Total Synthesis of Danshenspiroketallactone

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Abstract: Described herein is the first synthesis of the monobenzannulated 5,5-spiroketals danshenspiroketallactone and *epi*-danshenspiroketallactone, two components of the traditional Chinese medicine Danshen. Key features of the synthesis include a directed metallation–lactonisation sequence to install the isobenzofuranone moiety and an oxidative radical cyclisation to afford the monobenzannulated 5,5-spiroketal.

Key words: Danshen, spiroketal, oxidative radical cyclisation, natural product

Several diverse spiroketal-containing natural products have been isolated over the years,[1] but compounds of this class that contain aryl rings fused to the spiroketal moiety are relatively rare.[2] Two such examples are danshenspiroketallactone (**1**) and *epi*-danshenspiroketallactone (**2**), monobenzannulated 5,5-spiroketals isolated from Danshen, the traditional Chinese medicine consisting of dried roots of Chinese sage, *Salvia miltiorrhiza* that is used to treat renal failure, heart disease, and strokes.[3] Although **1** and **2** are epimeric at the spirocentre, subjecting **1** to prolonged acidic conditions has proven that **2** is a natural product and not an artefact of the isolation procedure. However, subjecting **2** to acidic conditions effects epimerization to **1**, suggesting that some (or all) of **1** is produced during isolation and purification of the natural product(s) on silica gel.[4] Further analysis of this medicinal plant afforded cryptoacetalide (**3**) and *epi*-cryptoacetalide (**5**),[5] and the acetone extract of the closely related folk medicine *Salvia aegyptiaca* has been shown to contain 6-methylcryptoacetalide (**4**) and 6-methyl-*epi*-cryptoacetalide (**6**,[6] Figure 1).

Due to an ongoing project aimed at identifying the compounds responsible for the therapeutic effect in traditional Chinese medicines, combined with our continued interest in the synthesis of benzannulated spiroketal natural products,[7] we decided to initiate a synthesis of danshenspiroketallactone (**1**). Furthermore, a recent total synthesis of cryptoacetalide (**3**, along with its epimer **5**)[8] prompts us to disclose our own efforts in this area.

Recently, we demonstrated that the oxidative radical cyclisation[9] of various benzofurans and chromans containing a hydroxyalkyl side chain could be used to construct a series of monobenzannulated spiroketals.[10] Encouraged by these promising model studies, we aimed to extend this methodology toward the synthesis of danshenspiroketallactone (**1**) and its retrosynthesis is based on this strategy (Scheme 1).

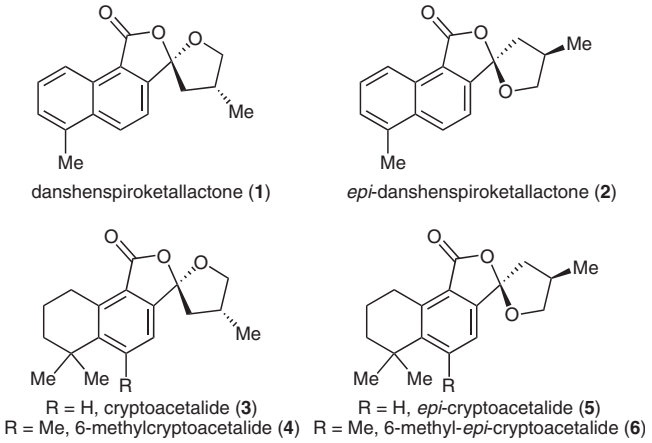
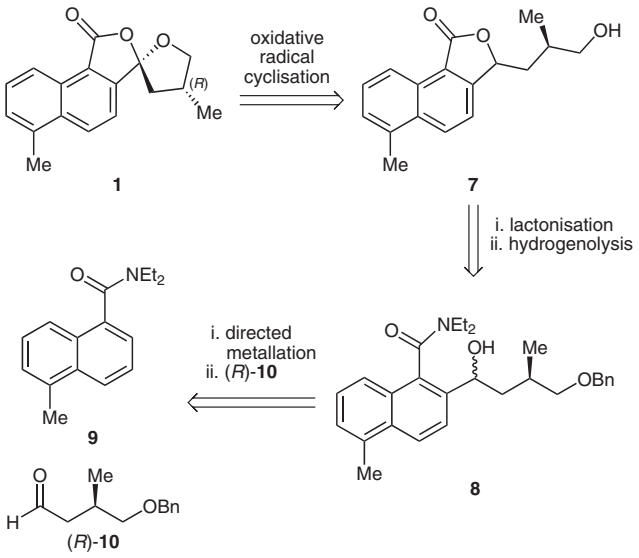


