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Enantio- and Diastereoselective Synthesis of all Four Possible Stereoisomers of 2-(Phenylhydroxymethyl)quinuclidine.

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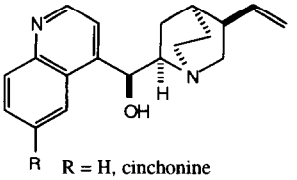
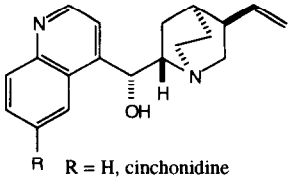
Abstract: An enantio- and diastereoselective synthesis of all four possible stereoisomers of 2-(phenylhydroxymethyl)quinuclidine is reported. Key steps involve the use of the Sharpless dihydroxylation protocol to induce asymmetry, and stereodivergent cyclisations of the resulting diol to form the quinuclidine ring. © 1997 Elsevier Science Ltd.

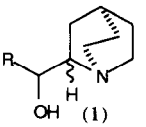
The *Cinchona* alkaloids[1] represent a family of bioactive structures that have had a tremendous impact both on medicinal chemistry[2] and asymmetric synthesis[3]. In the former context, quinine and its analogues have been used as effective therapeutic agents against malaria for over three centuries, and more recently a number of other medicinal applications of these alkaloids has received considerable attention[2]. Related quinuclidine systems have also been identified as muscarinic agonists and have potential for the treatment of Alzheimer's disease[4]. In the context of asymmetric synthesis, the *pseudo*-enantiomeric structural pairs cinchonine/cinchonidine and quinidine/quinine have received particular attention. These compounds and their derivatives have proved to be effective catalytic chiral control elements in a wide range of asymmetric processes including the dihydroxylation of alkenes[5], addition of dialkyl zinc species to aldehydes[6], hydrogenations[7], and a variety of phase-transfer reactions[8]. However, despite their wide use in asymmetric synthesis, relatively little work has investigated the use of related quinuclidine structures[9]. As part of a programme aimed at developing new chiral control elements for asymmetric synthesis we were interested in developing an efficient synthetic approach to the 2-hydroxymethylquinuclidine core (1) of these alkaloids. Here we report an approach that has culminated in the synthesis all four possible isomers of 2-(phenylhydroxymethyl)quinuclidine (1, R=Ph)[10], and which could in principle be applied to a wide variety of structural variants.



R = H, cinchonine
R = OMe, quinidine



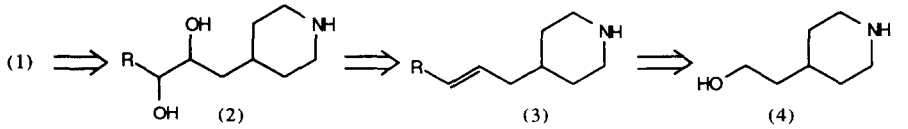
R = H, cinchonidine
R = OMe, quinine



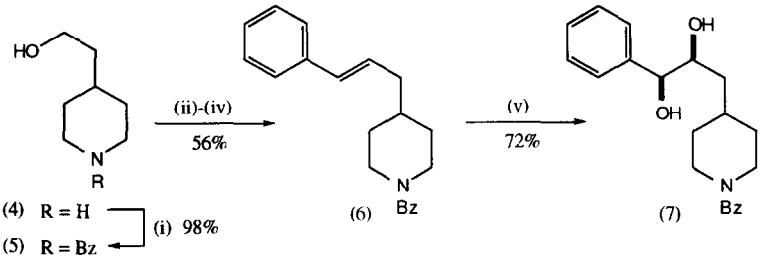
(1)

Our synthetic approach to (1) required the success of two key synthetic operations, the first being asymmetric dihydroxylation of the achiral intermediate (3), and the second being stereo- and regioselective

cyclisation of the resulting diol (2) to the desired quinuclidine system (1). It was envisaged that intermediate (3) should be readily accessible from commercially-available piperidine-4-ethanol (4)[11].



