of interesting abietane diterpenoid quinones.[2-4] Unfortunately, the identification of the most active individual components in *Salvia miltiorrhiza* has been frustrated by the extreme scarcity of some of these substances, and to date all of the medical properties of the crude drug have not been reproduced in the purified natural products.

Previously we have shown that the addition of vinylketenes to acetylenes provides an efficient annulation route to highly substituted aromatic systems.[5] In order to test the utility of this methodology as applied to the assembly of *polycyclic* aromatic systems, we have examined its application to several tri- and tetracyclic diterpenoid quinones isolated from Dan Shen.[6] Herein we report the first total syntheses of (+)-danshexinkun A[7] and (-)-dihydrotanshinone I,[8,9] as well as syntheses of tanshinone I[10,11] and danshexinkuns B[7,9a] and C.[7] The syntheses described here can easily accommodate the production of gram quantities of these diterpenes, and these studies should thus serve to facilitate the systematic investigation of the pharmacological activity of the Dan Shen quinones.

Our synthetic approach to the Dan Shen diterpenes employs the recently developed "second-generation" version of our aromatic annulation strategy[5d] which has expanded the scope of the method to include the synthesis of *polycyclic* compounds which were not readily available using the original cyclobutenone-based reaction. The following retrosynthetic scheme outlines the application of this strategy to the assembly of the key tricyclic intermediate **6**, a precursor to (+)-danshexinkun A, (-)-dihydrotanshinone I, and tanshinone I (vide infra). Irradiation of the α-diazo ketone **2** triggers a photochemical Wolff rearrangement producing the arylketene **3**, which then combines with acetylene **1** in a regiospecific [2+2] cycloaddition. Continued irradiation (or thermolysis, vide infra) brings about the 4π electrocyclic opening of the resulting cyclobutenone **4**, providing a vinylketene (**5**) which undergoes 6π electrocyclization to afford (after tautomerization) the desired tricyclic phenol.

Siloxyalkyne **1** was selected as the acetylene component for the pivotal aromatic annulation step. Siloxyalkynes can be conveniently prepared from carboxylic esters using the Kowalski reaction[12] and function as outstanding ketenophiles in our aromatic annulation reaction.[5c-e,13] The requisite optically active siloxyalkyne **1** was prepared from commercially available (S)-(+)-methyl 3-hydroxy-2-methylpropionate in



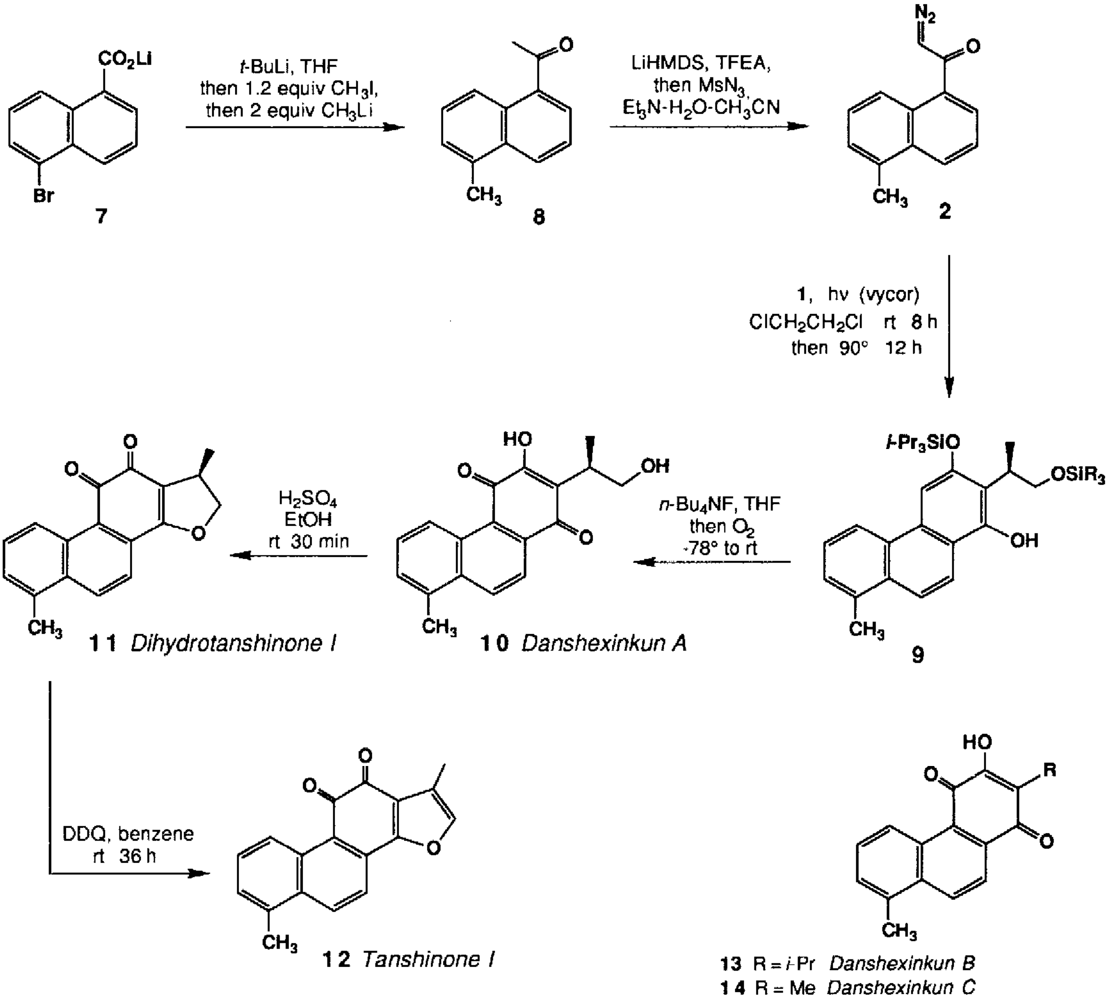
47-53% yield via (a) protection with *t*-butyldimethylsilyl chloride (imidazole, DMF, 25 °C, 45 min), followed by (b) sequential treatment (in one flask) with lithiodibromomethane, *n*-butyllithium, and triisopropylsilyl chloride according to the procedure of Kowalski.[12]

