Pergamon

Tetrahedron Letters 40 (1999) 6665–6668

TETRAHEDRON LETTERS

A Concise Synthesis of Homochiral Sedamines and Related Alkaloids. A New Reductive Application of Jacobsen's Catalyst

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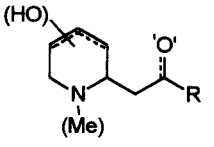
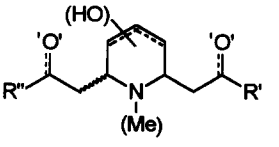
Received 7 June 1999; accepted 6 July 1999

Abstract: *Two methods for the generation of both enantiomers of sedamine [1-methyl-2-(2-phenyl-2-hydroxy-1-ethyl)piperidine] in high optical purity have been elaborated. The first utilises the lipase-mediated kinetic resolution of racemic acetates and the second involves the $NaBH_4$ mediated reduction of ketones catalysed by Jacobsen's catalyst. Some related applications of these reactions are also disclosed.*

In the foregoing paper[1] we disclosed an efficient route to 2-substituted and 2,6-disubstituted pyridines, piperidines and tetrahydropyridines, where the introduced substituent is an $RCOCH_2$-function. This feature is a common one in the large group of alkaloids derived from various *Sedum* and *Lobelia* species, a summary of much of their characteristics being shown in formulae **1** and **2**. Thus, both one-armed and two-armed derivatives, containing every combination of C=O or CHOH functionality, *cis/trans* geometry and chirality exist, combined with a variety of terminal R groups, both similar and different, and occasionally bearing extra OH or unsaturated features in the region of the 3,4,5-carbons. The group includes both NH and NMe analogues.

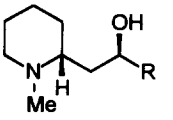


1



2

A summary of most of the various types of alkaloids found in Sedum and Lobelia species. Brackets (X) and dotted bonds indicate that the functionality enclosed is optional and 'O' implies OH or =O.



3

(+)-sedamine

These systems have long been known to exhibit interesting biological properties[2], *Lobelia inflata* (also known as Indian tobacco) having been recognised as memory enhancing as well as having other useful properties. We therefore initiated a programme to develop a unified and practicable route to any of these alkaloids and investigate their biological properties. This paper discloses our endeavours in the one-armed series. A number of interesting but impractical routes exist for the synthesis of sedamine **3** and its isomers in both racemic[3] and chiral[4] forms. Having to hand a rapid and large scale route to 2-phenacylpyridine **9** and 2-phenacylpiperidine **4** [(±)-sedaminone] (see previous paper[1]) we have now elaborated two routes to generate the asymmetric alkaloids in either enantiomeric form and in high enantiomeric purity. The first method employs kinetic resolution of the derived alcohol acetate utilising a lipase and the second utilises a novel catalytic ketone reduction employing Jacobsen's catalyst.

When racemic sedaminone is reduced with $NaBH_4$ an easily separated mixture[5] of two diastereomeric alcohols,

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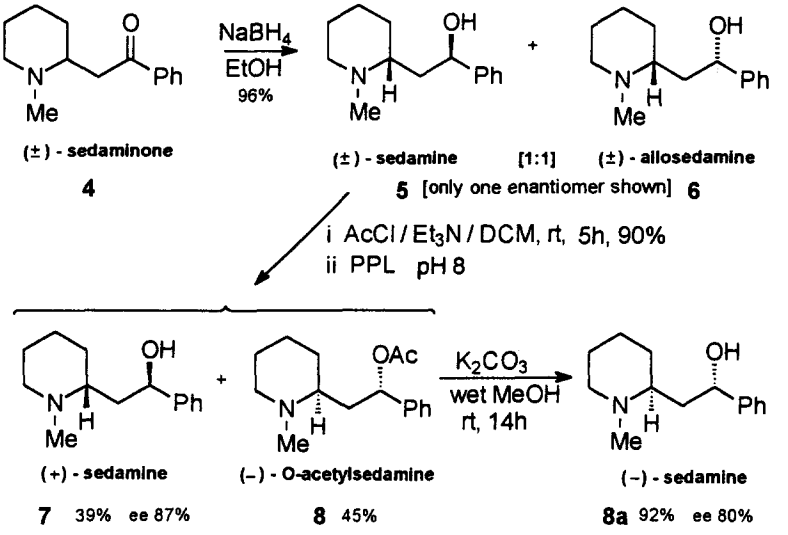
PII: S0040-4039(99)01341-6

(±)- sedamine and (±)- allosedamine, is obtained (Scheme 1). (±)-Sedamine is readily acetylated and on treatment with porcine pancreatic lipase (PPL) the expected enantiomer is hydrolysed to give easily purified (+)-sedamine.

