Concise synthesis of the (±)-N_b-desmethyl-*meso*-chimonanthine†

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Received (in Cambridge, UK) 21st July 2006, Accepted 14th September 2006
First published as an Advance Article on the web 3rd October 2006
DOI: 10.1039/b610497e

The first total synthesis of the bis-pyrroloindoline alkaloid (±)-N_b-desmethyl-*meso*-chimonanthine, having a pseudo C_2-symmetry, was realised in a seven-step convergent sequence without the use of protecting groups.

The synthesis of natural products having vicinal stereogenic quaternary carbon centres, in particular benzylic centres, remains one of the most challenging problems in organic chemistry.[1,2] In recent years increasing attention has been devoted to the synthesis of calycanthaceous alkaloids,[3] possessing such architectural motifs. The simplest analogues, (−)- and (+)-chimonanthine[4,5] (**1**), *meso*-chimonanthine[6] (**2**), and (−)- and (+)-calycanthine[7] (**4**) have dimeric structures (Fig. 1). More recently several new pyrrolidinoindoline alkaloids have been isolated, including N_b-desmethyl-*meso*-chimonanthine (**3**) from *Psychotria lyciiflora*, as well as three new alkaloids: quadrigemine I (**6**), oleoidine (**7**), and caledonine (**8**), from *P. oleoides*,[8] having a pseudo C_2-symmetric backbone (Fig. 1). As it has been suggested that the biosynthetic pathway involves an oxidative dimerisation of tryptamine derivatives, this biomimetic route has been exploited in several syntheses of this type of alkaloid.[3] More recently, the elegant work by Overman *et al.*, based on alkylation of isoindigo, has produced optically active *meso*-chimonanthine, calycanthine,[9] idiospermuline,[10] quadrigemine C, psycholeine,[11] hodgkinsine, hodgkinsine B,[12] ditryptophenaline and *ent*-WIN 64821.[13] While bidirectional strategies are the methods of choice for the preparation of symmetric compounds, the desymmetrisation of the advanced intermediates, and the access to non-symmetrical analogues, is difficult and remains elusive.

We wish to report herein a highly convergent approach to N_b-desmethyl-*meso*-chimonanthine (**3**), the structurally simplest member of this class of alkaloid, which can provide access to more complex desymmetrised pyrrolidinoindoline alkaloids. The key step of the sequence is a diastereoselective tandem [4 + 2]-cycloaddition–cyclisation, inspired by the elegant synthesis of (±)-perophoramidine achieved by Fuchs and Funk.[14] We envisaged that this reaction could be applied in the preparation of an advanced intermediate of N_b-desmethyl-*meso*-chimonanthine, and could be performed in a highly diastereoselective manner. According to our working hypothesis, the desymmetrised *meso*-chimonanthine core could be obtained by a diastereoselective tandem [4 + 2]-cycloaddition–cyclisation of a conveniently functionalised bromooxindole and tryptamine derivative. As

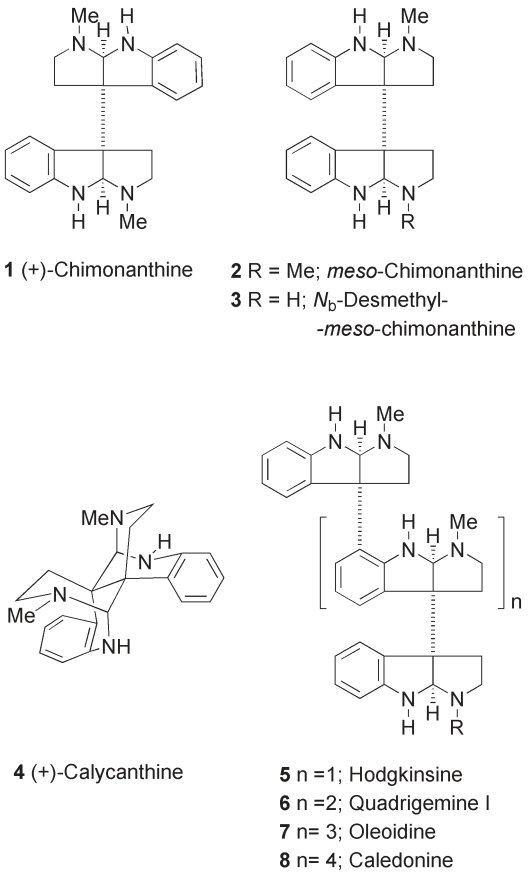

Fig. 1

described in Scheme 1, the primary cycloadduct should be unstable, and should spontaneously rearrange to the cyclic imine, which in turn will be trapped by the secondary amine to give the desired pyrrolidinoindoline skeleton.

