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Model support studies toward the total synthesis of the stemona alkaloid stemocurtisine

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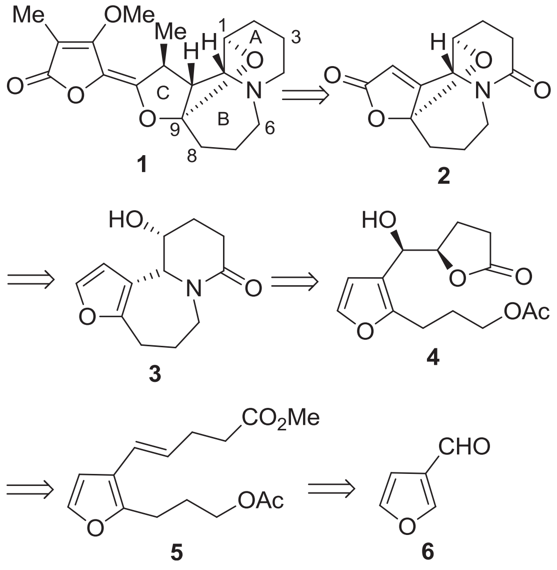
ABSTRACT

Herein we report the results of a furan-based approach toward the synthesis of the Stemona alkaloid, stemocurtisine **1** via the linearly fused tricyclic intermediate **3**, representing the key A,B,C-ring structural feature of the target molecule. A highly diastereoselective synthesis of compound **3** was achieved starting from 3-furfural **6**, in a synthetic sequence that involved; (1) a rapid *in situ* conversion of an *O*-mesylate to the corresponding chloride with inversion of configuration from assistance of the neighbouring 3-furanyl group; (2) an intramolecular aza-Wittig reaction to prepare the azepine ring; and (3) a base promoted lactam ring forming step. While methods were established to oxidize the furan ring of **3** to the corresponding γ-hydroxy-α,β-unsaturated lactone we were unable to affect cyclization of the lactam ring hydroxyl group to the γ-position of the lactone to create the cyclic ether feature of the natural product. Model studies were also unsuccessful.

1. Introduction

The extracts of roots of the Stemona species of plants have been used in traditional medicine in South–East Asia, China, and Japan to treat the symptoms of bronchitis, pertussis, and tuberculosis and have been used as anti-parasitics on humans and animals.[1,2] Some of the pure alkaloids derived from the extracts of the leaves and roots of Stemona species have been shown to have significant anti tussive activity in guinea pig after cough induction[3] as well as insect toxicity, antifeedant and repellent activities.[4–6] The Stemona group of alkaloids includes more than 120 different natural products, the majority of which have a common pyrrolo[1,2-*a*]azepine nucleus. Stemocurtisine **1** (Scheme 1) was the first Stemona alkaloid to be isolated with a pyrido[1,2-*a*]azepine A,B-ring system.[7]

Our retrosynthetic analysis of **1** (Scheme 1) indicated that the tricyclic intermediate **3**, representing the key A,B,C-ring structural feature of the target molecule, would be an attractive key intermediate toward this endeavour. We envisaged that oxidation of the furan moiety of **3** could give an intermediate that would allow for the introduction of the more synthetically challenging ether bridge between the A and B-rings and result in the tetracyclic compound **2** (Scheme 1). Our earlier attempts at the synthesis of a linearly fused tricyclic akin to compound **3** were unsuccessful. For example, the $Sc(OTf)_3$ catalysed cyclization reaction of the tethered furan-4,5-diacetoxypiperid-2-one **7** gave the spirotricyclic product **9** and not the desired linearly fused tricyclic compound **8** (Scheme 2).[8]



Scheme 1. Retrosynthetic analysis of stemocurtisine **1**.

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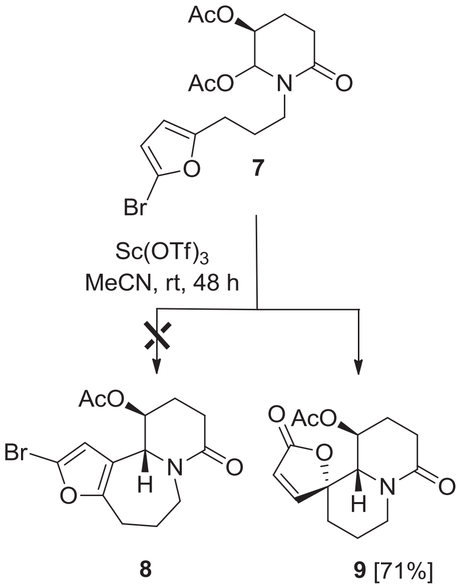
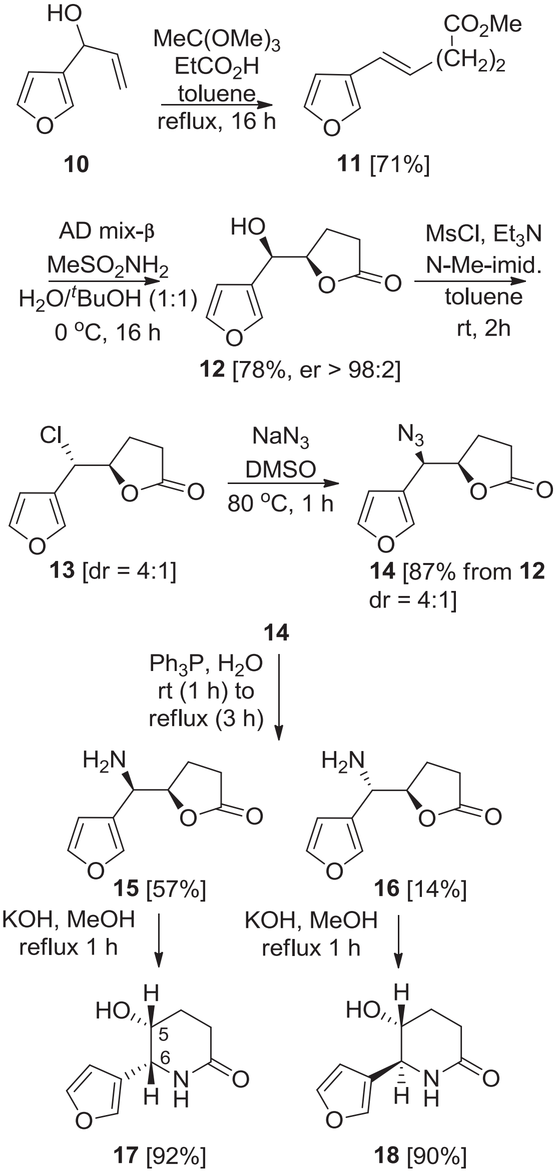