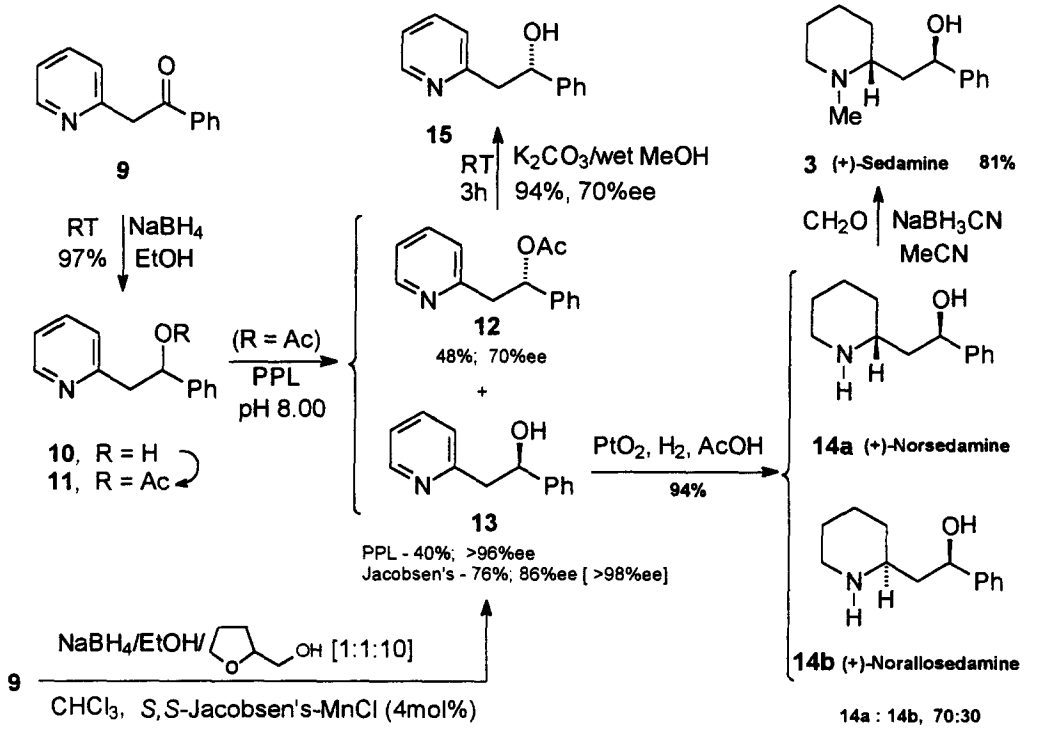


Scheme 1

In a similar manner, 2-phenacylpyridine **9** can be reduced, acetylated and subjected to the same kinetic resolution (Scheme 2). It is of interest that although the alcohol **13** has been reported before, in one case the reported chirality was wrong[6a] and in both cases the specific rotation was poor.[6] (+)-Sedamine is obtained in high overall yield and in ≥99 %ee. [The specific rotations of (+)-sedamine was +90 compared with the natural material[7] +91.5, while the specific rotation of (+)-norsedamine was +36 compared with that of the natural material +33.2.[8]] In a similar manner starting with enantiomerically pure (≥98%ee) (-)-(*S*)-1-phenyl-2-(pyrid-2-yl)-ethanol **15**, (-)sedamine was obtained in ≥98%ee and in an overall yield of 42% based on **15**. and showing a similar rotation to that reported previously.[7]

Seeking a method that would produce solely one homochiral product we examined the reduction of ketones such as the 2-phenacylpyridine and 2-phenacylpiperidine. Baker's yeast proved without effect on both the pyridine **9** and the piperidine **4**. (+)-DIP-Cl[9] gave only a moderate yield and ee (65%, 61% ee) of the (+)-*R* -alcohol **10**. Corey's (*R*)-2-CBS-oxazaborolidine[10] was ineffective as was hydrogenation catalysed by *R*-(+)-BINAP-(p-cymene)RuCl[11] which gave the alcohol with zero ee, or *R*-(+)-BINAP-PdCl which was totally without effect. It appears that the ketone (perhaps as its enol[12] - 3:1 keto-to-enol in $CDCl_3$ solution) is a potent ligand and thereby inactivates the above systems. We therefore sought a chiral Lewis acid that would utilise this ligand character and thereby present facial selectivity to a borohydride reagent. While equimolar aluminium chloride/(+)-diethyl tartrate in DCM/ethanol solution with $NaBH_4$ gave a small ee [22% - (*R*)-(+)-alcohol **13**], Jacobsen's catalyst[13] was remarkably effective. Thus using modified $NaBH_4$ (as used by Mukaiyama[14] - $NaBH_4$/EtOH/tetrahydrofurfuryl alcohol [1:1:10molar] in chloroform solution and 4mol% Jacobsen's Mn(III)Cl catalyst at -20 °C, the *R,R*-catalyst converted 2-phenacylpyridine **9** into the (*S*)-(-)-alcohol **15** in 76% yield and 86% ee.[15] Similarly the *S,S*-catalyst gave the (*R*)-(+) -alcohol **13** in 82% yield and 85% ee. Both enantiomers produced >96%ee material on one recrystallization. Other pyridylCH_2COR derivatives reacted similarly with