The bromooxindole intermediate **9** was prepared in a five-step sequence (Scheme 2). Friedel–Crafts acylation of indole with oxalyl chloride followed by *in situ* esterification with methanol led to the indolyl-3-methylglyoxylate, which was converted to the corresponding alcohol by reduction with $LiAlH_4$ (quantitative). The azido function was introduced after standard iodination of the obtained alcohol under Garreg's conditions (PPh_3, imidazole, I_2), followed by substitution with sodium azide. Finally, oxindole **9** was obtained by oxidation with NBS (2.0 equiv, *t*-BuOH–H_2O). It is noteworthy that when the reaction was performed under standard conditions, at room temperature by addition of NBS in one portion, the desired product was isolated in low yield due to the competing dibromination of the indole. However, it was observed that the slow addition of a solution of NBS in THF (2 h)

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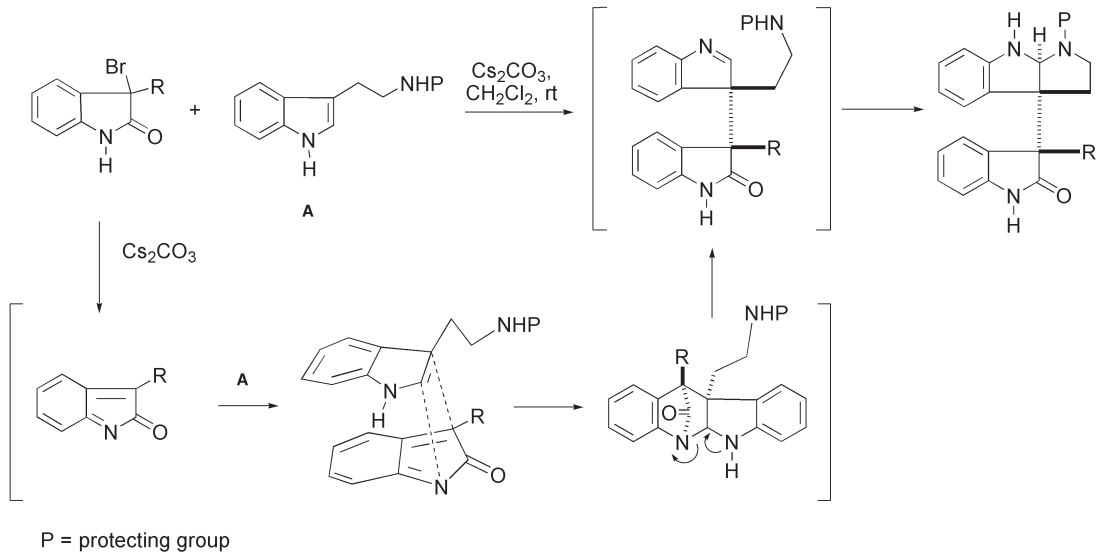
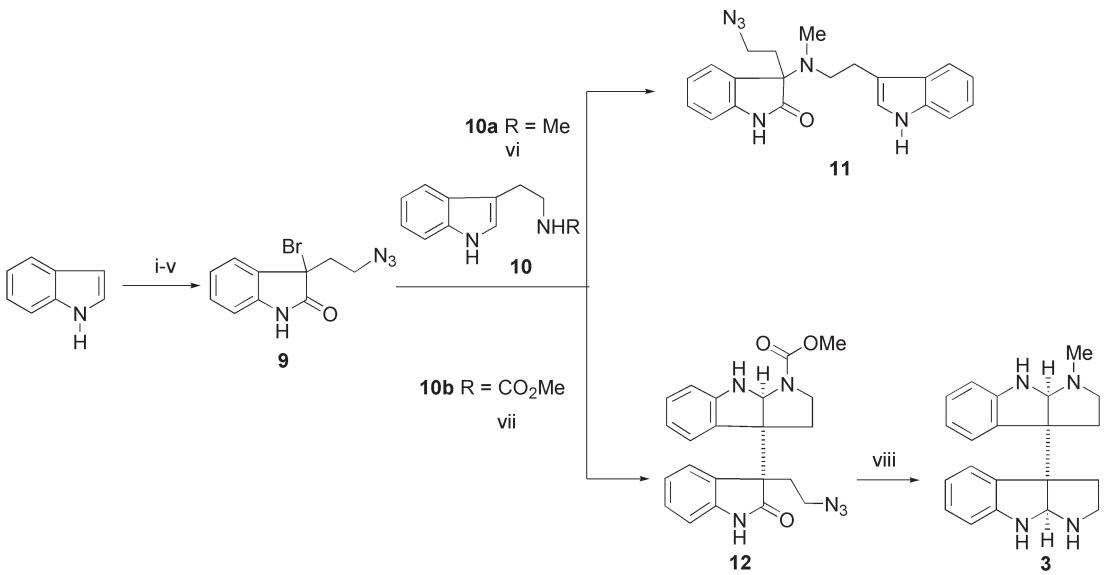
† Electronic supplementary information (ESI) available: Spectroscopic data (IR, ^1H and ^{13}C NMR, MS) of (±)-N_b-desmethyl-*meso*-chimonanthine (**3**) and of compound **12**. See DOI: 10.1039/b610497e



