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STEREOSPECIFIC NUCLEOPHILIC RING-OPENING OF A DEUTERIATED CYCLOPROPYLCARBINOL

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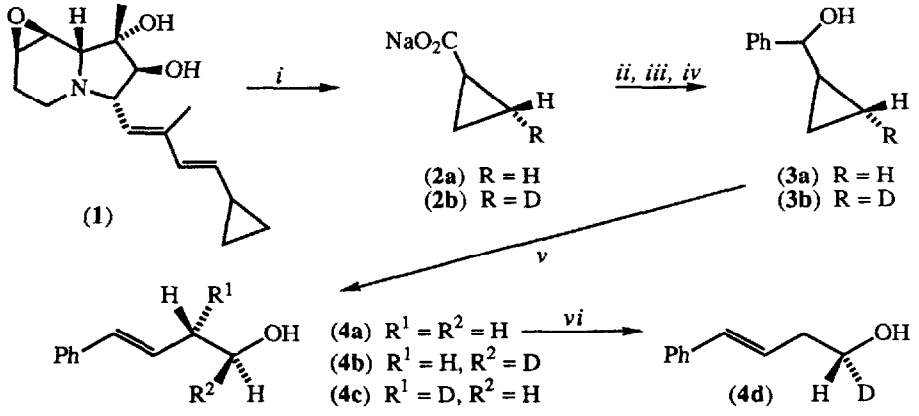
The cyclopropyl phenyl carbinol (3) was obtained by degradation in the course of biosynthetic studies on the unique cyclopropane alkaloid cyclizidine (1). The stereochemistry of the ring-opening to the homoallylic alcohol (4) was investigated by synthesis of chirally deuteriated (3) followed by ^1H n.m.r. spectroscopy of the ring-opened product with a chiral shift reagent. It was found to proceed with inversion of configuration.

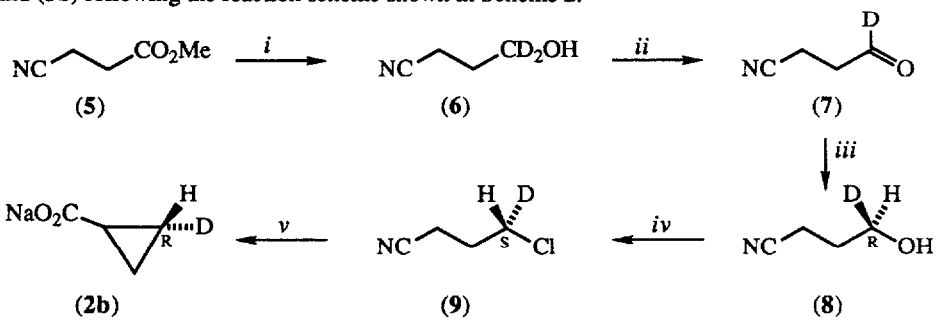
The indolizidine alkaloid cyclizidine (**1**) contains a most unusual monosubstituted cyclopropane ring. As part of our biosynthetic studies[1] we are interested in the stereochemistry of deuterium or tritium incorporation at the methylene groups of the cyclopropyl ring as a first step towards elucidating the mechanism for the formation of this type of ring (which has not been studied before). In order to analyse this stereochemistry we have developed the degradation shown in Scheme 1. Kuhn-Roth oxidation of (**1**) gave sodium cyclopropanecarboxylate (**2a**). This was converted to the acid chloride and thence, by a Friedel-Crafts reaction with benzene and reduction with $NaBH_4$, to the racemic cyclopropyl phenyl carbinol (**3a**). Heating this alcohol in acetic anhydride[2] caused ring-opening to give the homoallylic acetate, which was hydrolysed to the corresponding alcohol (**4a**).



Scheme 1 *Reagents: i* CrO_3, H_2SO_4; NaOH *ii* $(COCl)_2$; *iii* PhH, $AlCl_3$; *iv* $NaBH_4$; *v* Ac_2O; KOH; *vi* HLADH, NAD, NADH, diaphorase, D_2O.

It was envisaged that the stereochemistry of the label at C-1 of (**4**) could be analysed either by n.m.r. spectroscopy[3,4] or by enzymic means,[5] but this would only reveal the stereospecificity of the labelling of the original cyclizidine (**1**) if it could be shown that the opening of the cyclopropane ring occurs stereospecifically with either inversion or retention of configuration.

