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

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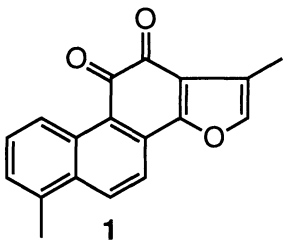
Employing a strategy for the construction of fused furans based on an intramolecular [3+2] dipolar cycloaddition reaction of nitrile oxide, the BCD ring system **3** found in the tanshinone family as a common structural unit has been synthesized.

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 miltiorrihza* Bunge, which has been used widely in China to treat coronary heart and cerebrovascular diseases as well as neurasthenic insomnia.[1] Inspired by the promising biological activities and intriguing structural features several groups have approached to the synthesis of tanshinones.[2] 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,[3] reductive hydrolysis and acid catalyzed cyclization.[4, 5] 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.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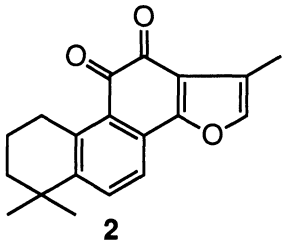
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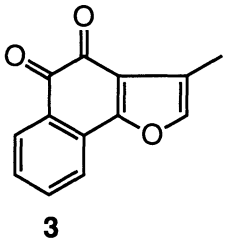
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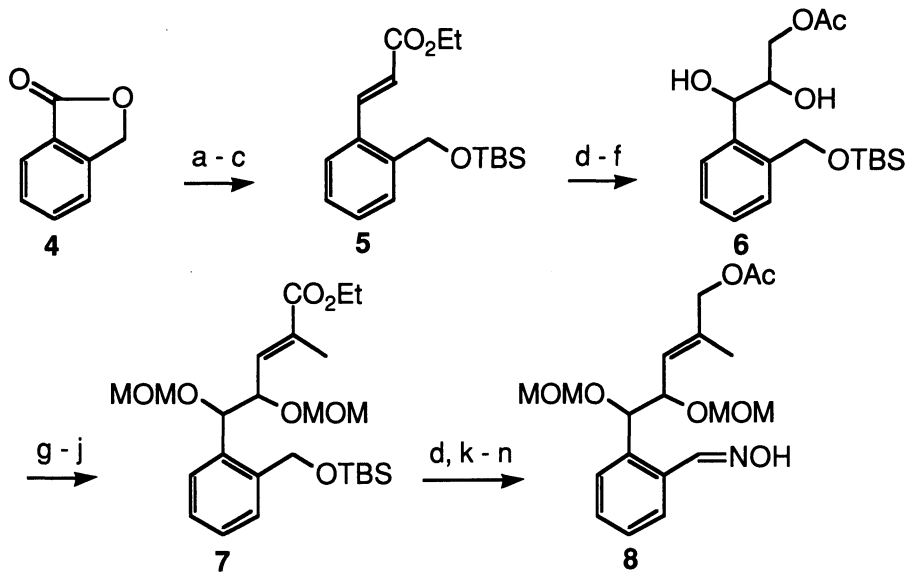
The oxime **8**, a precursor of nitrile oxide for the key transformation into a requisite fused furan, was prepared uneventfully from phthalide **4** via a standard sequence of reactions. Thus, reduction of **4** with diisobutylaluminium hydride (DIBAH) followed by Wittig reaction and protection of the 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 α,β-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).

