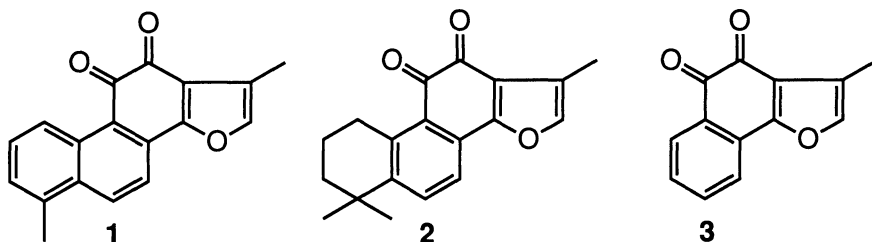


## New Synthetic Strategy for the Construction of the BCD Ring System of Tanshinones

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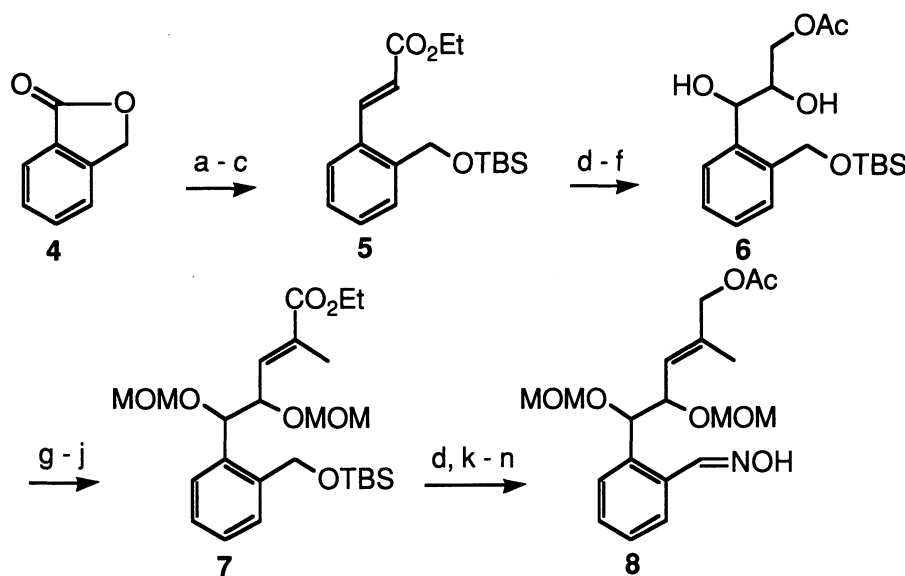
Employing a strategy for the construction of fused furans based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide, the BCD ring system **3** found in the tanshinone family as a common structural unit has been synthesized.

Tanshinones (e.g. tanshinone I **1** and tanshinone IIA **2**), the quinoidal abietane-derived diterpenes, are active components isolated from the Chinese folk medicine Dan-shen, *Salvia miltiorrhiza* Bunge, which has been used widely in China to treat coronary heart and cerebrovascular diseases as well as neurasthenic insomnia.<sup>1)</sup> Inspired by the promising biological activities and intriguing structural features several groups have approached to the synthesis of tanshinones.<sup>2)</sup> We recently developed a general and efficient route to fused furans which utilized a series of reactions, intramolecular [3+2] dipolar cycloaddition of nitrile oxide,<sup>3)</sup> reductive hydrolysis and acid catalyzed cyclization.<sup>4, 5)</sup> We report here a synthesis of the BCD ring system **3**, a common structural unit of tanshinones, as an extension of the intramolecular cycloaddition based methodology for the preparation of functionalized furans.



The oxime **8**, a precursor of nitrile oxide for the key transformation into a requisite fused furan, was prepared uneventfully from phthalide **4** via a standard sequence of reactions. Thus, reduction of **4** with diisobutylaluminium hydride (DIBAH) followed by Wittig reaction and protection of the resulting primary alcohol moiety as tert-butyldimethylsilyl (TBS) ether gave **5**. Reduction with DIBAH, acetylation, and dihydroxylation with osmium tetroxide in the presence of N-methylmorpholine N-oxide provided the *vic*-diol **6**. After protection of the diol moiety as methoxymethyl (MOM) ether, the  $\alpha,\beta$ -unsaturated ester **7** was synthesized by a conventional chain-elongation in a good overall yield. Treatment of the allylic acetate, derived from **7** via DIBAH

reduction and acetylation, with tetrabutylammonium fluoride followed by PDC oxidation gave the corresponding aldehyde, which was then converted into the oxime **8** in an excellent overall yield (Scheme 1).

