

# A new and enantioselective indolizidine synthesis by *meso*-epoxide $\alpha$ -deprotonation–transannular N–C insertion

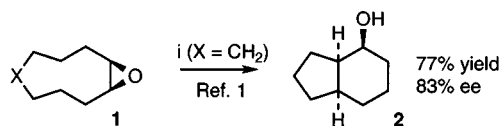
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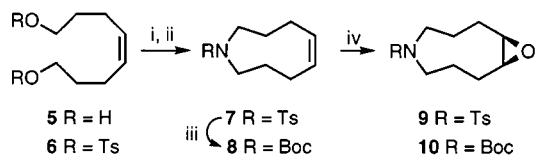
**Enantioselective  $\alpha$ -deprotonation–rearrangement of *N*-Boc hexahydroazonine oxide **10** using organolithiums in the presence of (–)-sparteine **3** gives the ester **12** in up to 89% ee.**

We recently reported the enantioselective  $\alpha$ -deprotonation–rearrangement of medium-sized (8-, 9- and 10-membered) cycloalkene-derived achiral epoxides using a secondary organolithium in combination with a chiral ligand such as (–)-sparteine **3**, which gives bicyclic alcohols in good yields and ees (77–84% ee, e.g. Scheme 1, X = CH<sub>2</sub>).<sup>1</sup> However, only a single functional group is generated in the desymmetrised bicycles. One strategy to enhance the utility of this transformation would be to examine heterocycloalkene-derived achiral epoxides. Here we communicate our preliminary results concerning the synthesis and novel rearrangement chemistry of an azacyclic epoxide of this type (**1**, X = NR).



**Scheme 1** Reagents and conditions: i, Pr<sup>t</sup>Li (2.4 equiv.), (–)-sparteine **3** (2.5 equiv.), Et<sub>2</sub>O, –98 °C (5 h) to 25 °C (15 h).

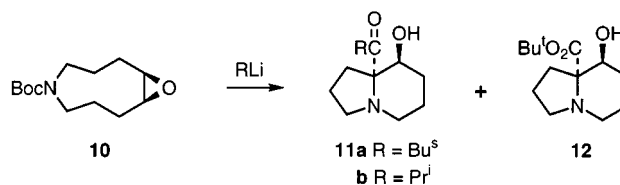
An important aspect of the study of transannular reactions of a medium-sized heterocycle concerns the potential problem of preparing the substrate.<sup>2</sup> However, application of methodology<sup>3</sup> used in the synthesis of the azacycloundecene system found in manzamine C led to a highly satisfactory route to the azacyclic epoxide **9** (Scheme 2). Thus, cyclisation under dilute conditions of the ditosylate **6** of the known diol **5** (readily available from cycloocta-1,5-diene)<sup>4</sup> gave the reduced azonine **7** in 62% yield; to the best of our knowledge this is the most efficient cyclisation reported which gives a simple reduced azonine.<sup>2</sup>



**Scheme 2** Reagents and conditions: i, TsCl (4.9 equiv.), Py, 0 °C (5 h) to 25 °C (15 h), 74%; ii, TsNH<sub>2</sub> (1.7 equiv.), NaOH (200 equiv.), Bu<sub>4</sub>NI (1.4 equiv.), toluene–H<sub>2</sub>O, reflux, 5 h, 62%; iii, Na naphthalenide (2.5 equiv.), THF, –78 °C, then HCl(g), then Et<sub>3</sub>N (1.5 equiv.), Boc<sub>2</sub>O (1.5 equiv.), DMAP (0.1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 64% from **7**; iv, MeCO<sub>3</sub>H (1.2 equiv.), Na<sub>2</sub>CO<sub>3</sub> (3 equiv.), NaOAc (0.02 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (10 min) to 25 °C (15 h), 82% (R = Ts), 87% (R = Boc).

