Asymmetric Synthesis *via* Allenes: Synthesis of (*R*)-(−)-Coniine

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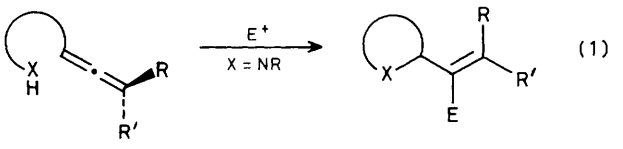
The silver(I)-catalysed cyclisation of an amine to a chiral allenic unit is described; the efficiency of this process has been evaluated by a synthesis of (*R*)-(−)-coniine.

The tremendous progress made in recent years in the field of asymmetric synthesis has been, for the most part, stimulated by the chirality exhibited by the majority of naturally occurring compounds.[1] Suitable synthons have often been prepared using the pool of readily available natural products such as carbohydrates and amino acids. In addition, the development of optically active reagents now allows the enantioselective synthesis of important intermediates to be carried out efficiently. The cyclisation of a nucleophilic species, an alcohol or amine, to a suitably positioned and activated allene is a useful reaction leading to a range of functionalised heterocycles,[2] some of which have also found synthetic application.[3] Recently our own efforts have focused on the incorporation of an optically active allenic residue into this sequence [reaction (1)] with particular emphasis on the asymmetric synthesis of alkaloids.

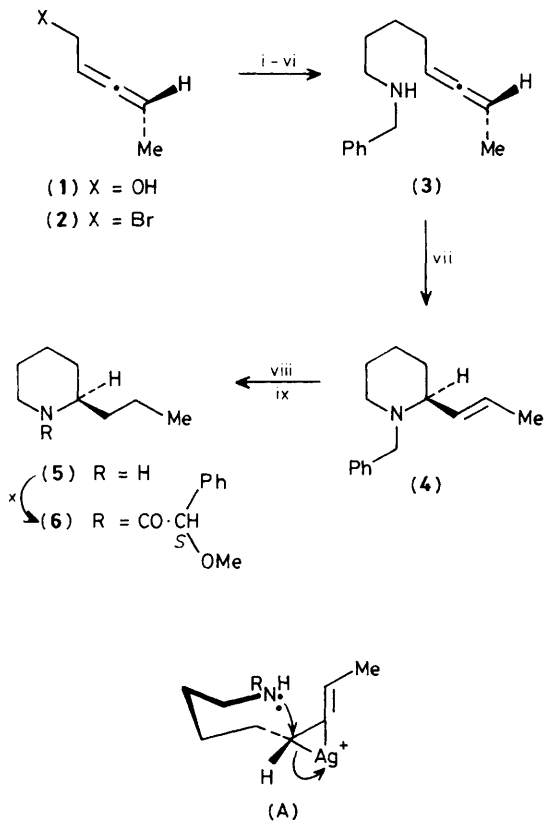
The electrophilic addition reaction of chiral allenes, *e.g.* alkoxymercuration or halogenation, has been the subject of a number of elegant studies.[4] Although, under certain conditions, a high degree of chirality is retained in the product, these studies have, however, been almost completely limited to the intermolecular process. The intramolecular variant is therefore of interest and when considering an asymmetric approach to alkaloid synthesis two other aspects of this process require examination. The first involves the use of an amine as the nucleophilic component; secondly, is the use of silver(I) as the electrophilic reagent compatible with the transfer of chirality during the cyclisation step?

These aspects of allene chemistry have been evaluated for a simple allenic amine (**3**) in the synthesis of (*R*)-(−)-coniine (**5**) (Scheme 1).[5†] (*R*)-(−)-*N*-Benzylocta-5,6-dienylamine (**3**) [containing 10% of the (*S*)-(+)-isomer] was prepared, in five steps (47% overall yield) from the known (*R*)-(−)-bromide



(1)

† All new compounds gave satisfactory spectral data (i.r., ^{1}H n.m.r., and high resolution mass).



Scheme 1. *Reagents and conditions:* i, $LiCH_2CO_2Bu^t$, tetrahydrofuran (THF), −78 to −20 °C; ii, $LiAlH_4$, Et_2O, 0 °C; iii, *p*-$MeC_6H_4SO_2Cl$, pyridine, 0 °C; iv, NaCN, Me_2SO, 70 °C; v, $LiAlH_4$, Et_2O, 0 °C; vi, PhCHO, EtOH, followed by $NaBH_4$, 20 °C; vii, $AgBF_4$, CH_2Cl_2, 20 °C; viii, *p*-$MeC_6H_4SO_2NHNH_2$, NaOAc, THF–H_2O, 70 °C; ix, $PdCl_2$, H_2, EtOH, 20 °C; x, (*S*)-(±)-*O*-methylmandelic acid, dicyclohexylcarbodiimide, CH_2Cl_2, 0 °C.

(**2**).[6]‡ Treatment of (**3**) with silver tetrafluoroborate (0.5 equiv.) gave (**4**) (86%) which was reduced in two steps, by treatment with *p*-tolylsulphonylhydrazine–sodium acetate followed by catalytic hydrogenation, to yield (*R*)-(−)-coniine (**5**) (76%) which was isolated as the hydrochloride salt and identified by comparison with an authentic sample.§ The optical purity of (**5**) was determined by conversion into the diastereoisomeric mixture of derivatives (**6**) [(*S*)-(+)-*O*-methylmandelic acid–dicyclohexylcarbodiimide]. The methoxy signals of (**6**) were clearly resolved by 400 MHz ^{1}H n.m.r. spectroscopy and synthetic coniine (**5**) was shown to be a mixture of (*R*)- and (*S*)-isomers in a ratio of 8 : 1.

The absolute configuration of the product (**5**), (*R*)-(−) produced from (*R*)-(−)-(**3**), is in accord with observations previously made in the related intermolecular alkoxymercuration reaction.[4b] The relatively small amount of racemisation (<10%) is also promising, being indicative of the formation of a dissymmetric silver allene complex (A) rather than a significant amount of an achiral allylic cationic species.[7]

Finally, it should be noted that the preparation of (**1**) requires a resolution of (±)-but-3-yn-2-ol. However in recent work by both Brown and Midland the reduction of acetylenic ketones with chiral boranes is reported to give propynylic alcohols in high enantiomeric excess.[8] In principle this makes available a wide range of allenic alcohols related to (**1**) and increases the potential application of the cyclisation process.

‡ Alcohol (**1**), the precursor of bromide (**2**), was prepared as a 9 : 1 mixture of (*R*)- and (*S*)-isomers. This was based on both specific rotation {$[\alpha]_D$ −87° (*c* 9.5, MeOH), lit.[6a], $[\alpha]_D$ −87.6° (*c* 9.5, MeOH)} and ^{1}H n.m.r. analysis of the corresponding (*S*)-(+)-*O*-methylmandelate. The enantiomeric ratio of (**3**) is based on the composition of (**1**). It was assumed that the conversion of (**1**) into (**3**) proceeded without loss of chirality.

§ An authentic sample of (*R*)-(−)-coniine was obtained by resolution of the commercially available material (J. C. Craig and A. R. Pinder, *J. Org. Chem.*, 1971, **36**, 3648). This was converted into derivative (**6**) and used for purposes of comparison.

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