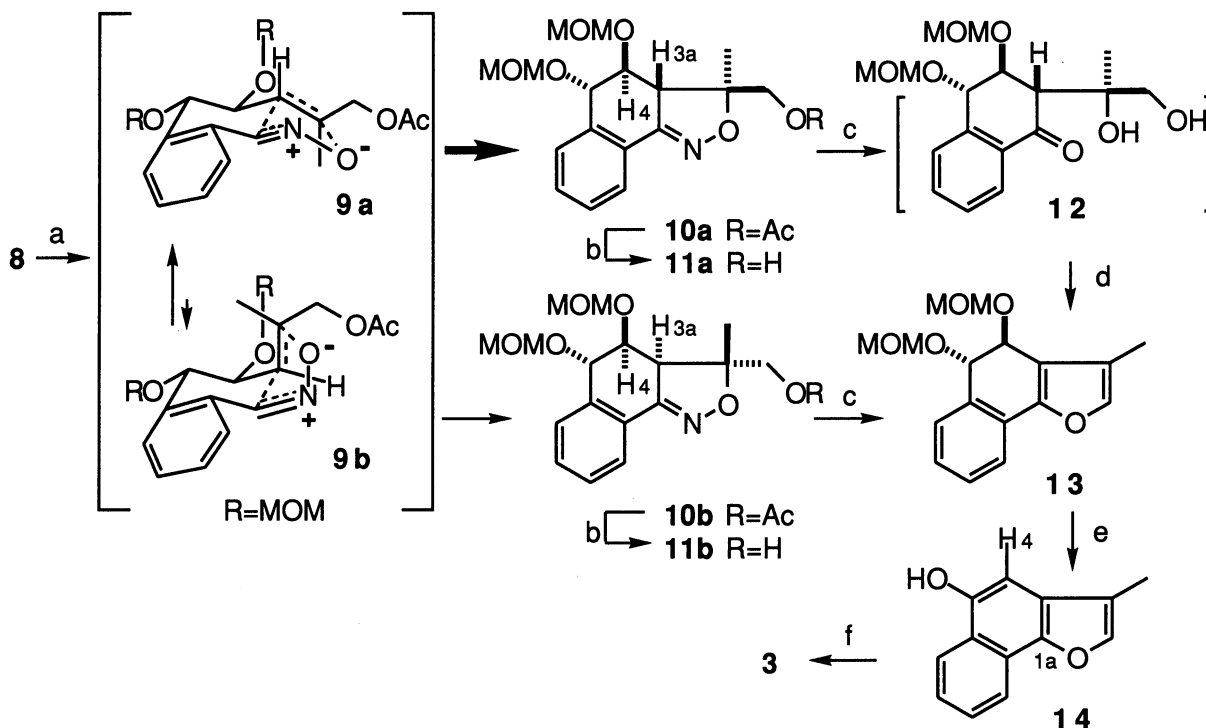


(a)  $i\text{Bu}_2\text{AlH}$ , toluene. (b)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ , benzene, 75% for the 2 steps. (c) TBSCl, imidazole, DMAP, 73%. (d)  $i\text{Bu}_2\text{AlH}$ , THF. (e)  $\text{Ac}_2\text{O}$ ,  $i\text{Pr}_2\text{EtN}$ , THF, 98%, 2 steps. (f)  $\text{OsO}_4$  (cat.), NMO, acetone,  $\text{H}_2\text{O}$ . (g) MOMCl,  $i\text{Pr}_2\text{EtN}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , 87%, 2 steps. (h)  $\text{LiAlH}_4$ , THF. (i)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . (j)  $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ , benzene, 87%, 3 steps. (k)  $\text{Ac}_2\text{O}$ , pyridine, 95%, 2 steps. (l)  $n\text{Bu}_4\text{NF}$ , THF, 93%. (m) PDC,  $\text{CH}_2\text{Cl}_2$ . (n)  $\text{NH}_2\text{OH}\cdot\text{HCl}$ ,  $\text{AcONa}$ , MeOH, 96%, 2 steps.