Subjection of the epoxide **9**, derived from reduced azonine **7**, to typical asymmetric rearrangement conditions<sup>1</sup> [Bu<sup>s</sup>Li (2.4 equiv.) and (–)-sparteine **3** (2.5 equiv.) in Et<sub>2</sub>O at –78 °C for 5 h, followed by warming to 25 °C over 15 h, cf. Scheme 1] led only to the recovery of starting epoxide **9**, whereas quenching the reaction with D<sub>2</sub>O led to essentially complete *o*-deuterium incorporation into the tosyl group of the recovered starting

material (64%). An attempt to induce reaction at the epoxide group subsequent to *ortho*-deprotonation using double the quantities of reagents indicated above led to no identifiable products; an alternative protecting group was therefore required. Removal of the tosyl group from **7** using sodium naphthalenide and immediate Boc re-protection of the amine hydrochloride salt gave the reduced azonine **8** (64%). Epoxidation provided **10**, which could potentially undergo deprotonation with an organolithium either  $\alpha$  to the epoxide oxygen, or  $\alpha$  to nitrogen. Beak has reported a 6-*exo-tet* cyclisation onto an epoxide *via* deprotonation  $\alpha$  to NBoc; the deprotonation site was however also benzylic in this case.<sup>5</sup> Beak has also reported that the rate of deprotonation of Boc-protected azacycles decreases on moving from pyrrolidine to piperidine to perhydroazepine.<sup>6</sup> In the event, reaction of the epoxide **10** with Bu<sup>s</sup>Li (2.4 equiv. in Et<sub>2</sub>O at –78 °C for 5 h, followed by warming to 25 °C over 15 h) led to an inseparable 1 : 1 mixture of epimers (due to the stereogenic centre in the Bu<sup>s</sup> group, *vide infra*) of ketone **11a** (48%, 70% based on recovered epoxide **10**, Scheme 3).



**Scheme 3**

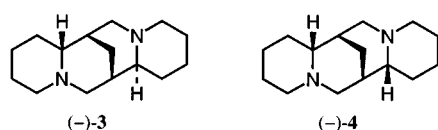
In contrast, reaction of the epoxide **10** with Bu<sup>s</sup>Li, under the same conditions but in the presence of TMEDA (2.5 equiv.), led to the formation of ester **12** as the major product (**12**: **11a**, 8 : 1 by <sup>1</sup>H NMR analysis; 74% isolated yield of **12**). Using (–)-sparteine **3** as the ligand in an otherwise identical experiment gave an equal mixture of **11a** and **12** (66% ee for **12**).<sup>†</sup> Experiments were then carried out to examine the possibility of increasing both the proportion and ee of ester **12** formed from epoxide **10** (Table 1).

Maintaining the reaction at –78 °C for 18 h and then quenching at this temperature gave ester **12** in improved ee (74%, Table 1, entry 1), but the ketone **11a** predominated. However, repeating the same procedure at –98 °C significantly improved the proportion of ester **12** (**12**: **11a**, 5 : 1) and increased the ee of **12** to 79% (entry 2). Using Pr<sup>i</sup>Li at –98 °C gave mainly the ester **12** (**12**: **11a**, 10 : 1) and with the highest level of asymmetric induction (89% ee, entry 3),<sup>‡</sup> as also observed with our earlier work on cycloalkene-derived epoxides.<sup>1</sup> Using (–)- $\alpha$ -isoparteine **4** as ligand with either Bu<sup>s</sup>Li or Pr<sup>i</sup>Li slowed the reaction considerably (entries 4 and 5), particularly in conjunction with Bu<sup>s</sup>Li; the ees were also reduced compared with the corresponding (–)-sparteine **3** reactions. In an attempt to allow Pr<sup>i</sup>Li/(–)- $\alpha$ -isoparteine **4** to completely consume the epoxide **10**, the reaction was left for 40 h at –98 °C (entry 6), but it still remained only 50% complete after this time and no change in the ee of ester **12** was observed. The use of catalytic amounts of ligand was also investigated

