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Diastereo- and enantioselective alkaloid syntheses

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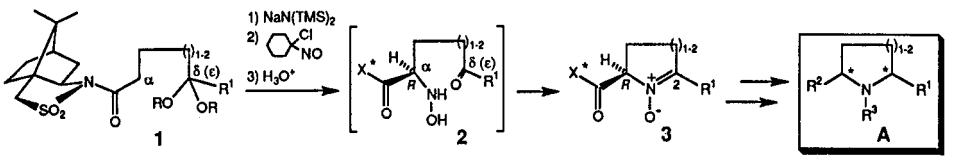
Abstract:
Enantiomerically pure cyclic nitrones, readily available *via* electrophilic hydroxyaminations of *N*-acylsultams, serve as key intermediates in the syntheses of optically pure (-)-allosedamine, (-)-pinidine, (-)-coniine, (-)-solenopsin-A, (-)-2-heptylpyrrolidine, (-)-solenopsis fugax venom and (-)-xenovenine. This work also features a new deoxygenative decarboxylation of *N*-hydroxylamines carrying an acyl substituent at C(α). *N*-4-Alkenylhydroxylamine cyclizations proceed in a suprafacial manner, consistent with a retro-Cope elimination pathway. This reaction is strategically employed in short and efficient syntheses of (±)-α-lycorane and the enantiomerically pure alkaloid (+)-trianthine.

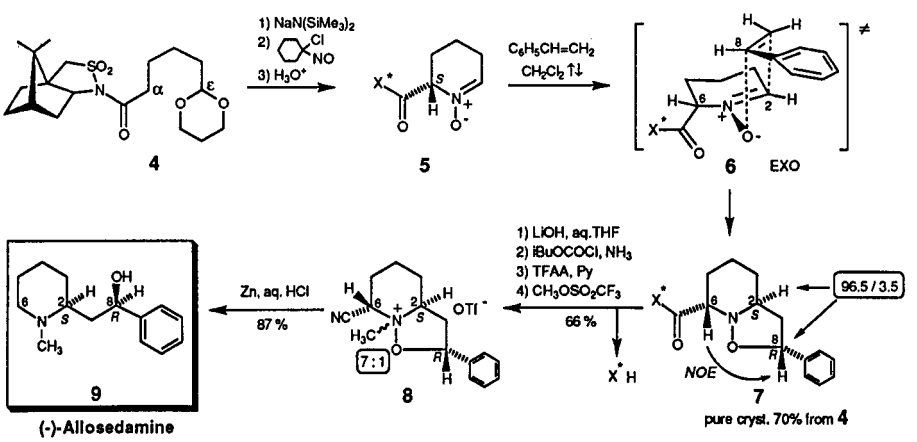
Piperidine and pyrrolidine nuclei are common structural elements of numerous naturally occurring alkaloids. We describe here the use of chiral cyclic nitrones **3** (and **ent-3**) as a platform to construct these ring systems (A) in enantiomerically pure form (Scheme 1). Our approach to nitrones **3** relies on the ~ 100% diastereoface selective C-N bond formation when enolates of *N*-acylsultams **1** were reacted with the unconventional electrophile 1-chloro-1-nitrosocyclohexane (ref. 1). Acidic hydrolysis of the resulting, non-isolated nitrone-acetals prompts deprotection and spontaneous condensation of the carbonyl and *N*-hydroxylamine units in **2**.

Scheme 1



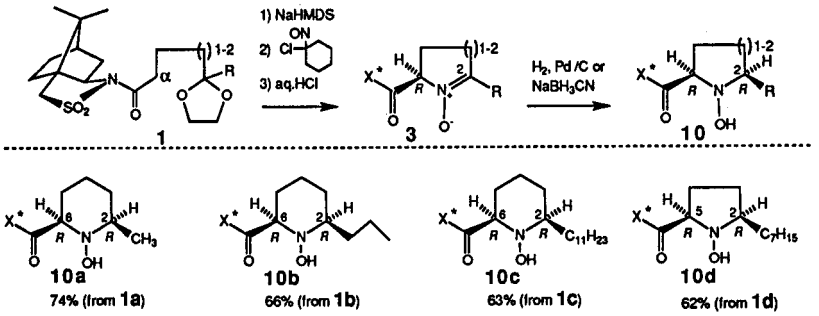
This concept is exemplified by an asymmetric synthesis of (-)-allosedamine (**9**, ref. 2, Scheme 2). Successive treatment of *N*-acylsultam **4** with $NaN(TMS)_2$, 1-chloro-1-nitrosocyclohexane and aq. HCl furnished crude tetrahydropyridine-1-oxide **5**. Non-purified nitrone **5** underwent a ~100% *exo*-selective 1,3-dipolar addition to styrene with 96.5% preference at the face opposite to the C(6)-substituent (*c.f.* transition state **6**) giving cycloadduct **7** in 70% overall yield from **4**. Key-cycloadduct **7** was then transformed into alkaloid **9** *via* *N*-methylation and the interesting zinc promoted *N*/*O*-cleavage-decyanation step **8** → **9**.