Scheme 2. Attempted synthesis of the linearly fused tricyclic compound **8**.

2. Results and discussion

To test the feasibility of securing the desired *cis*-configuration in our proposed synthesis of **3** we first examined the diastereoselective synthesis of (5*R*,6*R*)-6-(3-furyl)-5-hydroxy-piperidin-2-one **17** (Scheme 3). While the first two synthetic steps were similar to that reported by Sudalai[9] for the synthesis of (5*R*,6*S*)-5-hydroxy-6-phenylpiperidin-2-one from benzaldehyde, rather than 3-furanal in this synthesis, our synthesis required modification of the latter steps because of the presence of the more readily oxidisable furan ring in Schemes 3 and 4 and our requirement for lactams with the 6*R* configuration. The known vinyl alcohol **10**,[10] prepared by Grignard reaction of vinylmagnesium bromide with 3-furfural **6**, was subjected to a Johnson–Claisen rearrangement[9] to form the methyl ester **11** in 71% yield (Scheme 3). Asymmetric dihydroxylation[11] of the *trans* alkene of **11** with AD mix-β gave the lactone **12** in good yield (78%) and high enantioselectivity (*dr* >99:1 (from ^{1}H NMR); *er* >98:2 from Mosher's ester analysis). The desired 5,6-stereochemistry in the target molecule **17** required converting the secondary hydroxyl group in **12** into an amino group with overall retention of configuration. In pursuit of this result we first attempted to convert the secondary hydroxyl of **12** into the corresponding mesylate using standard conditions (MsCl, Et_3N, CH_2Cl_2, 0 °C).[12] All attempts were unsuccessful and only unreacted starting material was obtained. However we were very delighted to find that by using the conditions of Tanabe,[13] for the mesylation of secondary alcohols with MsCl and *N*-methylimidazole (*N*-MeIm) in toluene, the alcohol **12** was converted to the secondary chloride **13** with inversion. There is precedence for this type of *in situ* reaction of chloride with activated mesylates (e.g., mesylates of benzylic and allylic alcohols).[14] In contrast, the related phenyl analogue of **12** (i.e., **12** in which the 3-furyl group is replaced by a Ph) is readily converted to its corresponding mesylate, which is relatively stable under standard conditions.[9] The more electron rich 3-furanyl group in **12** is clearly responsible for this enhanced instability and can stabilize the expected S_N2 and S_N1 processes that lead to **12** and its epimer, respectively. When the diastereomeric mixture of the chlorides **13** was heated at 80 °C with sodium azide in DMSO the inverted azides **14** were obtained in 87% overall yield from **12** as a 4:1 mixture of inseparable diastereomers. The Staudinger reaction of this azide mixture with triphenylphosphine and water gave the primary amines **15** and **16**, which could be separated by column chromatography providing these compounds in yields of 57 and 14%, respectively. Compounds **15** and **16** were individually converted, in excellent yields (90–92%) to their respective piperidin-2-one derivatives, **17** and **18**, by heating a solution of these compounds in KOH/MeOH. The relative *cis* and *trans* 5,6-configurations of **17** and **18** were based on their respective ^{1}H NMR coupling constants $J_{5,6}$. For compound **17**, $J_{5,6}$ was 2.2 Hz, while that for **18** was 6.6 Hz. These values were consistent with those of *cis* ($J_{5,6}$=2.7 Hz)[15] and *trans*-5-hydroxy-6-phenylpiperidin-2-one ($J_{5,6}$=6.8 Hz),[16] respectively.



Scheme 3. Synthesis of *cis* and *trans*-6-(3-furyl)-5-hydroxy-piperidin-2-ones **17** and **18**.

This chemistry was then further developed to the synthesis of the more demanding tricyclic system **3** (Scheme 4). The known allyl alcohol **19**,[17] synthesized from the reaction of allylmagnesium bromide and 3-furfural, was converted to the diol **20** in 86% yield by hydroboration of the terminal alkene with 9-BBN followed by an oxidative work up with basic H_2O_2. Diol **20** was then subjected to the oxidative rearrangement reaction conditions developed by Walsh[18] by treatment with NBS in aqueous THF. This procedure