Previous studies on cyclopropylmethyl cations (which would be intermediates in the process), by n.m.r. spectroscopy in superacid media, have indicated that the stereochemistry might[6] or might not[7] be scrambled at this stage depending on the substituents on the ring. The only example (to our knowledge) where the stereochemistry at the site of nucleophilic attack of a cyclopropane ring-opening reaction has been determined was a model reaction for the rearrangement of presqualene to squalene and it was found to proceed with only a low net inversion (26%).[8] In the case of the reaction (**3**) → (**4**), we thought that the phenyl substituent might allow a higher degree of stereoselectivity but it was important for our biosynthetic studies that the stereochemistry of the reaction should be proved. Consequently we undertook a synthesis of the stereospecifically deuteriated compound (**3b**) following the reaction scheme shown in Scheme 2.



(**5**) (**6**) (**7**) (**8**) (**9**) (**2b**)

Scheme 2 *Reagents: i* $LiBD_4$; *ii* $(COCl)_2$, DMSO; *iii* (*S*)-Alpine borane.; *iv* $SOCl_2$, pyr; *v* KOH; H^+; NaOH.

Reduction of methyl 3-cyanopropionate with $LiBD_4$ gave the deuteriated alcohol (**6**),[9] which was oxidized using Swern's reagent to the aldehyde (**7**) (*ca.* 95% deuteriated by n.m.r. spectroscopy). Chiral reduction using (*S*)-Alpine borane (from Aldrich Chemical Co.) gave the monodeuteriated alcohol (**8**). The ^1H n.m.r. spectrum of its (*R*)-α-methoxy-α-trifluoromethylphenylacetate (Mosher's ester) showed an e.e. of 77% (after correction for 5% undeuteriated material). The expected (*R*)-configuration was confirmed by the ^1H n.m.r. spectrum of its (–)-camphanate ester after addition of $Eu(fod)_3$.[3] Conversion of the alcohol to the chloride (**9**) was accomplished using thionyl chloride in pyridine, conditions which were expected to cause clean inversion of configuration.[10] Cyclization and hydrolysis of the nitrile was effected by KOH[11] to give the cyclopropane carboxylate, again isolated as its sodium salt (**2b**). This cyclisation was also expected to proceed with clean inversion of configuration but it did not prove possible to check the stereochemistry at this stage and so the salt was converted as before to the desired phenyl carbinol (**3b**), *ca.* 82% monodeuteriated by n.m.r. spectroscopy.

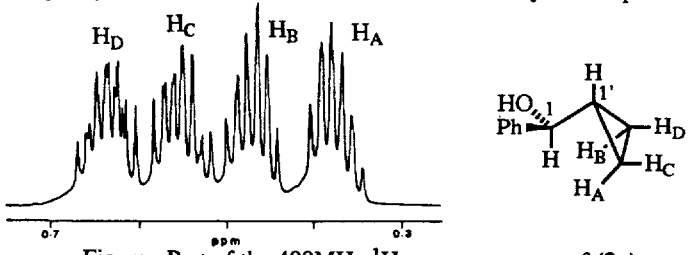
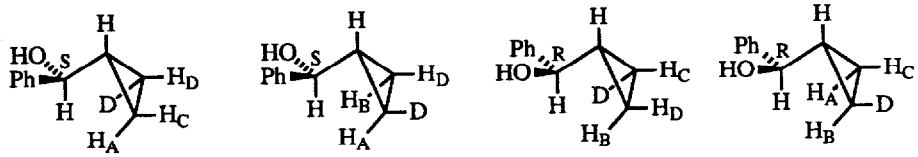


Figure. Part of the 400MHz ^1H n.m.r. spectrum of (**3a**).

The 400 MHz n.m.r. spectrum of the unlabelled phenyl carbinol (**3a**) showed distinct multiplets for each of the four methylene protons on the cyclopropane (see Figure). N.O.e. experiments, chemical shift considerations,

and europium-induced shifts were consistent with the conformation shown in the Figure as the preferred one and led to the following assignments: δ 0.38 (H_A), 0.47 (H_B), 0.55 (H_C), and 0.66 (H_D).

As the stereochemistry of the deuteriated alcohol (**3b**) was not controlled at either the carbinol carbon (C-1) or at C-1' of the cyclopropane, the four different species shown in Scheme 3 should be present in equal proportions even if there is only one stereochemistry at the deuteriated carbon. Consequently the deuterium appears evenly distributed among the four methylene positions in the ^1H n.m.r. spectrum. However each enantiomer of the alcohol at the carbinol centre should only have the label distributed over two of these positions, if the labelling is specific, and this fact was use to measure the degree of stereospecificity.