Scheme 2



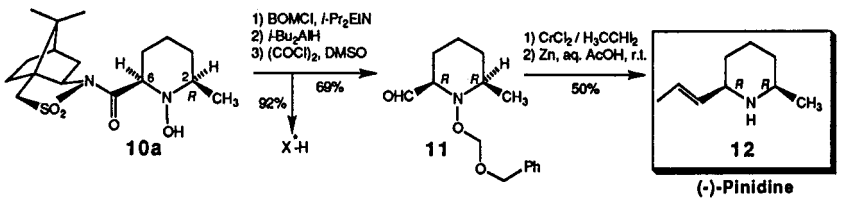
Nitrones **3** (and **ent-3**) display high facial discrimination not only in cycloadditions but also in other reactions. For instance, in the reduction of 2,3,4,5-tetrahydropyridin-1-oxides and 1-pyrroline-1-oxides **3** (with H_2/Pd and $NaBH_3CN$, respectively) a hydrogen atom was exclusively delivered at the C(2)-face opposite to the acyl substituent (Scheme 3). Hence, a series of *cis*-disubstituted *N*-hydroxypiperidines **10a-c** and *N*-hydroxypyrrolidine **10d** were readily prepared.

Scheme 3



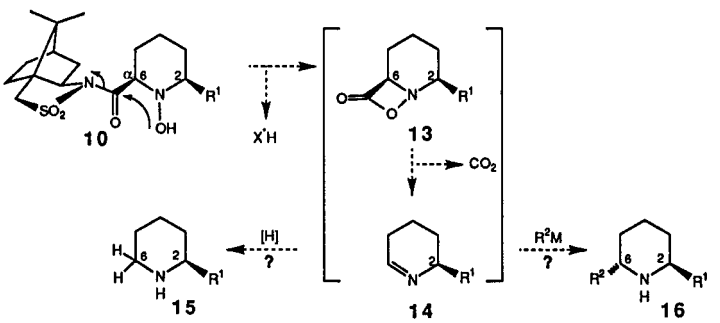
Modification of the acylsubstituent in compounds **10** offers a convenient route to 2,6-disubstituted piperidines (and to 2,5-disubstituted pyrrolidines) as exemplified by the conversion of **10a** into (-)-pinidine (**12**, ref. 3, Scheme 4).

Scheme 4



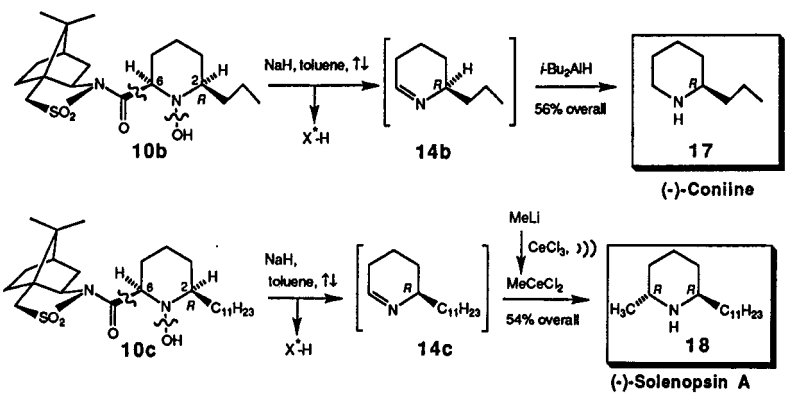
We then pursued the more challenging idea of removing the C(6)-substituent with simultaneous *N/O*-cleavage. Although unprecedented, it seemed plausible that an internal 'transesterification' **10** → **13** (with recovery of the auxiliary) followed by a spontaneous decarboxylation of oxazetidin-4-one **13** would lead to cyclic imines **14** (Scheme 5). Hydride or organometal additions to imines **14** could yield C(2)-monosubstituted or C(2,6)-disubstituted piperidines **15** or **16**.