Figure 1 Naturally occurring monobenzannulated 5,5-spiroketals



Scheme 1 Retrosynthetic analysis of danshenspiroketallactone (**1**)

We planned a late-stage spiroketalisation by oxidative radical cyclisation of alcohol **7** which in turn was to be obtained by lactonisation of intermediate **8**. Directed metallation of naphthalene amide **9** followed by addition of *R*-aldehyde **10**[11] was proposed as the key carbon–carbon bond-forming step to deliver **8** (Scheme 1).

Thus, our initial attention was aimed towards the synthesis of the two coupling partners **9** and **10**. The synthesis of

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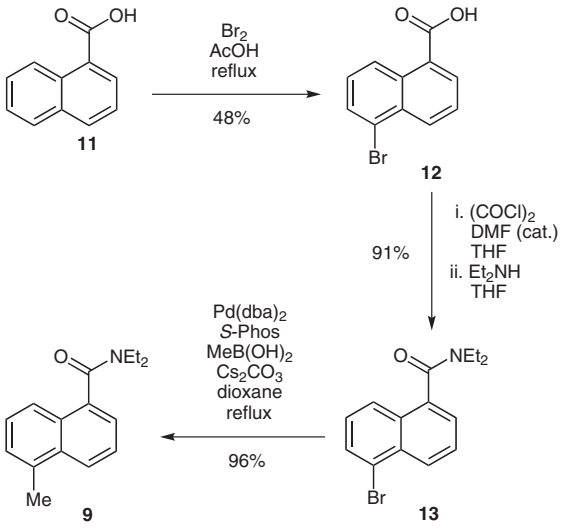
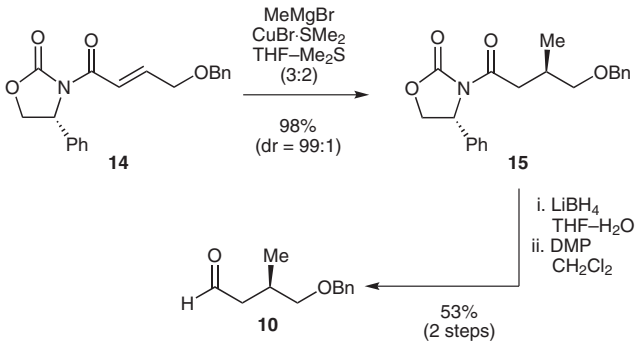
naphthalene **9** commenced with the regioselective bromination[12] of 1-naphthoic acid **11**, delivering 5-bromonaphthoic acid **12** which underwent facile diethylamide formation giving **13**. Finally, Suzuki coupling of **13** with methylboronic acid delivered the desired naphthalene fragment **9** in good overall yield (Scheme 2).



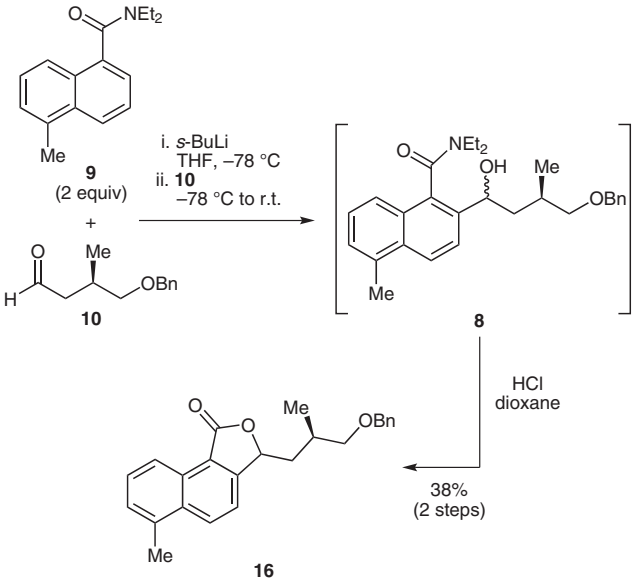
Scheme 2 Synthesis of naphthalene amide **9**