After consideration of a variety of N-protecting group strategies we finally established that the use of the benzoyl moiety resulted in the most successful reaction sequence. This protecting group was readily introduced under standard conditions, and the resulting alcohol (5) could be converted into the desired alkene intermediate (6) *via* an oxidation-Wittig reaction sequence. It should be noted that the Wittig reaction was not stereoselective, typically giving a 3:2 mixture of *E*- and *Z*-olefin isomers, however, the mixture could be readily isomerised to >95% *E*-isomer by exposure to iodine and sunlight. The *E*-olefin (6) proved to be an excellent substrate for the Sharpless asymmetric dihydroxylation[5], and on treatment with AD-mix-α gave the resulting diol (7) in good yield. Since we were ultimately interested in knowing the enantiomeric purity of quinuclidine (9), we chose not to assess the enantiomeric excess at this stage.



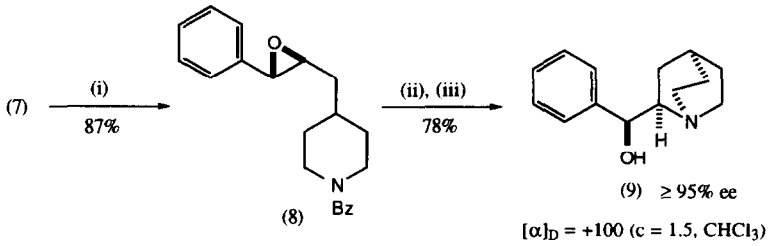
Scheme 1

Reagents: (i) PhCOCl, NaOH, 0°C; (ii) $(COCl)_2$, DMSO, Et_3N, -78°C-RT; (iii) Ph_3PCHPh, THF, -78°C; (iv) I_2, $CHCl_3$, hν, RT; (v) AD-mix-α, $CH_3SO_2NH_2$, t-BuOH, H_2O, 0°C.

With the diol (7) in hand we were able to investigate cyclisation to the corresponding quinuclidine system. At this stage we needed to address three specific problems, the first being how to selectively activate the C-2' hydroxyl group to displacement, the second being how to remove the N-benzoyl group in the presence of this activation, and the third being how to promote cyclisation to give either diastereoisomer of the quinuclidine stereospecifically. The solution to all three problems seemed to be conversion of the diol to an epoxide function. Since this process could in principle be achieved with net retention of stereochemistry at both hydroxyl centres[12], or with net inversion at one centre (*vide infra*), this should allow access to both diastereoisomers from the same diol precursor. The epoxide function also activates the C-2' position to nucleophilic attack and cyclisation of the nitrogen function onto this position should be preferred over C-3' on stereoelectronic grounds[13]. The only issue that seemed of concern was whether the N-benzoyl group could be selectively removed in the presence of the epoxide function. Although such a deprotection has been achieved in related systems[14], generally the yields were not good, and the substrates involved did not contain such highly activated epoxide functions.

Initially we decided to investigate formation of the epoxide with net overall retention of stereochemistry, and this was achieved by sequential treatment of the diol with trimethylorthoacetate, trimethylsilylchloride, and potassium carbonate[12]. This gave the desired epoxide (8) in good overall yield as a single diastereoisomer. Initial attempts at deprotection of the nitrogen utilised diisobutylaluminium hydride, the reagent that had previously been successful in related systems[14]. Unfortunately the transformation was not clean, and after attempted cyclisation in ethyl acetate-methanol at reflux[14], a number of different products could be isolated, in

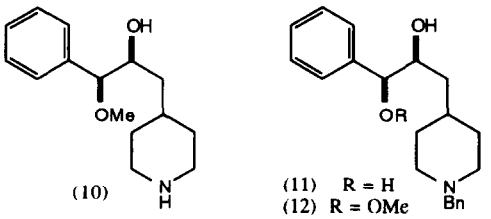
low yield. These included the desired quinuclidine (9), and a number of products arising from alternative ring-opening of the epoxide function (10)-(12). It appears that a substantial by-product in the diisobutylaluminium hydride reaction was the N-benzyl product which was incapable of cyclisation to the desired quinuclidine. Despite considerable investigation only very low yields (0-10%) of the desired product (9) could be isolated *via* this sequence.



