A study of asymmetric protonation with chiral β-hydroxy sulfoxides. Asymmetric synthesis of (−)-epibatidine

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The asymmetric synthesis of (−)-epibatidine 1, employing as the key step the asymmetric protonation of the achiral lithum enolate of cyclohexanone derivative 5 with chiral β-hydroxy sulfoxide 3b, is described.

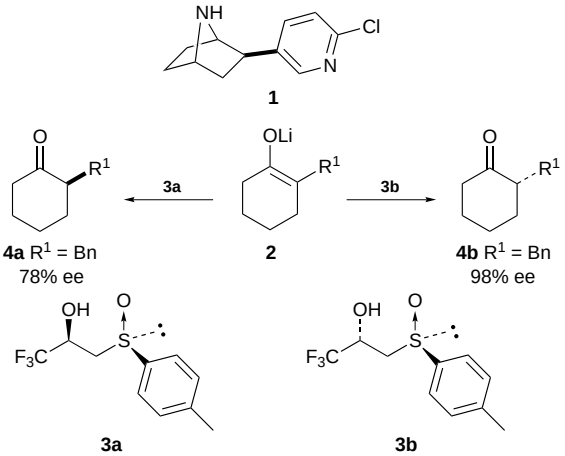
Epibatidine **1** was isolated from the poisonous Ecuadoran frog *Epipedobates tricolor*, and was found to be a novel potent antinociceptive agent that acts through nicotinic receptors.[1] Because of the scarcity of **1** in nature, the determination of its absolute stereochemistry was extremely difficult. In 1994, Fletcher *et al*. reported the absolute stereochemistry of **1** to be 1*R*,2*R*,4*S* by the HPLC comparison of synthetic specimens with natural **1**.[2f] Owing to interest in this novel biological activity and its intriguing chemical structure, many synthetic routes to **1** have been reported.[2] The synthetic approaches to optically active **1** are somewhat limited and involve an optical resolution of either a product at some stage of the synthesis or the final product **1**. [2g,3] Here we report the asymmetric synthesis of (−)-**1** based on the asymmetric protonation of achiral lithium enolates derived from cyclohexanone derivatives with chiral β-hydroxy sulfoxides.

We have recently developed, using enantiomerically pure β-hydroxy sulfoxides **3a** or **3b** as protonating reagents, the effective asymmetric protonation of achiral lithium enolates of 2-substituted cyclohexanones **2** to give enantiomers **4a** and **4b**, respectively, with high enantiopurity (Scheme 1).[4] Extension of the methodology to other substituted cyclohexanones, especially 4,4-ethylenedioxycyclohexanone derivatives, would be useful for procurement of chiral synthetic intermediates for natural product synthesis. For example, as shown in Scheme 2, when the asymmetric protonation is applied to the cyclohexanone acetal bearing a 4-chloropyridinyl moiety at the C(2) position, the compound (*R*)-**5** obtained might be readily converted to **6**, which has been employed as the common synthetic intermediate for the construction of the 7-azabicyclo-[2.2.1]heptane system of epibatidine, in the synthesis originally developed by Broka.[2a]

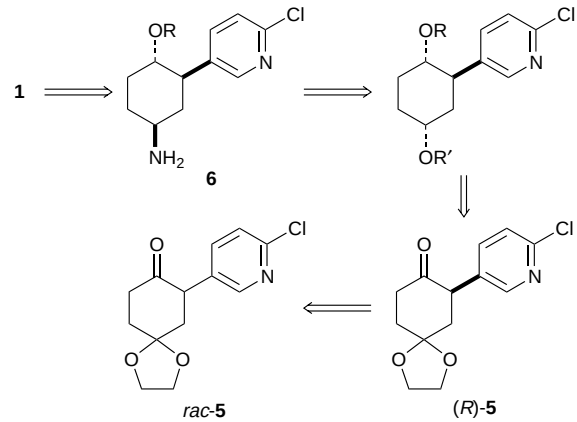
The starting cyclohexanone derivative *rac*-**5** was synthesized from 4-*tert*-butyldimethylsilyloxycyclohex-2-en-1-one[5] by a sequence of conventional reactions: (i) conjugate addition of 4-lithio-2-chloropyridine in the presence of lithium thienylcyanocuprate according to a reported procedure,[2i] and (ii) acetalisation and deprotection of the silyloxy group, followed by Swern oxidation to give *rac*-**5** (Scheme 3).

Regioselective enol acetate formation was accomplished by treatment of *rac*-**5** with Bu^{t}OK, followed by addition of Ac_2O to give enol acetate **7** in 99% yield. The asymmetric protonation was performed as follows. The lithium enolate generated from **7** by treatment with MeLi (2 equiv.) in Et_2O was protonated by adding **3b**[6] (2.5 equiv.) in CH_2Cl_2 at −90 °C for 1.5 h, during which time the reaction temperature rose to −60 °C. The product (*R*)-**5** [63% yield, $[\alpha]_D^{25}$ + 18.3 (*c* 0.316, $CHCl_3$)] obtained was found to have an enantiomeric excess of 82% by HPLC (Daicel AD chiralcel column). The chiral **5** was reduced with $NaBH_4$ in MeOH to the *trans*-alcohol **8** (77%) accompanied by some of the *cis*-alcohol (18%). It is worthwhile to mention that, at this stage, optical purification to obtain the enantiomerically pure **8a** was achieved using achiral silica gel chromatography.† The absolute stereochemistry was determined to be 3*R*,4*S* by applying the exciton coupled circular dichroic (CD) method[6] to the benzoate **8b** [UV (MeOH) λ_{max} 218 nm (ε 16 700); CD (MeOH) λ_{ext} 227.4 nm ($\Delta\varepsilon$ +12.9), 215.4 (−1.04)] derived from **8a**. Consequently, the absolute structure of (+)-**5** is suggested to be 3*R*, as depicted in Scheme 3. It should be noted that the sense of the enantiofacial recognition of cyclohexanone derivatives bearing an acetal moiety at the C(4) position is the reverse of that of simple 2-substituted cyclohexanones in the asymmetric protonation with **3b**.[4]