**Table 1** Effect of experimental conditions on the yields and enantioselectivities of formation of indolizidine **12** from epoxide **10** using ligand/RLi in Et<sub>2</sub>O

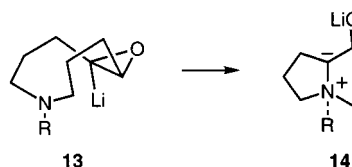
Entry <sup>a</sup>	Ligand	RLi	<b>10</b> : <b>11</b> : <b>12</b> <sup>b</sup>	Yield of <b>12</b> <sup>c</sup> (%)	Ee of <b>12</b> (%)
1 <sup>d</sup>	<b>3</b>	Bu <sup>s</sup> Li	0 : 1.6 : 1.0	32 (20)	74
2	<b>3</b>	Bu <sup>s</sup> Li	0.1 : 0.2 : 1.0	58 (50)	79
3	<b>3</b>	Pr <sup>i</sup> Li	0.3 : 0.1 : 1.0	57 (49)	89
4	<b>4</b>	Bu <sup>s</sup> Li	5.0 : 0 : 1.0	14	64
5	<b>4</b>	Pr <sup>i</sup> Li	2.0 : 0.1 : 1.0	29	79
6 <sup>e</sup>	<b>4</b>	Pr <sup>i</sup> Li	1.3 : 0.1 : 1.0	40	78
7 <sup>f</sup>	<b>3</b>	Pr <sup>i</sup> Li	0.7 : 0.6 : 1.0	36	82
8 <sup>f</sup>	<b>4</b>	Pr <sup>i</sup> Li	1.2 : 0.1 : 1.0	33	77
9 <sup>e,f</sup>	<b>4</b>	Pr <sup>i</sup> Li	0.4 : 0.2 : 1.0	54	89

<sup>a</sup> Ratio of ligand : RLi : epoxide **10**, 2.45 : 2.4 : 1 and carried out at -98 °C with a reaction time of 18 h unless otherwise indicated. <sup>b</sup> Ratios determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> Yield of **12** as measured by <sup>1</sup>H NMR analysis using methyl diphenylacetate as an internal standard. Isolated yields given in parentheses. <sup>d</sup> Carried out at -78 °C. <sup>e</sup> Reaction time 40 h. <sup>f</sup> Ratio of ligand : RLi : epoxide **10**, 0.24 : 2.4 : 1.



(entries 7–9) with interesting results. Using 24 mol% (–)-sparteine **3** (10 mol% with respect to Pr<sup>i</sup>Li), high levels of ee (82%) were still achieved, but the reaction was found to be much slower. In contrast, (–)-α-isosparteine **4** was more effective when used in a catalytic fashion (entry 8), with no apparent change in the ee (compare entry 5). Repeating this last reaction but leaving it for 40 h at -98 °C allowed the reaction to proceed further to completion and also gave a much higher level of ee (entry 9).

The structures of indolizidinols **11** and **12** were assigned by extensive spectroscopic investigations and were later further supported by X-ray crystallographic analysis of ketone **11b**.§ A mechanistic explanation for the formation of the indolizidinols is that they arise *via* lithiation α to the epoxide oxygen to give **13**, followed by transannular reaction using the N lone pair to give an ammonium ylide **14** which undergoes [1,2] migration of the exocyclic N substituent (Scheme 4); direct insertion of the lithiated epoxide into the exocyclic C–N bond is also possible. Incorporation of the organolithium to give the ketones **11** could occur before or after the transannular reaction. The latter



Scheme 4

process seems most likely, since reducing the equivalents of organolithium from 2.5 improves (at the expense of conversion of starting epoxide **10**) the ratio of ester **12** : ketone **11**, and in a separate experiment ester **12** could be quantitatively converted to ketone **11b** using Pr<sup>i</sup>Li (1.1 equiv., -78 °C for 1 h, followed by warming to 0 °C over 2 h).