Scheme 5



Indeed, heating *N*-hydroxypiperidine **10b** with NaH in toluene under reflux, followed by addition of *i*-Bu_2AlH provided the C(2)-monosubstituted, optically pure alkaloid (-)-coniine (**17**) in 56% overall yield (ref. 4, Scheme 6).

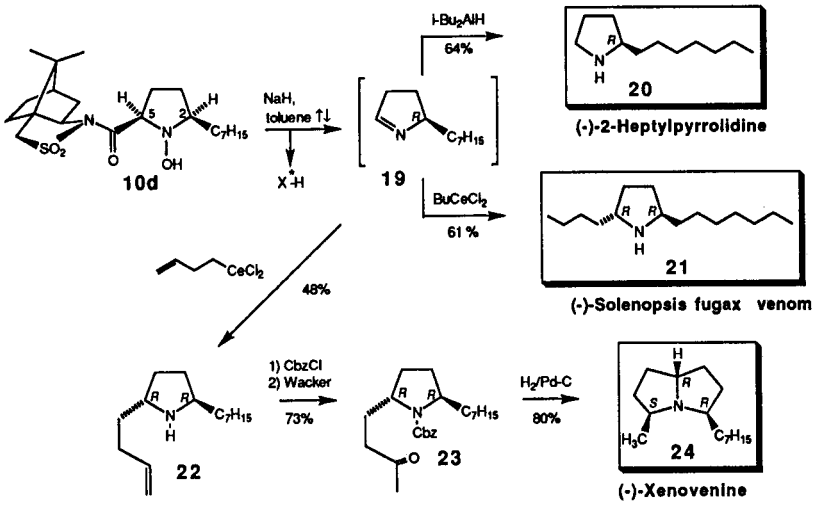
Scheme 6



Applying this novel deoxygenative decarboxylation protocol to *N*-hydroxypiperidine **10c** and trapping of transient imine **14c** with (*in situ* prepared) $MeCeCl_2$ furnished the C(2,6)-*trans*-disubstituted piperidine (-)-solenopsin-A (**18**, 54% overall) with none of its *cis*-isomer (ref. 4, Scheme 6).

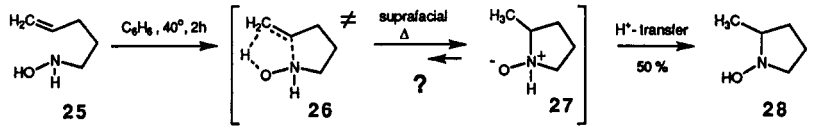
Extension of the "oxazetidin-4-one route" to the flexible preparation of enantiomerically pure pyrrolidines is straightforward as demonstrated in Scheme 7. Thus, *N*-hydroxypyrrolidine **10d** was smoothly transformed into (-)-2-heptylpyrrolidine (**20**), into *trans*-disubstituted (-)-solenopsis fugax venom **21**, as well as into the pyrrolizidine (-)-xenovenine (**24**, ref. 4).

Scheme 7



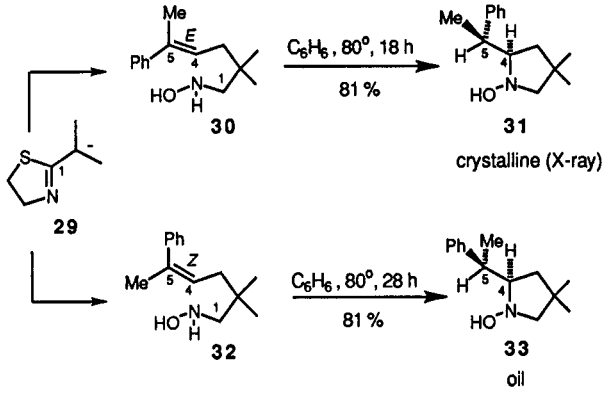
The second part of this account deals with the thermal cyclizations of *N*-4-alkenylhydroxylamines, such as the transformation **25** → **28**, first reported by House et al. (ref. 5) and independently discovered by us (ref. 6, Scheme 8).