aliphatic derivatives (e.g. R = 1-adamantyl) requiring lower temperatures (≤ -50 °C) for efficient asymmetric reduction[e.g. using *R,R*-catalyst, 80% yield, 72%ee]. Cobalt (II) Jacobsen's catalyst was without effect on the reduction.

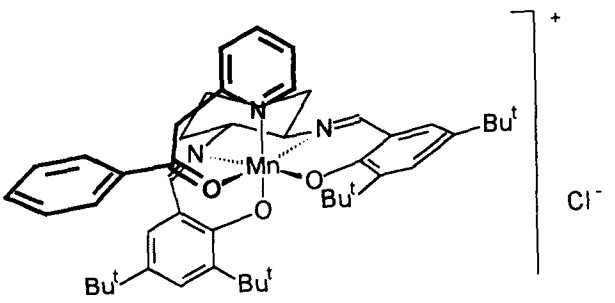


(yields in square brackets are after one recrystallisation)

Scheme 2

The mechanism of this catalysis is not yet certain but chelate replacement by the pyridyl ketone (possibly as its enol) followed by facially selective hydride reduction (Scheme 3) is supported by the fact that phenacylbenzene as well as 2-acetyl- and 2-benzoyl- pyridine were not reduced in an enantioselective manner. Furthermore, models predict that *R,R*-Jacobsen's catalyst should indeed give *S*-1-phenyl-2-(2-pyridyl)ethanol **15**, in agreement with our findings (Scheme 3).

In conclusion, we have presented some concise routes to homochiral sedamine and related compounds, utilising either a lipase-mediated kinetic hydrolysis, or more interestingly, via catalytic ketone reduction employing a Jacobsen's catalyst and sodium borohydride. We are currently examining the optimal catalyst, scope of application and best reducing agent system and will report fully in due course.



A model of the complex of 2-phenacylpyridine with *R,R*-Jacobsen's catalyst to show the open *Re* face that would lead to the *S*-2-(2-pyridyl)-1-phenylethanol on hydride reduction.

Scheme 3

Acknowledgements: We thank Servier for most generous support and Chirex for a gift of Jacobsen's catalysts.

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15. *Enantioselective reduction of 2-phenacylpyridine (9) catalysed by Jacobsen's catalyst:* A solution of $NaBH_4$ (1.5mmol) modified[13] with ethanol (1.5mmol) and tetrahydrofurfuryl alcohol (15mmol) in $CHCl_3$ (3 ml) was added dropwise to a solution of **9** (1mmol) and (*R,R*)-(-)-Jacobsen's MnCl catalyst[13] (0.04 mmol) in $CHCl_3$ (8 ml) at -20-C under a nitrogen atmosphere. The reaction was monitored by TLC and quenched by addition of sat. NH_4Cl solution (15 ml) on completion. The aqueous solution was extracted with DCM, and the extract dried and evaporated. The residue was purified by column chromatography (silica gel, AcOEt-petroleum) to afford *S*-(-)-1-phenyl-2-(pyridin-2-yl)ethanol (**15**)[6] in 76% yield, 86% e.e. (≥96%e.e on one recrystallization from AcOEt-petroleum, as determined by HPLC[16]), m.p. 122-124 °C, [α] = - 42 (c=1, $CHCl_3$). By the same procedure with (*S,S*)-(+)-Jacobsen's MnCl as catalyst, *R*-(+)-1-phenyl-2-(pyrid-2-yl)ethanol (**13**)[5] was produce in 82% yield, 85% e.e. (≥96%e.e on one recrystallization from AcOEt-petroleum, determined by HPLC[16]), m.p. 122-124 °C, [α] = + 42 (c=1, $CHCl_3$).

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