Tetrahedron Letters,Vol.29,No.39,pp 4977-4980,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

IMINE-EPOXIDE REARRANGEMENTS IN THE FORMATION OF SUBSTITUTED PIPERIDINES. A STEREOSELECTIVE SYNTHESIS OF (±)SOLENOPSIN-A.

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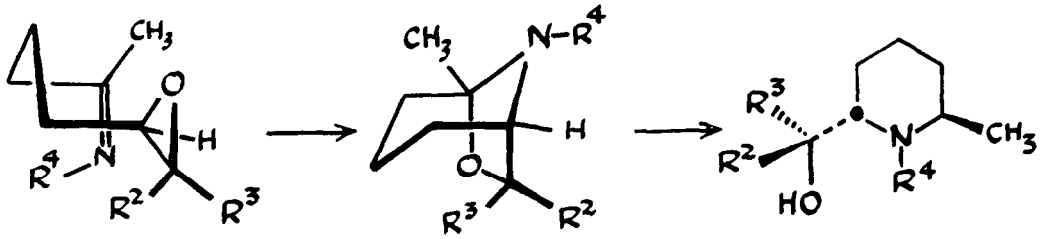
Summary: The imine-epoxide rearrangement, followed by hydride reduction has been used to prepare substituted piperidine derivatives with control of stereochemistry. An application to the synthesis of (±) solenopsin A is reported.

In the preceding paper[1] we described work showing that δ, ε-epoxy imines such as (1) undergo stereospecific intramolecular epoxide ring opening with the formation of 6-oxa-8-azabicyclo[3.2.1]octanes (2). These transformations are analogous to the carbonyl-epoxide rearrangements which we have recently applied to the syntheses of naturally-occurring pheromones.[2]

We now report that the substituted oxatropanes (2) may be further converted to 2,6-disubstituted piperidines with a high degree of stereochemical control. In particular, reduction of the bicyclic derivatives (2) with $NaBH_4$, $NaBH_3CN$, or LAH leads predominantly to the trans-2,6-disubstituted derivative (3) containing the stereochemistry found in a large family of piperidine alkaloids. An application of this novel sequence to an efficient synthesis of (±)solenopsin A[3,4] (12) is outlined below.



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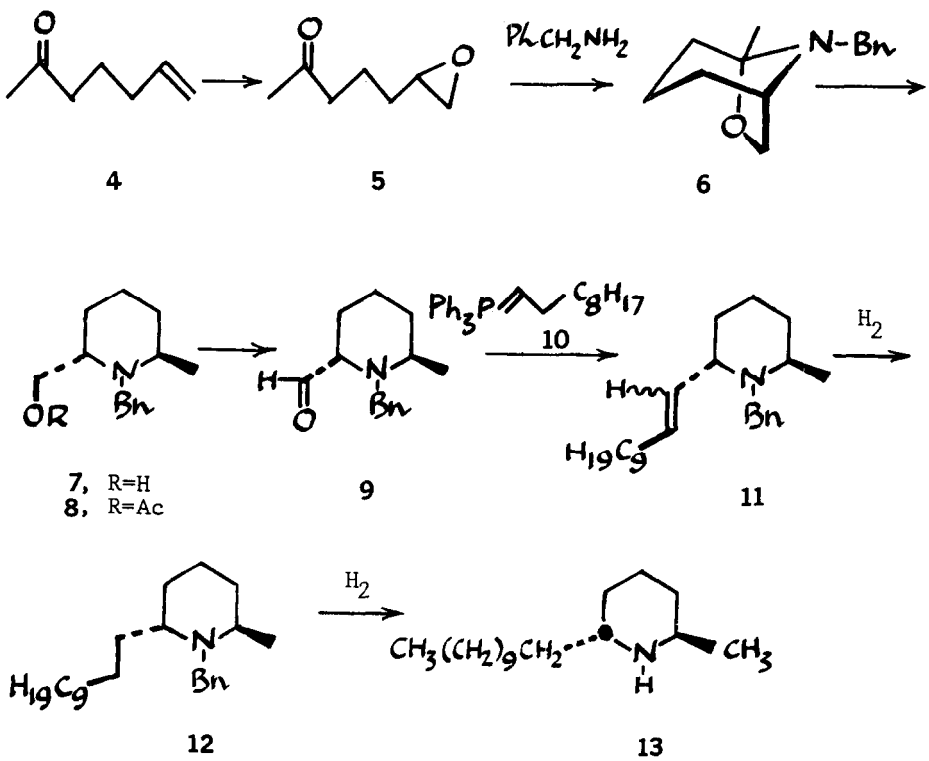
Our synthesis began with the known 6-hepten-2-one (4).[5] Epoxidation with MCPBA gave the keto-epoxide (5), which was treated with benzylamine in the presence of 3Å molecular sieves for 5h at reflux in benzene to form the bicyclic product (6) (87%). Reduction of (6) with $NaBH_4$ in methanol gave the piperidine derivative (7) (ca. 100%) as a mixture of trans and cis-isomers with the trans product predominating (9:1). As indicated in Table 1, the trans:cis ratio varied (3:1 to 99:1) depending on the conditions of reduction.

