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Synthesis of the isoquinoline alkaloid, crispine C

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ABSTRACT

The first total synthesis of the isoquinoline alkaloid, crispine C is described in seven steps using a Henry reaction and the Pictet–Gams variant of the Bischler–Napieralski reaction to effect the key transformations.

Carduus crispus, a Mongolian thistle has long been used in Chinese folk medicine for the treatment of colds, stomach problems and rheumatism. In 2002, pharmacological screening of an extract revealed significant cytotoxicity against some human cancer cell lines.[1] The search for the active compounds led to the discovery of five novel alkaloids, crispines A–E (Fig. 1). (+)-Crispine A (**1**) and crispine B (**2**) have pyrrolo[2,1-*a*]isoquinoline skeletons whereas crispine C (**3**) and crispine D (**4**) are isoquinoline alkaloids with guanidinyl side-chains. (+)-Crispine E (**5**) is a tetrahydroisoquinoline with a guanidine-derived propyl side-chain at the C-1 position. On isolation, testing of these compounds against SKOV3, KB and Hela human cancer cell lines showed crispine B (**2**) to have significant cytotoxic activity.[1]

Due to their novel structures and the potential of these compounds as pharmaceutical agents, there has been much interest in their synthesis.[2–4] Crispine A (**1**) in particular has been prepared using a variety of methods,[2] including a lipase-catalysed kinetic resolution of a C-1 substituted tetrahydroisoquinoline[2n] as well as by a stereoselective electrochemical cyanation of a chiral tetrahydroisoquinoline.[2r] Crispine B (**2**) has been prepared using a Bischler–Napieralski reaction,[3] while (+)-crispine E (**5**) was synthesised using asymmetric transfer hydrogenation as the key step.[4b] To date, there have been no reported syntheses of crispine C (**3**) or crispine D (**4**). Our research group has had a long-standing interest in the synthesis of guanylated natural products and medicinally active agents using in particular, various protected pyrazole-1-carboxamidines for the efficient incorporation of the guanidine group.[5] Using this approach in combination with a Pictet–Gams reaction to effect the key step, we now report the first total synthesis of crispine C.

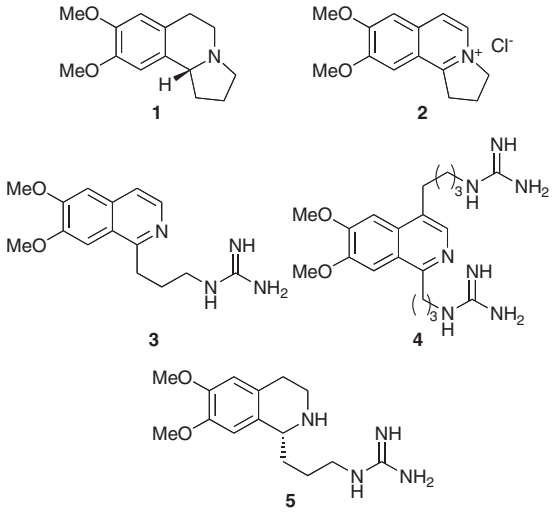

Figure 1. Structures of crispines A–E (**1**–**5**).

Our strategy for the synthesis of crispine C (**3**) involved the preparation of a suitably functionalised phenethylamine that would be coupled with 4-aminobutyric acid (Scheme 1). The resulting amide was to be used in a Bischler–Napieralski type reaction to form the isoquinoline ring system and the synthesis would then be completed by the incorporation of the guanidine moiety.

Our first attempt at the synthesis of crispine C (**3**) involved using 3,4-dimethoxyphenethylamine (**6**) as a starting material

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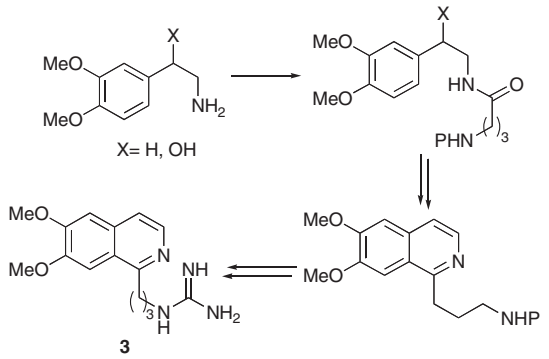
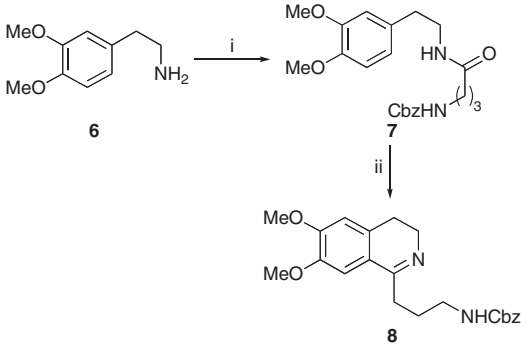