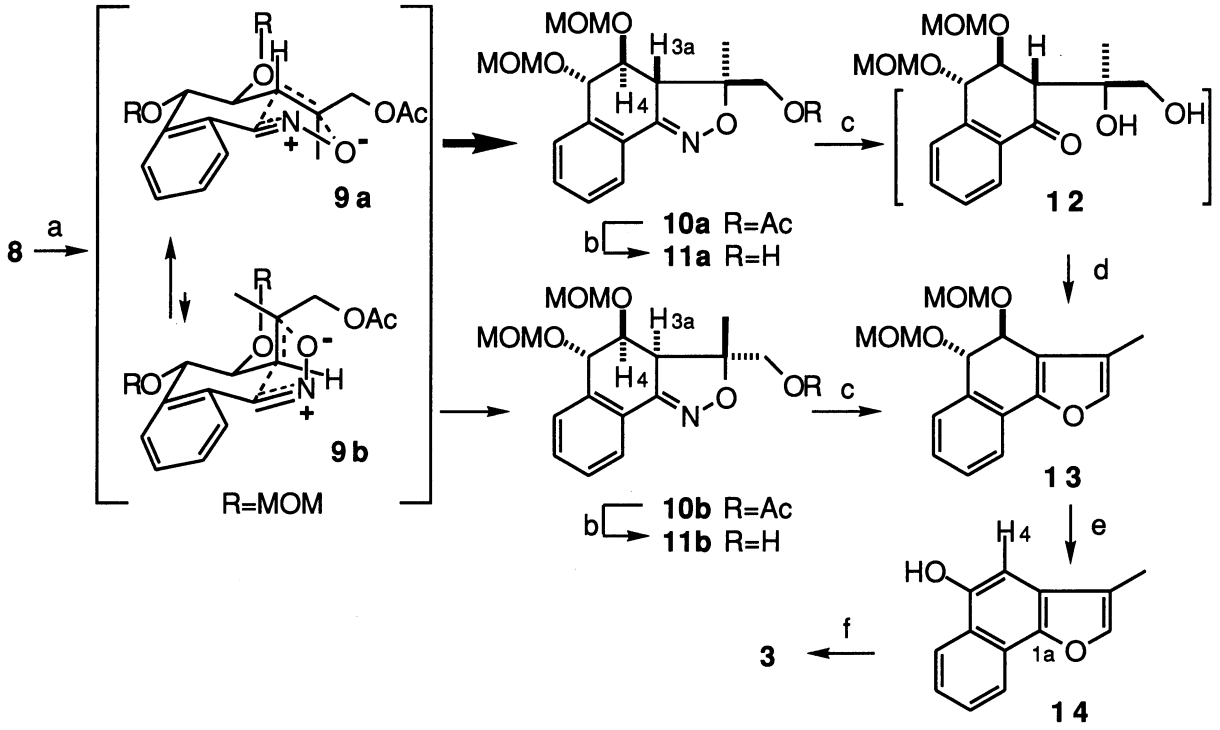


(a) $^{i}Bu_2AlH$, toluene. (b) $Ph_3P{=}CHCO_2Et$, benzene, 75% for the 2 steps. (c) TBSCl, imidazole, DMAP, 73%. (d) $^{i}Bu_2AlH$, THF. (e) Ac_2O, iPr_2EtN, THF, 98%, 2 steps. (f) OsO_4 (cat.), NMO, acetone, H_2O. (g) MOMCl, $^{i}Pr_2EtN$, DMAP, CH_2Cl_2, 87%, 2 steps. (h) $LiAlH_4$, THF. (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (j) $Ph_3P{=}C(Me)CO_2Et$, benzene, 87%, 3 steps. (k) Ac_2O, pyridine, 95%, 2 steps. (l) $^{n}Bu_4NF$, THF, 93%. (m) PDC, CH_2Cl_2. (n) $NH_2OH{\cdot}HCl$, 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[6] 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[7] and the stereochemistry was confirmed by the ^1H NMR spectroscopy. Thus, the ^1H 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 ^1H 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[8] of **11a**, obtained from **10a** by alkaline hydrolysis, with a catalytic amount of Raney nickel (W-2) and trimetyl borate in aqueous methanol under a pressure of hydrogen (2 kg/cm^2) gave the β,γ-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**[9] as a single product in 80% yield. The location of the hydroxy group in **14** was determined mainly based on a ^{1}H-^{13}C long range correlation spectrum, in which the correlative signals between H_4 (δH 6.90) and the C_{1a} (δC 145.69) was diagnostic. Finally, oxidation of **14** with potassium nitrosodisulfonate (Fremy's salt)[10] provided a 63% yield of the ortho-quinone **3**, mp 170 - 173 °C (lit.[2b] 170 - 172 °C), whose spectral properties (^{1}H NMR and IR) were completely identical with those of authentic material (Scheme 2).



(a) 7% aq. NaOCl, CH_2Cl_2, 100%. (b) LiOH•H_2O, THF, H_2O. (c) Raney Ni (W-2), $(MeO)_3B$, H_2, 2 kg/cm^2, MeOH, H_2O, 40% for **11b**. (d) *p*-TsOH, CH_2Cl_2, 47% (2 steps) from **11a**. (e) concd HCl, EtOH, 80%. (f) Fremy's salt, KH_2PO_4, H_2O, 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^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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^+); HR MS Found: 198.0678. Calcd for $C_{13}H_{10}O_2$: 198.0678.

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