Table 1. Reduction of (6) to the Piperidine Derivative (7)

reducing agent	solvent	trans/cis ratio	yields
$NaCNBH_3$	dry HOAc	6:1	100%
$LAH/AlCl_3$	THF	3:1	40%
$NaBH_4$	MeOH	9:1	100%
LAH	THF	99:1	46%
DIBAL-H	THF	99:1	17%

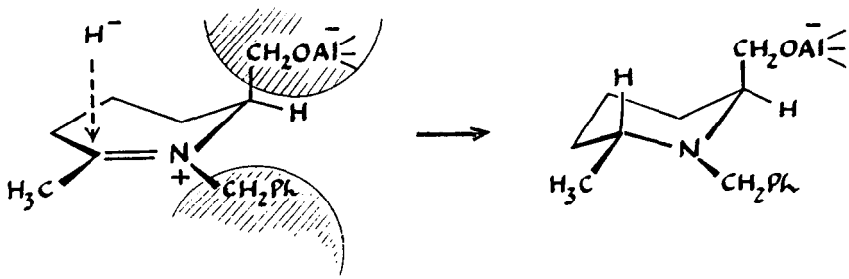
The mixture of alcohols (7) could be separated by conversion to the acetates (8) (98%) followed by flash chromatography.[6] The pure trans-acetate was then deprotected (MeOH, K_2CO_3)[7] (94%) to afford the pure trans-alcohol which was then oxidized under Swern conditions.[8] The aldehyde (9) thus formed (68%) was then coupled with ylide (10) in THF to yield the olefin (11) (74%) as a mixture of cis and trans isomers. Reduction of the double bond (PtO_2, HOAc/PhH) yielded the saturated N-benzylpiperidine (12) (94%). This was then debenzylated with (10% Pd/C, HOAc/PhH) (95%) to yield trans-2-methyl-6-undecylpiperidine (13), identical with an authentic sample of solenopsin A.[9,10]



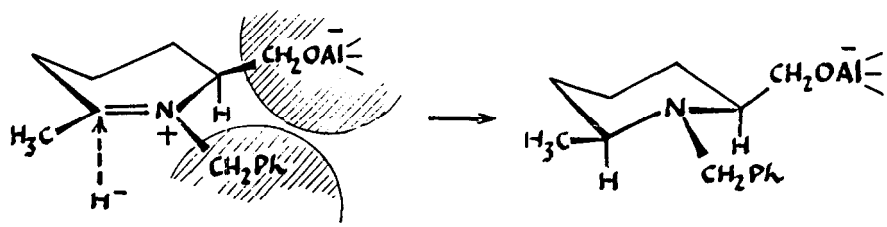
The formation of predominantly trans product (7) in our reduction of (6) parallels the findings of Yamamoto in an earlier synthesis of solenopsin A.[11] In that work he was able to prepare trans-2,6-disubstituted piperidines by the trimethylaluminum-promoted Beckmann rearrangement-alkylation of oxime mesylates, followed by stereoselective hydride reduction of the resulting imine.

Along lines similar to Yamamoto's explanation,[11] we suggest that the reduction of the oxatropane system (6) takes place through an iminium ion (6a) (Figure 1). In conformation a, the metallooxymethylene group occupies an axial position where an unfavorable steric interaction with the bulky benzyl group is minimized. Delivery of the hydride ion (chair transition state) would take place as shown to yield the trans-product. On the other hand, addition of hydride ion to the iminium ion occupying conformation (6b) would yield the cis-product at the expense of unfavorable steric crowding of the metallooxymethyl and benzyl groups.

We are exploring the application of the above reaction sequence in the stereocontrolled synthesis of other members of the piperidine alkaloid family.



6a



6b

Figure 1

Acknowledgements: We thank Ms. Karen Rodriques for her contribution to the studies on the reduction of the oxatropane derivative (6) outlined in Table 1.

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9. We thank Professors Keiji Maruoka and R.K. Hill for samples of natural and synthetic solenopsin A.

10. The two-stage reduction was considered necessary in order to avoid double bond migration and accompanying loss of configuration in the Pd/C reduction.

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(Received in UK 8 August 1988)