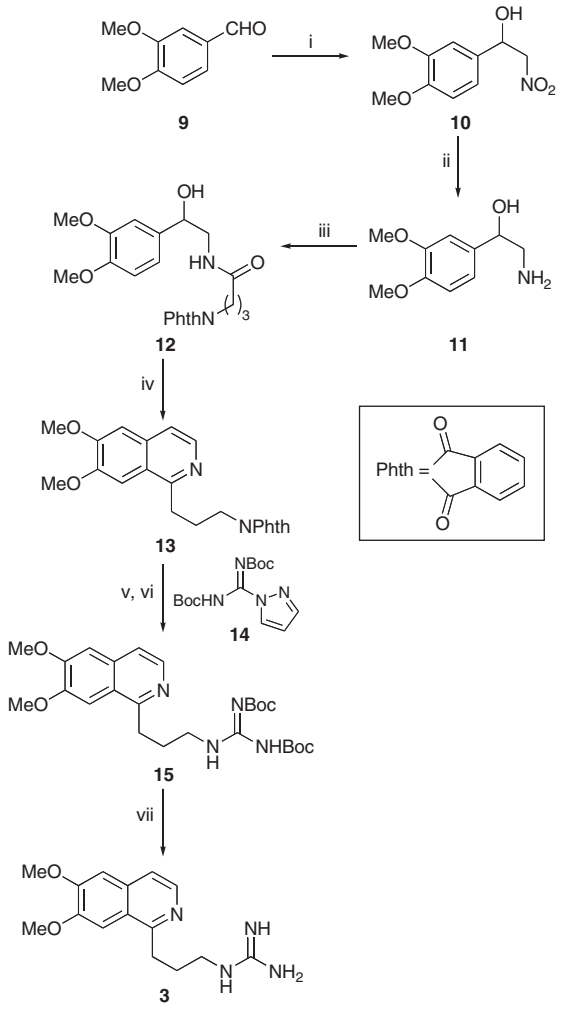
Scheme 1. Synthetic approach for the synthesis of crispine C (**3**).

and a Bischler–Napieralski reaction to form a C-1 substituted 3,4-dihydroisoquinoline (Scheme 2). 3,4-Dimethoxyphenethylamine (**6**) was coupled with Cbz-protected 4-aminobutyric acid[6] using EDCI as the coupling agent to give the corresponding amide **7** in 89% yield. Amide **7** was then treated with neat phosphorus oxychloride to effect the Bischler–Napieralski reaction[4b,7] and this gave 3,4-dihydroisoquinoline **8** in 73% yield. The next stage of the reaction sequence required dehydrogenation of **8** to complete the synthesis of the isoquinoline ring system. A number of well-precedented methods were investigated including heating **8** in diphenyl ether at 170 °C in the presence of palladium on carbon,[8] as well as oxidation of **8** with selenium dioxide[9] and DDQ.[10] However, all attempts led to decomposition or returned only 3,4-dihydroisoquinoline **8**.

While the oxidation of dihydroisoquinolines to give isoquinolines is well known, problems with electron-rich ring systems have been reported.[11] These issues have been overcome by using the Pictet–Gams modification of the Bischler–Napieralski reaction.[12] A suitable substrate for this reaction was prepared in three steps from 3,4-dimethoxybenzaldehyde (**9**) (Scheme 3). Initially, **9** was subjected to a Henry reaction[13] with nitromethane which gave β-nitro alcohol **10** in 85% yield. Hydrogenation under standard conditions gave β-amino alcohol **11** in quantitative yield and this was then coupled with phthalimido-protected butyric acid[14] using EDCI to give β-amido alcohol **12** in 75% yield.[15] With β-amido alcohol **12** in hand, this was subjected to the key Pictet–Gams reaction using phosphorus oxychloride. Although the reaction does proceed when performed neat, the best yield of 66% for isoquinoline **13** was obtained using toluene as the solvent. The phthalimido-protecting group was then removed using hydrazine hydrate. The resulting amine was coupled with commercially available *N*,*N*′-bis



Scheme 2. Reagents and conditions: (i) 4-Cbz-aminobutanoic acid, EDCI, DMAP, CH_2Cl_2, rt, 89%; (ii) $POCl_3$, Δ, 73%.



Scheme 3. Reagents and conditions: (i) CH_3NO_2, 4 Å MS, DMSO, 85%; (ii) H_2, 10% Pd/C, MeOH, 100%; (iii) 4-Phth-aminobutanoic acid, EDCI, DMAP, CH_2Cl_2, 75%; (iv) $POCl_3$, Δ, toluene, 66%; (v) $NH_2NH_2{\cdot}H_2O$, Δ, EtOH; (vi) **14**, EtN(*i*-Pr)$_2$, MeOH, 82% over two steps; (vii) TFA, CH_2Cl_2, 73%.

(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**14**) in the presence of Hünig's base which gave guanidine **15** in 82% yield over the two steps.[5,16] Treatment of **15** with TFA to remove the Boc-protecting groups gave crispine C (**3**) in 73% yield. The spectroscopic data obtained for our synthetic material were in complete agreement with those reported for the natural product by Zhao and co-workers.[1]

In summary, the first total synthesis of crispine C is reported in seven steps and 25% overall yield. Although a two-step strategy involving a Bischler–Naperialski reaction followed by oxidation was unable to yield the C-1 substituted electron-rich isoquinoline, a more direct ring-forming process utilising a Pictet–Gams reaction was successful. The flexible approach described here is currently being used to prepare a wide range of isoquinoline ring systems with C-1 substituted guanylated side-chains. The results of these studies as well as biological evaluation of these novel compounds will be communicated in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.113.

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