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Asymmetric synthesis of (+)- and (−)-deoxyfebrifugine and deoxyhalofuginone

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ABSTRACT

Both enantiomers of deoxyfebrifugine (**4**) and deoxyhalofuginone (**5**), analogues of the quinazolinone-containing biologically active compounds febrifugine (**1**) and halofuginone (**3**), have been prepared in a six-step reaction sequence featuring an organocatalyzed Mannich reaction as the key stereo-inducing step. The compounds were isolated as their dihydrobromide salts in 29–42% overall yield and in 74–80% enantiomeric excess.

Febrifugine (**1**) is a naturally occurring substance found in *Dichroa febrifuga* (Chinese quinine) and a species from the Hydrangea family of plants.[1] *Dichroa febrifuga* has been used for centuries in traditional Chinese medicine for the treatment of a variety of ailments and since the first scientific papers concerning the plant-based active ingredient appeared (approximately sixty years ago) febrifugine (**1**) and its analogues have received attention[2] from both a biological[3] and a chemical standpoint.[4] In relation to the latter, the precise structure of febrifugine (**1**) was only finally confirmed in 1999—partly due to its isomerisation into isofebrifugine (**2**) (Fig. 1).[4b,5]

Despite potent antimalarial activity febrifugine (**1**) proved too toxic to develop as an antimalarial medicine and attempts to mitigate this produced halofuginone (**3**), an analogue in which the metabolically vulnerable aromatic protons are masked.[6] This compound has been used as a racemate in veterinary medicine to cure protozoal infections in livestock (particularly poultry) and serendipitously the anti-fibrotic activity of this compound was also uncovered.[7] Since this discovery a great deal of effort has been dedicated to investigating and understanding halofuginone's properties in animal models for numerous diseases.[8] These studies have ultimately supported the development of **3** as a human drug candidate and racemic halofuginone, has been the subject of clinical trials associated with its anticancer activity and its ability to improve the clinical indications in Muscular Dystrophy patients.[9] We have previously synthesised both (+)- and (−)-febrifugine (**1**) and halofuginone (**3**)[4v] and were keen to investigate how the presence of the 3-hydroxyl group affected activity. In part this was because the epimerisation event, likely occurring via a *retro*-conjugate addition, is complicated by hemiketal formation to generate isofebrifugine (**2**).[2] 'Deoxyfebrifugine' (**4**) has previously been prepared in racemic form three times and in one report its antimalarial activity was compared with febrifugine itself.[10] As yet there are no reports concerning the synthesis of deoxyhalofuginone (**5**). In this work we wish to report the first asymmetric synthesis of both enantiomers of deoxyfebrifugine (**4**)

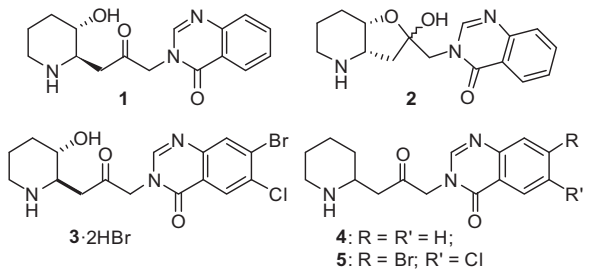

Figure 1. Naturally occurring febrifugine (**1**) and isofebrifugine (**2**) and the synthetic analogues: halofuginone (**3**), deoxyfebrifugine (**4**) and deoxyhalofuginone (**5**).

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and deoxyhalofuginone (**5**) as well as a preliminary racemisation study.

The asymmetric Mannich reaction between an imine and an enolizable ketone, proceeding via enamine-based organocatalysis,[11] has been reported.[12] Recently, the range of imines utilised in this type of process has been widened to incorporate Δ^1-piperideine (**6**),[13] which Bella and co-workers have demonstrated reacts with several methyl ketones in the presence of several secondary amines possessing a Brønsted acidic group.[14] Proline itself performs well in this chemistry and in this manner unnatural pelletierine was prepared in good yield and enantioselectivity. Since the functionalisation and alkylation of a methyl ketone with quinazolin-4(3*H*)-one (4-hydroxyquinazoline) has been well-established in febrifugine synthesis[4b,10b] we felt that the asymmetric Mannich chemistry would be ideally suited for the synthesis of deoxyfebrifugine and deoxyhalofuginone.

As Scheme 1 illustrates, at room temperature **6** undergoes a rapid Mannich reaction with L-proline and excess acetone in a DMSO–water mixture (8:1). The crude material obtained after aqueous work-up was directly converted into the corresponding carbamate in order to minimise the loss of enantiomeric purity of the β-amino ketone by a *retro*-conjugate addition process[15] and (−)-**7** was isolated in reasonable to good yields with enantiomeric ratios ranging from 85:15 to 90:10.[16] Use of D-proline provided (+)-**7** in an otherwise identical sequence.[17]