With a scalable synthesis of arene **9** successfully completed, attention turned to the synthesis of aldehyde (*R*)-**10**. Although an asymmetric synthesis of (*R*)-**10** exists,[11] we chose to develop a new route. This goal was ultimately achieved using Evans' auxiliary based conjugate addition of methylmagnesium bromide to oxazolidinone **14**,[13] affording **15** with a diastereomeric ratio of 94:6 which could be improved to >99:1 with a single recrystallisation. Reductive cleavage of the oxazolidinone followed, and oxidation of the resultant alcohol with Dess–Martin periodinane (DMP) delivered the desired *R*-aldehyde **10** {$[\alpha]_D^{21}$ +10.4 (*c* 0.7, $CHCl_3$); (lit.[11] $[\alpha]_D^{20}$ +10.7 (*c* 0.7, $CHCl_3$)} (Scheme 3).



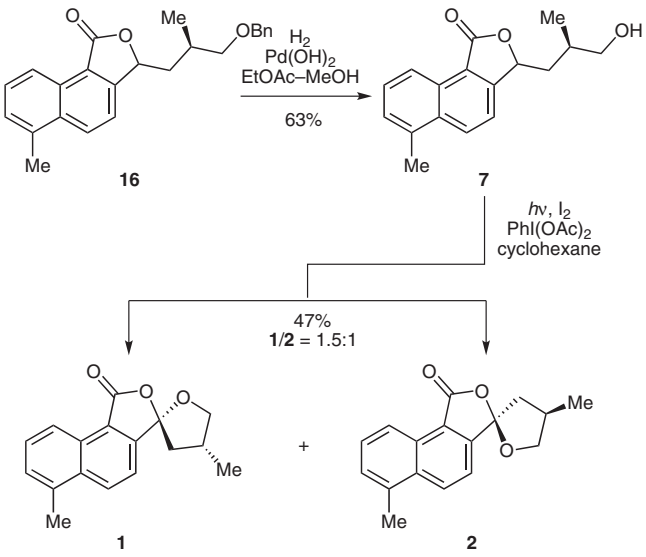
Scheme 3 Synthesis of *R*-aldehyde **10**

Next, the key coupling of fragments **9** and **10** could be conducted. Directed lithiation of the naphthalene amide **9** at –78 °C for one hour was followed by addition of the aldehyde **10**. When the reaction was complete, workup gave the crude product **8** (as a mixture of rotameric diastereomers) which was immediately subjected to lactonisation with anhydrous HCl in dioxane, delivering the desired isobenzofuranone **16** in moderate yield (Scheme 4).[14]



Scheme 4 Synthesis of isobenzofuranone **16**

With the successful synthesis of the key isobenzofuranone **16** completed, we were keen to complete the total synthesis of danshenspiroketallactone (**1**). Hydrogenolysis of the benzyl ether in **16** proceeded smoothly, affording the key radical cyclisation precursor **7** and setting the scene for the key spiroketalisation. Gratifyingly, subjecting **7** to the standard radical cyclisation conditions[9,10] afforded danshenspiroketallactone (**1**) along with its epimer **2** in a 1.5:1 ratio[15] (Scheme 5). A lack of stereocontrol from the anomeric effect contributed to the formation of a mixture of 5,5-spiroketals.[16] The spectroscopic data of synthetic **1**



Scheme 5 Total synthesis of danshenspiroketallactone (**1**) and *epi*-danshenspiroketallactone (**2**)

and **2** were in excellent agreement with that reported for the natural products.[4,17]

In conclusion, we have completed the first total syntheses of the naturally occurring monobenzannulated 5,5-spiroketals danshenspiroketallactone (**1**) and *epi*-danshenspiroketallactone (**2**). This synthesis has provided sufficient material for biological study to assess whether **1** and **2** are responsible for any of the therapeutic effects of the traditional Chinese medicine Danshen.

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References and Notes

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(15) At the conclusion of the previously reported total synthesis of a member of this family of natural products, cryptoacetalides **3** and **5** were obtained as an inseparable 2:1 mixture of spiroketal epimers, respectively (ref. 8).

