Synthesis of the core ring system of the stemona alkaloids by cascade condensation, cyclization, intramolecular cycloaddition†

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Condensation of an aldehyde with an α-amino-ester, followed by a tandem process involving cyclization to a seven-membered ring, deprotonation to an intermediate azomethine ylide and intramolecular dipolar cycloaddition gave tricyclic products related to stenine and neostenine.

The *Stemona* alkaloids contain a pyrrolo[1,2-*a*]azepine ring system.[1] Within this class are the polycyclic alkaloids stenine, neostenine and tuberostenine (Fig. 1), in which the seven-membered azepine ring is fused to a pyrrolidine and a cyclohexane ring. Extracts of stemonaceous plants have been used in traditional Chinese and Japanese medicine to relieve respiratory problems and neostenine has been found to have antitussive activity.[2] The biological activity and interesting structures have led to efforts towards the synthesis of this class of molecules.[1,3]

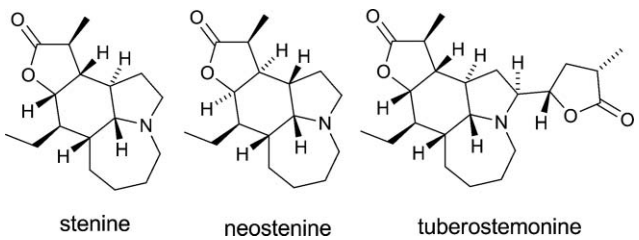
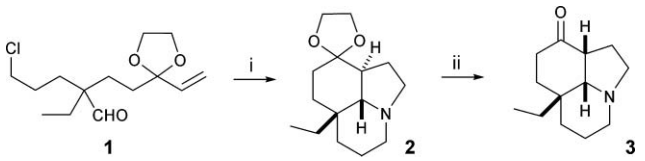


Fig. 1 Some *Stemona* alkaloids.

Recently, we applied a tandem condensation, cyclisation then cycloaddition cascade process to form fused tricyclic amines (Scheme 1).[4,5] The chemistry was successful using nitrone ylides (derived from hydroxylamine) or using unstabilised or stabilised azomethine ylides (derived from α-amino-acids or esters). For example, heating the aldehyde **1** with glycine and camphorsulfonic acid (CSA) gave the tricyclic product **2**. Glycine adds to the aldehyde **1** and cyclization (with loss of chloride) provides a six-membered nitrogen-containing ring. Loss of CO_2 leads to an azomethine ylide that undergoes intramolecular cycloaddition onto the alkene to give **2** as a single stereoisomer. Hydrolysis of the acetal **2** gave the ketone **3**. This chemistry was applied

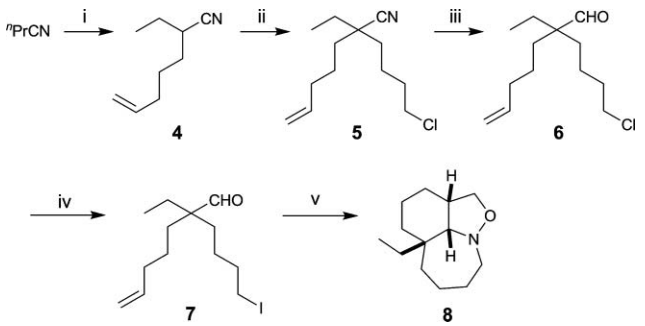


Scheme 1 Cascade chemistry to fused tricyclic amine **2**. *Reagents and conditions*: i, $H_2NCH_2CO_2H$, PhMe, CSA (10 mol%), heat, 18 h, 79%; ii, HCl (2 M), THF, heat, 1 h, 88%.

to the total synthesis of aspidospermidine, aspidospermine and quebrachamine.[4]

There is considerable structural similarity between compound **2** and the ring system found in stenine; therefore we wondered whether this cascade chemistry could be applied to the synthesis of the core of this alkaloid. This would require cyclization of the intermediate imine to give a seven-membered (rather than six-membered) ring, but we were encouraged that this should be feasible using the alkyl iodide, based on synthetic efforts towards the homoerythrina alkaloids by Pearson and co-workers.[5e] This communication reports the successful demonstration of this approach.