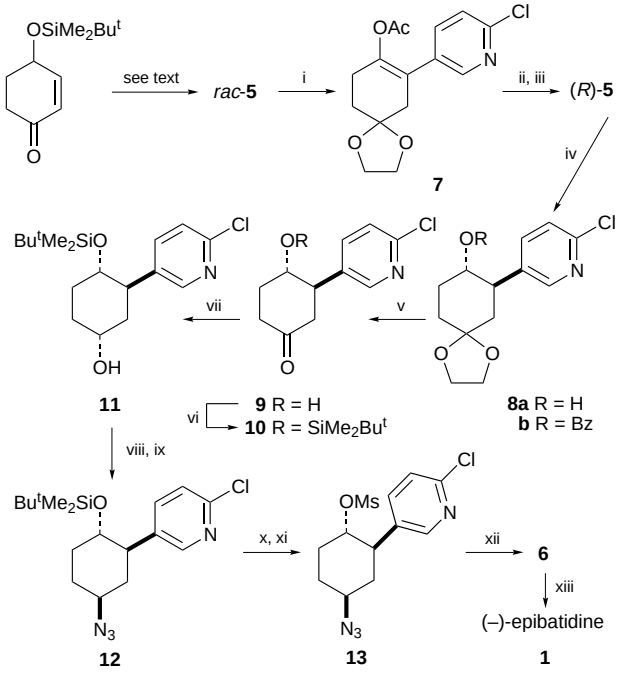
Conversion of the enantiomerically pure alcohol **8a** to epibatidine **1** was straightforward, employing the slightly modified procedure of Broka.[2a] Deprotection of the carbonyl group, followed by protection of the hydroxy group as the Bu^{t}Me$_2$Si ether afforded **10** in 81% overall yield from **8**. The carbonyl reduction of **10** with LiBBu$^s_3$H (L-selectride) in THF



Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions*: i, Bu^{t}OK, Ac_2O, THF; ii, MeLi (2 equiv.), Et_2O, 0 °C, 15 min; iii, **3b**, CH_2Cl_2, (2.5 equiv.), −90 to −60 °C; iv, $NaBH_4$, MeOH; v, 80% aq. AcOH; vi, Bu^{t}Me$_2$SiCl, Pr$^i_2$NEt, DMF; vii, LiBBu$^s_3$H, THF; viii, MsCl, Et_3N, CH_2Cl_2; ix, NaN_3, DMF; x, Bu_4NF, THF; xi, MsCl, Et_3N, CH_2Cl_2; xii, $SnCl_2·2H_2O$, MeOH–THF; xiii, $CHCl_3$, reflux

afforded the axial alcohol **11** (63%). Conversion of the hydroxy group to azide was performed *via* a two-step procedure to give **12** in 76% yield from **11**. Deprotection of the silyl ether, followed by mesylation ($MeSO_2Cl$, Et_3N, CH_2Cl_2) gave the mesylate **13** in 95% yield. Finally, the mild reduction of the azide function with $SnCl_2$ and ring closure of the resulting amine **6** in refluxing $CHCl_3$ for 3 d gave enantiomerically pure (−)-**1** {$[\alpha]^{25}_D$ −6.99 (*c* 0.229, $CHCl_3$): mp 62–62.5 °C, 69% yield from **13**} which was identical in all respects with the reported physical data.[2f]

In conclusion, the synthetic utility of asymmetric protonation of prochiral lithium enolates with chiral β-hydroxy sulfoxides has been demonstrated by the asymmetric synthesis of enantiomerically pure (−)-epibatidine. Further studies on the scope and limitations of the present asymmetric protonation are in progress.

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Footnotes and References

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† There have been a few examples of the chromatographic separation of partially enantio-enriched compounds under achiral conditions (ref. 8). When a sample of the hydroxy acetal **8a** (80% ee) was loaded on a silica gel column [MPLC: Kusano pre-packed silica gel column Si-10; eluted with 3 : 1 hexane–EtOAc; UV (254 nm) and RI detectors], enantiomerically pure **8a** was first eluted, followed by *rac*-**8a** as a shoulder. We have examined the separation of some partially enantio-enriched (23–80% ee) homologues such as *trans*-3-substituted 4-hydroxycyclohex-1-enone ethylene ketals {*e.g.* 3-benzyl and 3-[(*E*)-3-phenylprop-2-enyl] derivatives} as well as their *cis*-isomers by achiral silica gel column chromatography, and found that the chromatographic behaviour is quite general. The results will be reported elsewhere.

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