Scheme 3. Structures of the four stereoisomers of (**3b**).

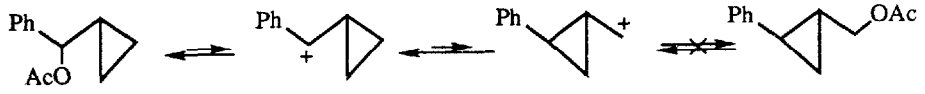
The labelled alcohol (**3b**) was resolved by h.p.l.c. separation of its diastereomeric (–)-camphanate esters followed by hydrolysis back to the enantiomeric alcohols. The configurations of the enantiomers were determined by comparison of the ^1H n.m.r. spectra of their (*R*)-Mosher's esters; for the ester from the (*R*)-alcohol the carbinol proton appears more upfield and the methoxyl protons more downfield than for the ester from the (*S*)-alcohol.[12] In the ^1H n.m.r. spectrum of the resolved deuteriated alcohols (**3b**), the (*R*)-enantiomer showed H_A and H_D reduced in size due to deuteriation whereas the (*S*)-enantiomer showed H_B and H_C reduced in size (e.e. estimated at *ca.* 75%). ^2H n.m.r. spectroscopy gave the complementary result. Thus it can be seen that it is the *proR* hydrogen at each methylene that carries the greater amount of deuterium as shown in Scheme 3 and as expected from the mechanism.

The ring-opening reaction of the cyclopropyl phenyl carbinol (**3b**) was now effected with acetic anhydride and was followed by hydrolysis of the acetate with KOH. If the reaction proceeds stereospecifically with inversion, the two isotopomers (**4b**) and (**4c**) would be produced in approximately equal amounts as either methylene of the cyclopropane could be attacked by the nucleophile. Consequently the maximum level of deuteriation at C-1 that could be achieved is 50%. The ^1H n.m.r. spectrum of the alcohol in the presence of the chiral shift reagent Eu(hfc)$_3$ showed separate peaks for the *proR* and *proS* hydrogens attached to C-1 and the downfield signal was the smaller one, indicating that the majority of deuterium was at this position. The e.e. was again estimated to be 75%. Thus the reaction is stereospecific, within experimental error, but until we had assigned the signal for the *proR* and *proS* hydrogens, we could not tell whether it proceeds with inversion or retention. It is generally found[4] that it is the *proS* hydrogen adjacent to an alcohol which appears more downfield with Eu(hfc)$_3$ but in order to confirm that this holds in the present case, a deuteriated alcohol of known stereochemistry was synthesized by an enzymic method.

Incubation of the unlabelled alcohol (**4a**) with horse liver alcohol dehydrogenase (HLADH), diaphorase, and NAD/NADH in D_2O[5] caused exchange of the *proR* hydrogen at C-1 for deuterium. This reaction proceeds *via* enzymic oxidation to the aldehyde, exchange of NADH to NADD by the flavin-containing diaphorase, and then

reduction of the aldehyde by the NADD. HLADH is known to introduce the hydrogen from NADH almost exclusively into the *proR* position when it reduces an aldehyde. The ^{1}H n.m.r. spectrum of the alcohol (**4d**) produced showed only the downfield signal in the presence of Eu(hfc)$_3$, thus confirming that this corresponds to the pro-S hydrogen.

Hence it is established that the product of the ring-opening reaction of (**3b**) is the (S)-isomer (**4b**) [mixed with (**4c**)] and that the reaction therefore occurs with clean inversion of configuration. We believe that scrambling of the stereochemistry does not occur because the phenyl substituent stabilizes the cation on the carbon adjacent to it. Thus rearrangement to isomeric cyclopropylmethyl cations, which have the charge on a primary carbon, (as in Scheme 4) is discouraged and formation of the corresponding isomeric acetates (which could lead to scrambling of the stereochemistry) does not occur to any significant extent. In the previously reported case, in which only low net inversion was observed,[8] rearrangement would lead to a relatively stable secondary allylic cation.



Scheme 4.

As a result of the studies reported in this paper, the proposed method for studying the stereochemistry of tritium or deuterium incorporation into cyclizidine (**1**) has been proved to be viable. It is intended to use this method to analyse the biosynthesis of cyclizidine from propionic acid chirally labelled in its methyl group with deuterium and tritium and work on this is in hand.

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