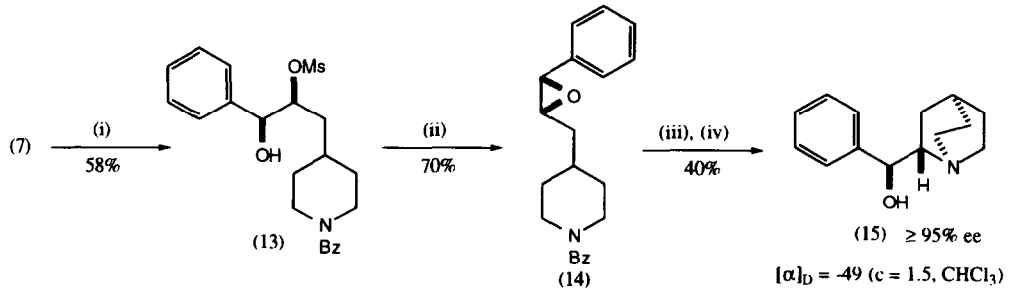
Scheme 2

Reagents: (i) $CH_3C(OCH_3)_3$, TMSCl; K_2CO_3, MeOH; (ii) MeLi, THF, -78°C; (iii) Xylenes, 135°C.

It was clear that alternative conditions needed to be developed for the deprotection/cyclisation sequence, and we decided to examine reagents that could not effect reduction of the benzoyl function to the corresponding benzyl group. It was found that treatment of the epoxide (8) with methyl lithium at -78°C, lead to rapid and selective cleavage of the N-benzoyl function, furthermore the resulting amine could be cyclised to the desired quinuclidine (9) in good overall yield by heating in xylenes. Any attempt to use an aqueous work-up in the deprotection step or an alcoholic solvent in the cyclisation, led to substantial amounts of unwanted epoxide-opening.



At this stage we were able to assess the enantiomeric excess of the quinuclidine product (9) (≥95% ee) by inspection of the ^1H nmr spectrum of the corresponding Mosher's ester derivative. We also were able to prepare the antipode[15] in similar overall yield *via* the same sequence, this time employing AD-mix-β for the asymmetric dihydroxylation step, and again the final product was obtained with ≥95% ee.



Scheme 3

Reagents: (i) MsCl, pyridine, -20°C; (ii) NaH, THF, RT; (iii) MeLi, THF, -78°C; (iv) Xylenes, 135°C.

With the success of this sequence, we next turned our attention to the preparation of the diastereoisomeric system (15). In this case we needed to be able to generate the epoxide (14) and this was simply achieved by selective mesylation of the diol (7), giving intermediate (13), followed by treatment with base. As in the previous sequence, the epoxide (14) was then subjected to deprotection/cyclisation, giving quinuclidine (15). As might be anticipated the *cis*-epoxide (14) was more reactive than the corresponding *trans*-isomer (8), consequently the cyclisation was significantly faster, but lower overall yields were obtained to due competing ring-opening processes. Again we were able to prepare the antipode in comparable overall yield by employing AD-mix-β in the dihydroxylation step, and again both sequences gave product with ≥95% ee as determined by ^{1}H nmr analysis of the corresponding Mosher's ester derivatives[15].

In conclusion, we have developed a short enantio- and diastereoselective synthetic approach to all four possible stereoisomers of 2-(phenylhydroxymethyl)quinuclidine. The chemistry developed should be applicable to a wide range of related quinuclidine systems, and will allow further investigation into the biological and synthetic potential of these materials.

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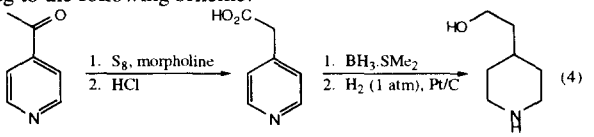
11. At the outset of this work piperidine-4-ethanol was commercially available from a variety of sources, however this is no longer the case. As a consequence we now prepare this material from 4-acetyl pyridine according to the following scheme:



(4)

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15. The absolute stereochemistry of compounds (9) and (15) is tentatively assigned based on comparison of optical rotation with the corresponding *Cinchona* alkaloids. This assignment is also in agreement with the absolute stereochemistry anticipated from the asymmetric dihydroxylation.

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