To test the key condensation, cyclization, cycloaddition chemistry, we initially prepared the aldehyde **6** (Scheme 2). This was achieved in three steps by alkylation of the anion of butyronitrile with 5-bromopentene, then alkylation with 1-bromo-4-chlorobutane and reduction of the nitrile with DIBAL-H.



Scheme 2 Preparation of aldehyde **7** and reaction with hydroxylamine. *Reagents and conditions*: i, LDA, THF, −78 °C, 5-bromopent-1-ene, 99%; ii, LDA, THF, −78 °C, 1-bromo-4-chlorobutane, 98%; iii, DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, then $HCl_{(aq)}$, 86%; iv, NaI, acetone, heat, 91%; $NH_2OH{\cdot}HCl$, $^i Pr_2NEt$, PhMe, heat, 22%.

As a test reaction, treatment of the aldehyde **6** with hydroxylamine hydrochloride did not yield cycloadduct **8** (the oxime of aldehyde **6** was obtained in 74% yield), and prolonged heating led only to decomposition. The lack of cyclization must be due to the increased difficulty in forming a seven-membered ring in the

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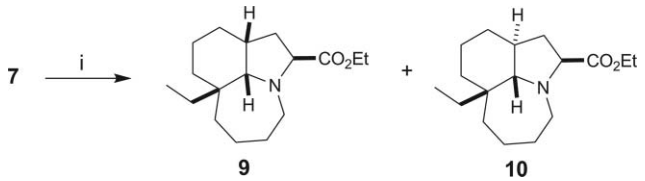
† Electronic supplementary information (ESI) available: Detailed experimental procedures and selected characterisation data. CIF and ORTEP diagrams of the *p*-bromobenzoate obtained from **9** and the sulfone **13**. CCDC reference numbers 782368 and 782369. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00408a

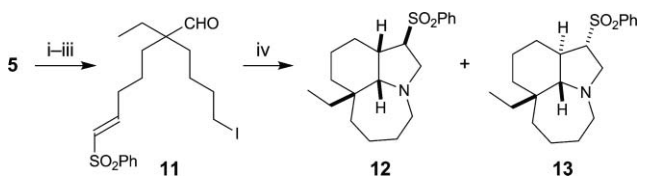
N-alkylation step. Conversion of the chloride to the iodide using a Finkelstein reaction gave the aldehyde **7**. Pleasingly, this substrate underwent the desired cascade chemistry to yield cycloadduct **8** as a single diastereoisomer, albeit in a disappointing yield of 22% (together with some oxime). The stereochemistry of **8**, with a *cis* relationship between the ring junction protons, was tentatively assigned from the coupling constant between these protons in the ^{1}H NMR spectrum (related tricyclic products have *cis* J <8 Hz, *trans* J 10–12 Hz).[4]

Aldehyde **7** was heated with glycine ethyl ester hydrochloride to give cycloadducts **9** and **10** in moderate yield (Scheme 3). The stereochemistry of tricyclic product **9** was determined by reduction of the ester, formation of the *p*-bromobenzoate and single crystal X-ray analysis of the HCl salt of this ester (see supplementary information). The product **10** was assigned with the *trans* ring junction stereochemistry (^{1}H NMR spectrum: NC*H*CH, d, J 11 Hz).



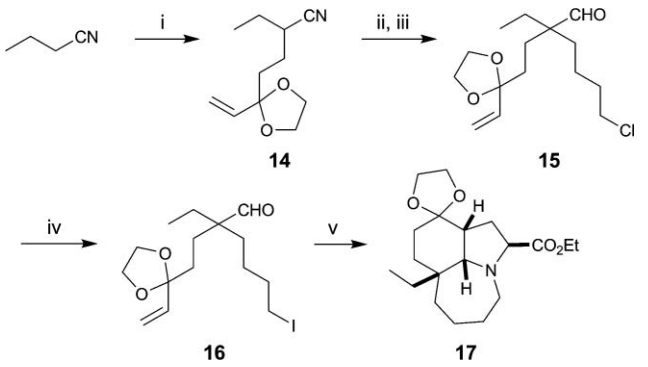
Scheme 3 Reaction of aldehyde **7** with glycine ethyl ester. *Reagents and conditions*: i, Cl·$H_3NCH_2CO_2Et$, $^iPr_2NEt$, PhMe, heat, 36 h, 51%, **9** : **10** 1.2 : 1.

