Asymmetric synthesis of protoberberine alkaloids *via* a tandem nucleophilic addition and intramolecular cyclisation of a chiral *o*-toluamide anion with 3,4-dihydroisoquinoline

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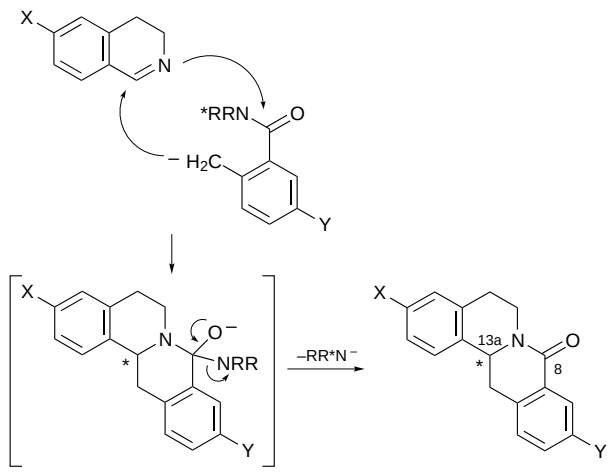
The reaction of *o*-toluamide anions, derived from the (*S*)-(−)- and (*R*)-(+)-1-phenylethylamine, with 6,7-dimethoxy-3,4-dihydroisoquinoline gives (13a*S*)-(−)- and (13a*R*)-(+)-8-oxoprotoberberine, respectively, with enantiomeric excesses > 96%.

The protoberberine alkaloids display a broad diversity of biological activities[1,2] and feature predominently as active components in many folkloric medicines especially in China and other Asian countries. A wide range of synthetic methods have been reported for the preparation of protoberberines and these have been the subject of several reviews.[2,3] In spite of this only a few methods deal with the enantioselective synthesis of protoberberines. Most asymmetric methods involve multi-step procedures, use of special reagents and occur in relatively low optical yields.[4,5] Recently, lateral metallation methodology has been developed for the synthesis of racemic heterocyclic compounds, including protoberberines, and shown to exhibit exceptional regiochemical control.[6] This feature, coupled with a direct approach to the products, offers efficient entry to the protoberberine skeleton and related structures.

In this communication we report the first successful application of lateral metallation to the efficient asymmetric synthesis of protoberberines *with* a chiral *o*-toluamide (Scheme 1).

The commercial availability of the two enantiomers of 1-phenylethylamine made this an attractive chiral auxiliary to incorporate into the *o*-toluamides. Our initial study, which involved the reaction the anion derived from the secondary *o*-toluamide **2a** (R = H) with the isoquinoline **1**, failed to afford any of the cyclised protoberberine **4** and only the ring-opened intermediate **3** could be detected. Whilst this intermediate could be cyclised by heating in refluxing toluene, the final product **4** exhibited very low enantiomeric purity (1.5% ee) (Table 1).

Since anions of tertiary amides, *e.g. N*,*N*-diethyl-*o*-toluamide, are known to condense with dihydroisoquinolines and



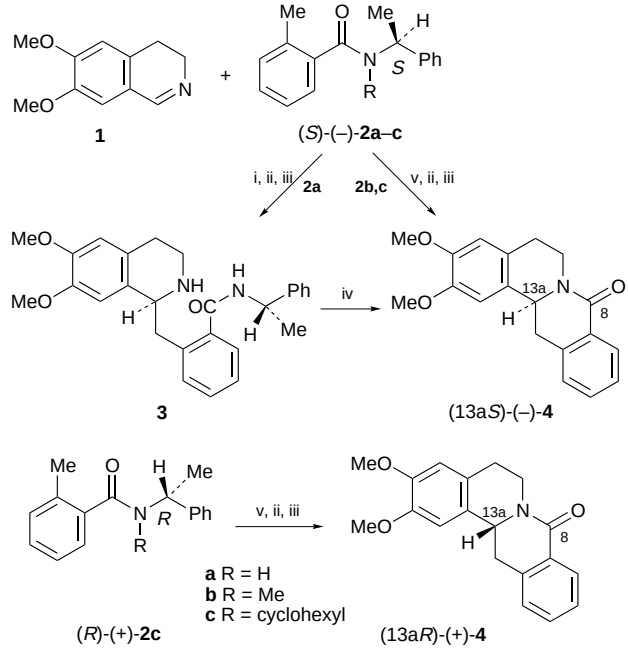
Scheme 1 An approach to the asymmetric synthesis of protoberberines based upon lateral metallation

Table 1 Chemical and optical yields of protoberberine **4** from reactions involving the toluamides **2a**–**c** with dihydrosioquinoline **3**

	Yield (%)[a]	$[\alpha]_D^{20}$[b]	Ee (%)[c]
(*S*)-**2a**	39	−5.6	1.5
(*S*)-**2b**	14	−19.9	5.2
(*S*)-**2c**	48	−372.4	97
(*R*)-**2c**	51	+366.6	96

[a] Chemical yields have not been optimised and refer to the sole product which was isolated by chromatography. [b] Rotations: *c* 0.359, $CHCl_3$. [c] Optical yields were calculated by comparison of the rotation with the reported data, *i.e.* rotations (in $CHCl_3$) of 10, 50, 67 and 73 corresponding to 3, 13, 18 and 19% ee.[5]

subsequently cyclise in the one pot,[7] we turned our attention to the chiral amide **2b**. Whilst reaction of **1** with **2b** afforded the 8-oxoprotoberberine in one step, there was only a slight improvement of the enantiomeric selectivity (5.2% ee) of the reaction. These rather disappointing results, we reasoned, were due to too great a conformational mobility of the chiral auxiliary and accordingly the more sterically demanding cyclohexyl group was introduced as a non-chiral substituent on the amide nitrogen atom, *i.e.* **2c**. The reaction of (*S*)-(−)-**2c** with the dihydroquinoline **1** gave as the product (*S*)-(−)-**4** (97% ee) in 48% chemical yield. Similarly pure (*R*)-(+)-**4** (96% ee) was prepared by replacement of the chiral auxiliary in the amide **2c** with (*R*)-(+)-1-phenylethylamine (Scheme 2), thereby provid-



Scheme 2 *Reagents and conditions*: i, Bu^nLi (2 equiv.), THF, 0 °C, 1 h; ii, **1**, THF, −78 to −30 °C, 1 h; iii, aq. NH_4Cl, −30 °C; iv, PhMe, 110 °C, 15 h; v, Pr^i_2NLi (1 equiv.) THF, −78 °C, 25 min

ing the desired one-pot synthesis of the protoberberine ring system.

Although our research is at an early stage, it is clear that we have developed an efficient asymmetric synthesis for chiral 8-oxoprotoberberines based upon the regiospecific addition–cyclisation reaction of chiral *o*-toluamide anions with 3,4-dihydroisoquinolines. The extension of this methodology to other heterocyclic compounds and the understanding of the mechanism leading to chiral induction is an ongoing study in our laboratories.

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Footnote and References

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