Pergamon

Tetrahedron Letters 39 (1998) 1023–1024

TETRAHEDRON LETTERS

Asymmetric Synthesis of Epibatidine by use of a Novel Enantioselective Sulfinate Elimination Reaction

Clifford D. Jones and Nigel S. Simpkins*

Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, U.K.

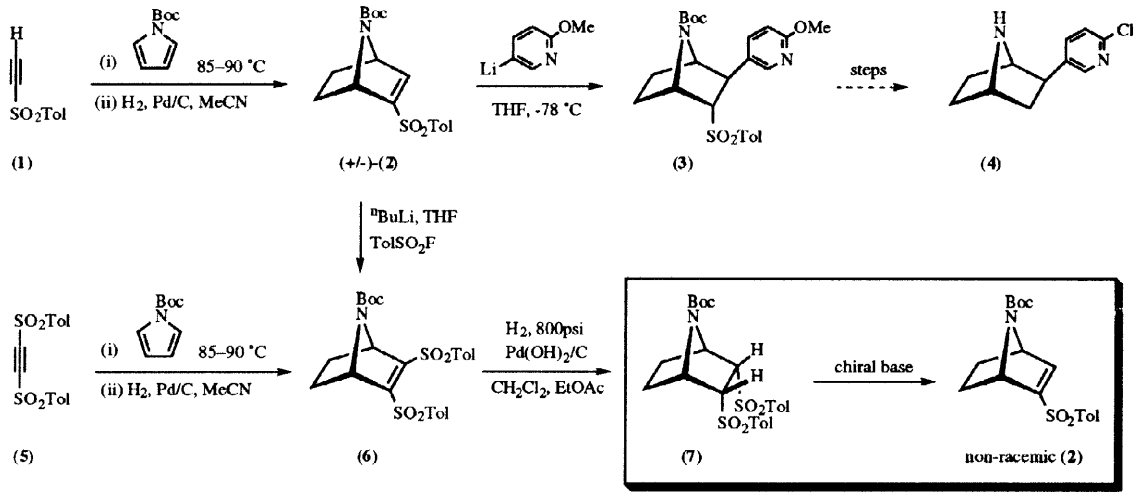
and Gerard M. P. Giblin

Medicinal Sciences, Glaxo Wellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY England, U.K.

Received 21 October 1997; revised 20 November 1997; accepted 21 November 1997

Abstract: A vicinal *bis*-sulfone having the 7-azabicyclo[2.2.1]heptane skeleton undergoes a novel type of asymmetric elimination on treatment with the sodium alkoxide derivative of (*1R, 2S*)-ephedrine, to give an alkenyl sulfone product, which is a key intermediate in the synthesis of the alkaloid epibatidine.

We recently described a stereoselective synthesis of the alkaloid epibatidine **4**, in racemic form, by a route involving Michael addition of a metallated pyridine to the key alkenyl sulfone **2**, which in turn was prepared by a well-established cycloaddition of alkynyl sulfone **1** with *N*-Boc pyrrole.[1] It was anticipated that this route would be amenable to a novel asymmetric variant whereby the alkenyl sulfone **2** would be accessed via chiral base mediated asymmetric elimination from a symmetrical *bis*-sulfone **7**.



As described in the preceding paper, access to useful quantities of the required precursor, alkenyl *bis*-sulfone **6**, was best achieved by regioselective metallation of **2**, rather than cycloaddition of **5**. Here we describe preliminary results which show that the novel elimination reaction highlighted (**7** → **2**) is indeed viable.

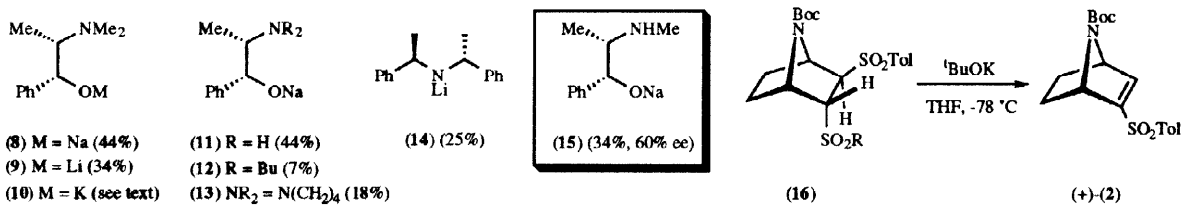
With quantities of alkenyl *bis*-sulfone **6** readily available, its hydrogenation was required in order to provide the symmetrical substrate for chiral base reactions. High pressure hydrogenation gave the desired *bis*-

0040-4039/98/$19.00
PII: S0040-4039(97)10693-1

sulfone **7**, but the reaction proceeded to only about 50% conversion. Routinely we obtained yields of 30–40% of **7**, with 45–55% recovery of starting alkene.

Although a considerable range of chiral bases could be applied to sulfone metallation–sulfinate elimination, including chiral lithium amides and alkyllithium–sparteine (or other ligand) mixtures, we chose to focus on the use of metal alkoxides derived from (*1R, 2S*) ephedrine.[2]

Enantiomeric excess values for asymmetric elimination (7 → (+)- 2)



All of the chiral base reactions examined (treatment of **7** with a slight excess of metal alkoxide in THF at -78 °C) proceeded to give (+)-**2**, the absolute configuration of which was assigned by conversion into natural epibatidine following our previously published route. This constitutes a new asymmetric synthesis of epibatidine.

Few generalisations concerning base efficacy are possible at this stage, although larger groups on nitrogen (e.g. **12** and **13**) resulted in lower ee values, and sodium bases appear superior to lithium or potassium. In fact, in the latter case (base **10**) none of the desired product was obtained, with Michael addition of the alkoxide to the alkenyl sulfone being observed. The only chiral lithium amide base examined, **14**, gave the desired product, but in modest ee. As highlighted, the sodium salt of ephedrine gave the best results; the eliminated product (+)-**2** being obtained in 34% yield and 60% ee, accompanied (unexpectedly) by *trans-bis*-sulfone **16** (28%) (this by-product was obtained in all cases). The structure of this compound was assigned following its conversion (97%) into (+)-**2** by treatment with ^{t}BuOK, making the assumption that sulfinate elimination occurs mainly by *exo*-hydrogen abstraction. Although this conversion improves the overall yield of **2** from **7**, the ee of material from **16** was low (*ca.* 31%) possibly due to competing *endo*-hydrogen abstraction.

Further work, involving optimization of enantiomeric excess, control of the competing pathways leading to eliminated or isomerised products, and applications to other systems are underway.[3]

Acknowledgements

We are grateful to the Engineering and Physical Sciences Research Council (EPSRC) and Glaxo Wellcome for support of C. D. J. under the CASE scheme.

References and Footnotes

1. Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *Synlett* **1997**, 589.
2. For a somewhat related asymmetric dehydrobromination, see Amadji, M.; Vadecard, J.; Plaquevent, J C.; Duhamel, L.; Duhamel, P. *J. Am. Chem. Soc.*, **1996**, *118*, 12483.
3. For an alternative desymmetrisation of *meso* compounds related to **6**, see Cossu, S.; De Lucchi, O.; Pasetto, P. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1504.