Heating aldehyde **7** with glycine led to decomposition. To promote the cascade chemistry, the alkene tether was activated with a sulfone electron-withdrawing group by preparing aldehyde **11** (using cross metathesis of nitrile **5** with phenyl vinyl sulfone,[4a] followed by DIBAL-H reduction and Finkelstein reaction). Heating aldehyde **11** with glycine in xylenes now led to the desired cycloadducts **12** and **13** (Scheme 4). The stereochemistry of the major cycloadduct **12** was established by single crystal X-ray analysis,† whereas the stereochemistry of cycloadduct **13** was assigned by analogy with related cycloadducts.[4]



Scheme 4 Reaction of aldehyde **11** with glycine. *Reagents and conditions*: i, phenyl vinyl sulfone, GrubbsII (5 mol%), CH_2Cl_2, 91%; ii, DIBAL-H, CH_2Cl_2, –78 °C, then $HCl_{(aq)}$, 82%; iii, NaI, acetone, heat, 100%; iv, $H_2NCH_2CO_2H$, xylenes, heat, 20 h, 66%, **12** : **13** 2.7 : 1.

Finally, we chose to test the cascade cyclization–cycloaddition chemistry with the aldehyde **16**. The acetal group has been found previously to allow cycloaddition with glycine and CSA (Scheme 1), and provides a handle for later functionalisation. Alkylation of butyronitrile with 2-(2-bromoethyl)-2-vinyl-[1,3]dioxolane (prepared from ethyl bromopropionate)[6] gave the nitrile **14** (Scheme 5). Alkylation of this nitrile with 1-bromo-4-chlorobutane followed by DIBAL-H reduction gave the aldehyde **15**. Treatment of aldehyde **15** with glycine or glycine ethyl ester gave only recovered starting



Scheme 5 Reaction of aldehyde **16** with glycine ethyl ester. *Reagents and conditions*: i, LDA, THF, –78 °C, 2-(2-bromoethyl)-2-vinyl-[1,3]dioxolane,[6] 78%; ii, LDA, THF, –78 °C, 1-bromo-2-chlorobutane, 95%; iii, DIBAL-H, CH_2Cl_2, –78 °C, then aqueous oxalic acid, 80%; iii, NaI, acetone, heat, 100%; v, Cl·$H_3NCH_2CO_2Et$, $^iPr_2NEt$, CSA (10 mol%), xylenes, heat, 16 h, 49%.

material and no cycloadduct. Conversion to aldehyde **16** and heating with glycine in xylenes also gave only starting material, even after prolonged heating or addition of CSA.

However, using glycine ethyl ester, the cycloadduct **17** was obtained as a single stereoisomer. The yield of the cycloadduct **17** was low (28%) in the absence of CSA, but improved to 49% by addition of 10 mol% CSA. The acid presumably protonates the acetal and activates the alkene as a dipolarophile.[4] The stereochemistry of the cycloadduct **17** was tentatively assigned with a *cis* ring junction relationship, due to a relatively small coupling constant between these ring junction protons in the ^{1}H NMR spectrum (J 6 Hz).

In summary, we have shown that the cascade condensation, cyclization, cycloaddition chemistry can be applied to the synthesis of the core ring systems of stenine and neostenine. Tricyclic products with an azepine ring fused to a pyrrolidine and a cyclohexane ring have been formed in a single pot from acyclic aldehyde precursors. The ethyl group in the natural products is located at the adjacent carbon atom of the cyclohexane ring and access to this substitution pattern using the cascade chemistry would require an alternative aldehyde. Such an aldehyde would be enolisable, although some successful cyclization–cycloaddition reactions with enolisable substrates are known.[5c–e]

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Notes and references

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