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(17) **Synthesis of Danshenspiroketallactone (1) and *epi*-Danshenspiroketallactone (2)**

A mixture of alcohol **7** (50 mg, 0.19 mmol), $PhI(OAc)_2$ (119 mg, 0.37 mmol), and iodine (108 mg, 0.43 mmol) in anhyd cyclohexane (15.3 mL) was degassed with nitrogen at r.t. for 15 min. The resulting solution was cooled in an ice-water bath (10 °C) and irradiated with a desk lamp (60 W) for 3.5 h. The solution was poured onto a mixture of sat. aq $Na_2S_2O_3$ (20 mL) and sat. aq $NaHCO_3$ (20 mL) and diluted with Et_2O (100 mL). The organic layer was separated and the aqueous layer further extracted with Et_2O (2 × 100 mL). The organic fractions were combined and dried over anhyd $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silca gel using hexanes–EtOAc (3:1, R_f = 0.52) as eluent to afford the title compounds **1** and **2** (23.3 mg, 0.09 mmol, 47%; Figure 2) as an orange solid and an inseparable mixture of diastereomers (1.5:1). IR (neat): ν_{max} = 2957, 2928, 2876, 1925, 1749, 1601, 1588, 1526, 1470, 1454, 1375, 1342, 1322, 1254, 1211, 1183, 1159, 1136, 1110, 1083, 1070, 1047, 1003, 981, 950, 928, 915, 882, 847, 811, 777, 769, 737, 700, 684, 658, 646, 628 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (1.5 H, d, *J* = 7.0 Hz, H-17), 1.32 (1.5 H, d, *J* = 7.0 Hz, H-17*), 2.11 (0.5 H, dd, *J* = 10.5, 13.0 Hz, H-16_a), 2.22 (0.5 H, dd, *J* = 4.7, 13.2 Hz, H-16_b*), 2.53 (0.5 H, dd, *J* = 7.0, 13.0 Hz, H-16_b), 2.70 (0.5 H, dd, *J* = 9.5, 13.4 Hz, H-16_a*), 2.74 (3 H, s, H-18, H-18*), 2.76 (0.5 H, m, H-15*), 2.95 (0.5 H, m, H-15), 3.82 (0.5 H, t, *J* = 8.2 Hz, H-14_a), 3.93 (0.5 H, dd, *J* = 7.2, 8.2 Hz, H-14_b*), 4.42 (0.5 H, t, *J* = 7.8 Hz, H-14_a*), 4.47 (0.5 H, t, *J* = 8.2 Hz, H-14_b), 7.46 (1 H, dd, *J* = 1.0, 7.0 Hz, H-3, H-3*), 7.53 (0.5 H, d, *J* = 8.8 Hz, H-7*), 7.57 (0.5 H, d, *J* = 8.4 Hz, H-7), 7.60 (1 H, dd, *J* = 7.0, 8.5 Hz, H-2, H-2*), 8.34 (1 H, m, H-6, H-6*), 8.87 (1 H, d, *J* = 8.4 Hz, H-1, H-1*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4 (CH_3, C-17), 18.2 (CH_3, C-17*), 19.9 (2 × CH_3, C-18, C-18*), 32.6 (CH, C-15), 33.5 (CH, C-15*), 44.6 (CH_2, C-16*), 45.4 (CH_2, C-16), 77.37, 77.39 (2 × CH_2, C-14, C-14*), 113.2 (2 × C, C-13, C-13*), 118.1 (ArH, C-7*), 118.2 (ArH, C-7), 121.7 (C, C-9*), 122.1 (ArH, C-1), 122.17 (ArH, C-1*), 122.21 (C, C-9), 128.5 (2 × ArH, C-3, C-3*), 129.0 (2 × ArH, C-2, C-2*), 129.2 (ArH, C-10*), 129.3 (ArH, C-10), 131.9 (ArH, C-6), 132.0 (ArH, C-6*), 133.4 (C, C-5*), 133.5 (C, C-5), 135.1 (2 × C, C-4, C-4*), 147.1 (C, C-8), 147.8 (C, C-8*), 168.4 (2 × C=O, C-11, C-11*). MS (ESI^+): *m/z* (%) = 291 (100) $[M + Na]^+$, 259 (29), 214 (18), 165 (22), 89 (27). HRMS: *m/z* calcd for $C_{17}H_{16}O_3Na$: 291.0992; found: 291.0991 $[M + Na]^+$. The spectroscopic data are in full agreement with that reported in the literature.[3,4]

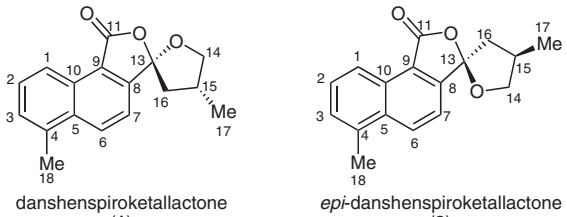

Figure 2