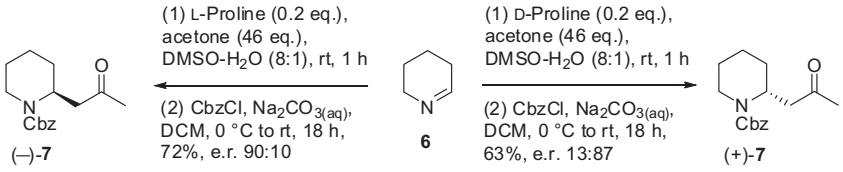
With the enantioenriched 2-substituted piperidines (−)- and (+)-**7** in hand their conversion into deoxyfebrifugine and deoxyhalofuginone was considered. As shown in Scheme 2, the methyl group in (−)-**7** was brominated using a two-step, one-pot procedure involving the formation of a trimethylsilyl enol ether. The crude bromide, obtained after work up, was then treated with quinazolin-4(3*H*)-one (**10**), or 7-bromo-6-chloroquinazolin-4(3*H*)-one (**11**), to form (−)-**8** and (−)-**9** respectively. The efficiency of this sequence was improved by the inclusion of activated 4 Å molecular sieves during silyl enol ether formation. Chiral HPLC confirmed that no change in stereochemical integrity had occurred over the three-step reaction sequence and it should be mentioned that recrystallisation of (−)-**9** from MeOH did not enhance its enantiomeric ratio.

Finally, the Cbz group was removed with HBr in acetic acid, providing either (+)-**4** or (+)-**5**, as their dihydrobromide salts, in yields of approximately 55% for the four steps. In the case of **8** this reaction was performed with DCM as a solvent, however, due to its poor solubility in this solvent the conversion of **9** into **5** was performed solely in neat HBr/AcOH. Similarly, (+)-Cbz protected pelletierine **7** was converted into the enantiomeric dihydrobromide salts of (−)-**4** and (−)-**5**.

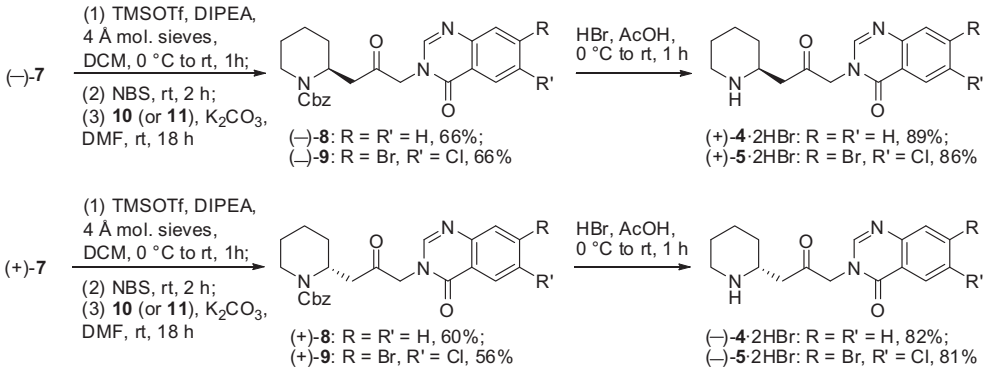
Since the interconversion between **1** and **2** (Fig. 1) has both been reported (and indeed taken advantage of synthetically)[2,4] and the epimerisation/racemisation of pelletierine (and related β-amino heterocycles like hygrine) is also well-known,[15] the integrity of the stereogenic centre (in **4** and **5**) was of interest. This point was addressed following the Cbz-protection of **5** to again give **9** and then analysing HPLC data.

Initially, (+)-**5** was converted into (−)-**9** using Et_3N, CbzCl at 0 °C to room temperature in a water–dichloromethane solvent mixture. Chiral HPLC analysis of (−)-**9** prepared in this manner indicated that the enantiomeric ratio of the re-protected material was identical to that used for the original preparation of (+)-**5**, thereby, confirming that no erosion of enantiomeric purity had taken place over the deprotection sequence. Next, salt (−)-**5** was dissolved in water and left to stand for five days before treatment with a mixture of Et_3N and CbzCl in dichloromethane. Similarly, (+)-**9** prepared in this manner demonstrated that racemisation had not taken place. Finally, (−)-**5** was dissolved in water and then treated with Et_3N in dichloromethane and stirred for five days. The biphasic mixture, containing the free-base, was then treated with CbzCl. After purification, chiral HPLC indicated that racemisation had taken place.

In summary, we report the Mannich-based stereoselective synthesis of both enantiomers of deoxyfebrifugine (**4**) and deoxyhalofuginone (**5**). Following the short, telescoped reaction sequence (+)- and (−)-**4** as well as (+)- and (−)-**5** were accessed from Δ^1-piperideine (**6**) in 29–42% overall yield and in 74–80% ee. We have shown that loss of stereochemical integrity does not readily take place when the secondary amine is stored as the corresponding ammonium salt. However, in solution the free-base does undergo racemisation. Studies concerning the enantiomer specific ability of deoxyfebrifugine and deoxyhalofuginone to



Scheme 1. Synthesis of (+)- and (−)-Cbz-protected pelletierine (**7**) via Bella's asymmetric Mannich reaction.



Scheme 2. Conversion of (+)- and (−)-Cbz-protected pelletierine (**7**) into (+)- and (−)-deoxyfebrifugine (**4**) and deoxyhalofuginone (**5**).

ameliorate the histopathology and muscle function in muscular dystrophies are currently underway.

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Supplementary data

Supplementary data (full experimental details, scanned proton and carbon spectra and HPLC traces) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.146.

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16. Performing the reaction at 5 °C, under otherwise identical conditions, led to the isolation of (−)-**7** in 23% and 75% ee.
17. In Bella's report (Ref. 14) PhCN at -20 °C (0.7 M) for 7 days gave optimal enantioselectivity (up to 95% ee) for this process. However, the high boiling point of this solvent and the lengthy reaction period meant that we opted for the practical and scalable conditions reported herein.