Scheme 1.

With the substrate for the key reaction in hand, the oxime acetate **8** was reacted with 7% aqueous sodium hypochlorite<sup>6)</sup> in methylene chloride at room temperature to give a chromatographically separable mixture of two diastereoisomeric isoxazolines, **10a** and **10b**, in a ratio of 5.3 : 1 quantitatively. The structures of these adducts are predictable from the mechanistic view point<sup>7)</sup> and the stereochemistry was confirmed by the  $^1\text{H}$  NMR spectroscopy. Thus, the  $^1\text{H}$  NMR spectrum of the major diastereomer **10a**, which would be generated via a more favorable transition state **9a**, showed  $J_{3a,4}$  to be 9.6 Hz, suggesting it to be a 3a, 4-trans arrangement. On the other hand, the  $^1\text{H}$  NMR spectrum of **10b**, derived from the transition state **9b**, revealed a relatively small value (2.1 Hz) for  $J_{3a,4}$  indicative of a cis relationship. Reductive hydrolysis<sup>8)</sup> of **11a**, obtained from **10a** by alkaline hydrolysis, with a catalytic amount of Raney nickel (W-2) and trimethyl borate in aqueous methanol under a pressure of hydrogen (2 kg/cm<sup>2</sup>) gave the  $\beta,\gamma$ -dihydroxy ketone **12** which was immediately treated with a catalytic amount of *p*-toluenesulfonic acid to give the desired fused furan **13** in 47% yield. Interestingly, the conversion of the minor diastereomer **11b** into **13** was achieved directly in 40% yield by exposure of **11b** to the reaction conditions of reductive hydrolysis. Hydrolysis of MOM ethers in **13** with a trace amount of 35%

hydrochloric acid in ethanol at room temperature proceeded cleanly with concomitant monodehydration to produce the furanonaphthol **14**<sup>9</sup>) as a single product in 80% yield. The location of the hydroxy group in **14** was determined mainly based on a <sup>1</sup>H-<sup>13</sup>C long range correlation spectrum, in which the correlative signals between H<sub>4</sub> (δH 6.90) and the C<sub>1a</sub> (δC 145.69) was diagnostic. Finally, oxidation of **14** with potassium nitrosodisulfonate (Fremy's salt)<sup>10</sup> provided a 63% yield of the ortho-quinone **3**, mp 170 - 173 °C (lit.<sup>2b</sup>) 170 - 172 °C), whose spectral properties (<sup>1</sup>H NMR and IR) were completely identical with those of authentic material (Scheme 2).



(a) 7% aq. NaOCl, CH<sub>2</sub>Cl<sub>2</sub>, 100%. (b) LiOH·H<sub>2</sub>O, THF, H<sub>2</sub>O. (c) Raney Ni (W-2), (MeO)<sub>3</sub>B, H<sub>2</sub>, 2 kg/cm<sup>2</sup>, MeOH, H<sub>2</sub>O, 40% for **11b**. (d) *p*-TsOH, CH<sub>2</sub>Cl<sub>2</sub>, 47% (2 steps) from **11a**. (e) concd HCl, EtOH, 80%. (f) Fremy's salt, KH<sub>2</sub>PO<sub>4</sub>, H<sub>2</sub>O, EtOH, 63%.

Scheme 2.

Thus, we synthesized the BCD ring system of tanshinones, demonstrating the validity of the methodology for assembling the functionalized furan.

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- 9) **14**: Colorless prisms, mp 142-144 °C; IR (KBr) 3382 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.86 (1H, br s), 2.24 (3H, d, J=1.0 Hz), 6.90 (1H, s), 7.45-7.60 (2H, m), 7.49 (1H, d, J=1.0 Hz), 8.21 (1H, d, J=7.8 Hz), 8.27 (1H, d, J=8.3 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 8.03, 99.41, 116.42, 119.84, 119.92, 122.88, 123.08, 123.85, 124.22, 126.67, 140.79, 145.69, 148.03; MS *m/z* 198 (M<sup>+</sup>); HR MS Found: 198.0678. Calcd for C<sub>13</sub>H<sub>10</sub>O<sub>2</sub>: 198.0678.
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