Scheme 1 A plausible rationalisation for the stereoselective formation of pyrrolidinoindoline skeletons including tandem [4 + 2]-cycloaddition–cyclisation steps.



Scheme 2 The synthesis of (±)-N_b-desmethyl-*meso*-chimonanthine. (i) $(COCl)_2$, Et_2O then MeOH, rt, 12 h (88%); (ii) $LiAlH_4$, THF, rt, 12 h (quant.); (iii) I_2, imidazole, PPh_3, benzene, rt, 1 h (75%); (iv) NaN_3, DMF, 50 °C, 1 h, (98%); (v) NBS, H_2O, THF, *t*-BuOH, 30 min, (80%); (vi) Cs_2CO_3, CH_2Cl_2, rt, 12 h, (35%); (vii) Cs_2CO_3, CH_2Cl_2, rt, 12 h (75%, dr = 95/5); (viii) Red-Al, toluene, 0 °C, rt, 100 °C, 8 h (57%).

to a *t*-BuOH–H_2O–THF solution of indole, maintained at 0–5 °C, resulted in suppression of the overoxidation and **9** was isolated in 80% yield.

The coupling reaction of **9** with various tryptamine derivatives, under the Funk conditions,[14] (Cs_2CO_3, CH_2Cl_2, rt, 12 h) was tested (Scheme 2). It was observed that the chemoselectivity of the reaction is highly dependant on the nitrogen nucleophilicity of the tryptamine side chain. When the aforementioned conditions were applied to *N*-methyltryptamine **10a**, by using Cs_2CO_3 as the base, compound **11**, which results from the formal substitution of the bromide by the amine, was obtained in 35% yield. In turn, when these conditions were applied to the *N*-carbamate derivative **10b**, the desired adduct **12** was isolated in 75% yield, with very high diastereoselectivity (95/5). Finally, the desired product **3** was obtained by reductive cyclisation of **12** using Red-Al in refluxing toluene (8 h, 57%). As it was expected, under these reaction conditions, the conversion of the *N*-methylcarbamate to the *N*-methyl function was observed affording N_b-desmethyl-*meso*-chimonanthine.

In summary, the synthesis of (±)-N_b-desmethyl-*meso*-chimonanthine (**3**) was achieved in a seven-step sequence from indole in 22% overall yield. It is noteworthy that the described sequence does not require the use of protecting groups. The 3a,3a′-bis-quaternary carbon–carbon bond formation was completed *via* an efficient tandem [4 + 2]-cycloaddition–cyclisation between a conveniently functionalised bromooxindole **9** and the tryptamine

derivative **10b**. This highly convergent approach presents advantages in terms of diastereoselectivity, step number, and flexibility and should allow an easy entry to more complex desymmetrised bis-pyrroloindolinoindoline alkaloids.

The authors wish to acknowledge Dr Françoise Guéritte (CNRS-ICSN, Gif-sur-Yvette) for kindly sending the ^{1}H and ^{13}C NMR spectra of the natural N_b-desmethyl-*meso*-chimonanthine (**3**).

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