Scheme 8



Radical-chain (ref. 5) and retro-Cope elimination pathways (ref. 7) have been postulated for this reaction but without providing compelling proof of either mechanism. We felt that confirming the suprafaciality of this process would strongly support the occurrence of a retro-Cope elimination. It was indeed gratifying to find that the (*E*)- and (*Z*)-5,5-disubstituted 4-alkenylhydroxylamines **30** and **32** cyclized smoothly in oxygen-free benzene at reflux to give *N*-hydroxypyrrolidines **31** and **33**, respectively, in 81% yield and without cross-contamination (ref. 8, Scheme 10). The configurations of cyclization products **31** and **33**, unambiguously assigned by X-ray diffraction analysis of **31** (ref. 9), correspond to the expected suprafacial formation of the C(4)-N and C(5)-H bonds in the ring closure.

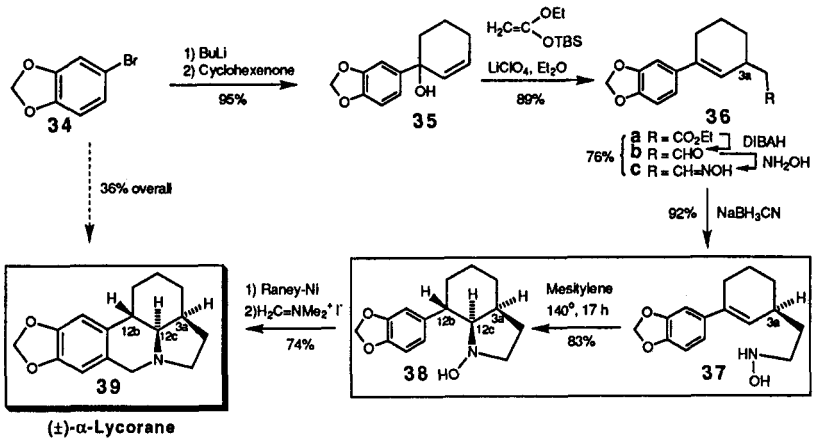
Scheme 9



Having settled the mechanistic question in favor of a retro-Cope elimination we set out to exploit the newly found stereospecificity of alkenylhydroxylamine cyclizations in alkaloid synthesis.

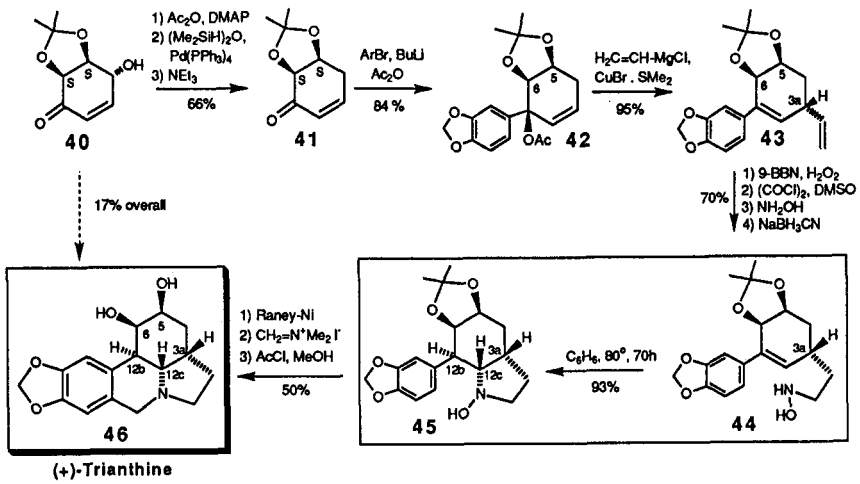
As depicted in Scheme 10, (±)-α-lycorane (**39**) was synthesized in 36% overall yield from aryl bromide **34** (ref. 8). In the strategic step, heating of hydroxylamine **37** in mesitylene under Ar at 140° for 17 h provided the expected retro-Cope elimination product **38** as a single isomer in 83% yield.

Scheme 10



A more ambitious example (ref. 8, Scheme 11), the first enantioselective synthesis of (+)-trianthine [**46** = (+)-zephyranthine], starts with optically pure 4-hydroxycyclohexenone **40** (readily accessible *via* microbial oxidation of chlorobenzene, ref. 10). A novel deoxygenation **40** → **41**, followed by aryl lithium-1,2-addition/*O*-acylation **41** → **42** and *anti*-selective S_N2'-substitution **42** → **43**, secured the desired configuration at C(3a). Center C(3a) induced then centers C(12b) and C(12c) with ~100% selectivity in the crucial retro-Cope elimination **44** → **45** (80°/70 h, 93% yield).

Scheme 11



Acknowledgements

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