Insertion of a lithiated epoxide into a C–N bond has not previously been reported and the present study illustrates an example of this process leading to a new and enantioselective entry to the important indolizidine framework. Further studies on the scope of this process are in progress and will be reported in due course.

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## Notes and references

† Ees were determined by GC (Chrompack chirasil-dex 25 m × 0.32 mm ID column; 6 psi, 120 °C). The absolute configurations of the predominant indolizidinol enantiomers are not known but can be tentatively assigned as shown in Scheme 3 by analogy with the selectivity for deprotonation at the R configured epoxide stereocentre with (–)-sparteine **3** observed in our earlier medium-ring studies (ref. 1).

‡ Freshly distilled (–)-sparteine (70 mm<sup>3</sup>, 0.30 mmol) in Et<sub>2</sub>O (1 cm<sup>3</sup>) was added dropwise over 0.5 h to a stirred solution of Pr<sup>i</sup>Li [1.09 mol dm<sup>-3</sup> in light petroleum (boiling range 40–60 °C); 270 mm<sup>3</sup>, 0.29 mmol] in Et<sub>2</sub>O (1 cm<sup>3</sup>) at -98 °C. The reaction mixture was allowed to stir for 1 h at -98 °C before the epoxide **10** (30 mg, 0.12 mmol) in Et<sub>2</sub>O (1 cm<sup>3</sup>) was added dropwise over 0.5 h. The reaction mixture was stirred for 18 h at this temperature and then H<sub>3</sub>PO<sub>4</sub> (0.5 mol dm<sup>-3</sup> in water; 1 cm<sup>3</sup>) added slowly dropwise. After warming to room temperature the organic layer was removed and the aqueous layer extracted with Et<sub>2</sub>O (3 × 5 cm<sup>3</sup>). The combined organic extracts were dried (MgSO<sub>4</sub>) and then evaporated under reduced pressure. Purification of the residue by column chromatography [(SiO<sub>2</sub>, 50% Et<sub>2</sub>O–light petroleum (boiling range 40–60 °C) → 100% Et<sub>2</sub>O)] gave the ester **12** (14.8 mg, 49%); [α]<sub>D</sub><sup>25</sup>+48.6 (c 0.3 in CHCl<sub>3</sub>).

§ Crystal data for **11b**: C<sub>12</sub>H<sub>20</sub>NO<sub>2</sub>, M = 210.29, orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (No. 19), a = 5.807(7), b = 13.393(2), c = 15.477(3) Å, V = 1203.7(3) Å<sup>3</sup>, Z = 4. 1038 independent reflections measured at 173 K on an Enraf-Nonius DIP2000 diffractometer. Mo-Kα radiation. 718 reflections with I > 8σ(I) and 137 variables yield R = 0.064, R<sub>w</sub> = 0.063. CCDC 182/1138. Crystal data are available in CIF format from the RSC web site, see: <http://www.rsc.org/suppdata/cc/1999/309/>

- D. M. Hodgson, G. P. Lee, R. E. Marriott, A. J. Thompson, R. Wisedale and J. Witherington, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2151.
- P. A. Evans and A. B. Holmes, *Tetrahedron*, 1991, **47**, 9131.
- Y. Torisawa, A. Hashimoto, M. Nakagawa, H. Seki, R. Hara and T. Hino, *Tetrahedron*, 1991, **47**, 8067.
- D. Raederstorff, A. Y. L. Shu, J. E. Thompson and C. Djerassi, *J. Org. Chem.*, 1987, **52**, 2337.
- P. Beak, S. Wu, E. K. Yum and Y. M. Jun, *J. Org. Chem.*, 1994, **59**, 276.
- P. Beak and W. K. Lee, *J. Org. Chem.*, 1993, **58**, 1109.

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