The diazo ketone **2** required for the key aromatic annulation step was prepared from 5-bromo-1-naphthoic acid[14] as outlined in the following scheme. First, sequential treatment of **7** in THF with 2.1 equiv of *t*-butyllithium (halogen-metal exchange), 1.2 equiv of methyl iodide (alkylation), 2.0 equiv of methyllithium, and 20 equiv of Me_3SiCl (conversion of carboxylate to ketone[15] using Rubottom quenching procedure[16]) provided **8** (mp 40-41 °C) in 83-86% yield after purification by column chromatography. Conversion of this ketone to the α-diazo derivative **2** was then achieved by employing the improved "detrifluoroacetylative" diazo transfer method recently developed in our laboratory.[17] The α-diazo ketone **2** was obtained as bright yellow needles (mp 84-85 °C) in 84-94% yield in this fashion.

The key aromatic annulation step was accomplished by irradiating a degassed 0.35 M solution of the diazo ketone **2** and 1.4 equiv of siloxyalkyne **1** in 1,2-dichloroethane in a vycor tube using a low-pressure mercury lamp (254 nm). After 8 h, the resulting solution of the desired annulation product and intermediate **4** was diluted with additional dichloroethane and heated at reflux for 12 h to complete the annulation.[18] Concentration and chromatographic purification furnished the phenol **9**, $[\alpha]_D$ -28.3° (c = 0.12, $CHCl_3$), in 70-75% yield. Cleavage of the silyl ether protective groups and oxidation to produce danshexinkun A was then achieved in a single operation (91% yield) by exposure of **9** to the action of 2.2 equiv of tetra-*n*-butylammonium fluoride in THF (-78 °C to rt, 12 h) in the presence of oxygen. Low temperature recrystallization from ether furnished (+)-danshexinkun A as orange crystals, mp 198-200 °C, $[\alpha]_D$ +30° (c = 0.01, $CHCl_3$), with spectral properties indistinguishable from those of an authentic sample of the natural product.[19,20] This efficient route, which constitutes the first total synthesis of (+)-danshexinkun A, requires only 5 steps from 1-naphthoic acid and proceeds in 37-46% overall yield.

Fang et al. have reported that treatment of (+)-danshexinkun A diacetate with acid results in its conversion to (-)-dihydrotanshinone I.[7] We have found that exposure of **10** to concd sulfuric acid in ethanol at 25 °C for 30 min affords (-)-dihydrotanshinone in 65% yield as red needles, mp 221-222 °C (lit.[21] 224-225 °C), with spectral characteristics identical to those of natural material.[19] In addition, dehydrogenation of **11** to produce tanshinone I was smoothly accomplished by treatment with 1.9 equiv of DDQ in benzene at 25 °C for 36 h. Recrystallization from chloroform furnished tanshinone I in 97% yield as dark red needles, mp 226-227 °C (lit.[21] 233-234 °C), identical in all respects with a sample of the natural product.[19]

In a similar fashion, our aromatic annulation strategy can provide efficient access to a number of other Dan Shen diterpenoid quinones. For example, danshexinkun B (**13**) was obtained in 53-68% overall yield from **2** by substituting i-Pr-C$\equiv$C-OSi(i-Pr)$_3$[5d] for siloxyalkyne **1** in the scheme described above. The synthesis of danshexinkun C (**14**) was achieved through an analogous sequence beginning with the photochemical reaction of 1-methoxypropyne with diazo ketone **2**. Deprotection of the resulting annulation product with boron tribromide in methylene chloride (-78 °C, 30 min) and exposure of the resultant crude phenol to oxygen (rt, 12 h) gave danshexinkun C in 72-77% overall yield.[22]



Acknowledgment. We thank the National Institutes of Health for generous financial support.

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18. In this annulation the accumulation of colored polymers on the walls of the reaction vessel impedes the complete photochemical conversion of intermediate **4** to product.
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20. The optical rotation of (+)-danshexinkun A has not been reported previously. We determined natural danshexinkun A[19] to have $[\alpha]_D$ +30° (c = 0.001, $CHCl_3$).
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(Received in USA 26 November 1991)