Diastereo- and enantioselective syntheses of heterocyclic natural products

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RESEARCH REPORT

DIASTEREO- AND ENANTIOSELECTIVE SYNTHESES OF HETEROCYCLIC NATURAL PRODUCTS (*) (**)

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Summary – Enantiomerically pure *syn*- or *anti*-β-acyloxy ketones, readily available by asymmetric *syn*- or *anti*-aldolizations of chiral *N*-acylsultams, undergo efficient, titanium-mediated cyclocondensations giving *cis*- or *trans*-2,3-dihydro-4*H*-pyran-4-ones such as the cigarette beetle pheromone (–)-serricorole, **6**.

Enantiomerically pure cyclic nitrones **F**, easily accessible *via* electrophilic α-hydroxyaminations of *N*-acylsultams, serve as pivotal key intermediates in the highly stereoselective synthesis of various chiral piperidine and pyrrolidine alkaloids such as (–)-allosedamine, **27**, and (–)-xenovenine, **44**.

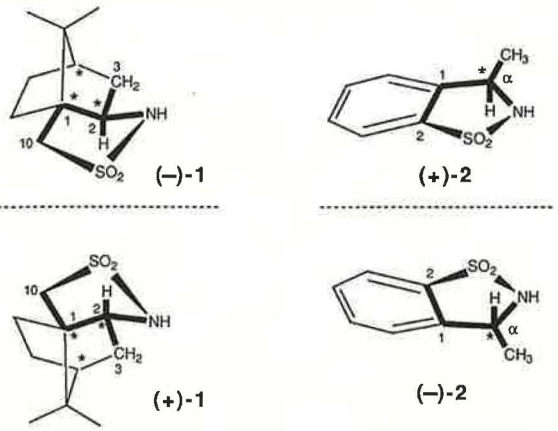
Thermal cyclizations of 4-alkenylhydroxylamines give *N*-hydroxypyrrolidines in a suprafacial manner, consistent with a retro-Cope elimination mechanism. For example, the stereospecific cyclization of alkenylhydroxylamine **64** serves as a key step in a short and efficient synthesis of the enantiomerically pure Amaryllidaceae alkaloid (+)-trianthine, **66**, thus obtained in 24% overall yield from the chlorobenzene-derived enone **60**.

It is a special privilege for me to receive this distinction in the memory of Professor Adolfo Quilico. As early as 30 years ago, working on the synthesis of cephalosporin-C under the guidance of Professor R. B. Woodward, I learned to admire Professor Quilico's groundbreaking article, where in 1950 he reported the stereospecificity of nitrile oxide additions to maleate and fumarate, pointing out the analogy of this reaction with diazoalkane/alkene additions and thus laying the foundations of 1,3-dipolar cycloaddition chemistry[1a]. Another research activity of Professor Quilico, his trendsetting contributions to the chemistry of natural products, such as insect constituents[1b], has spawned an impressive growth of this research area. In memory of Professor Quilico, I would like to focus the first part of this account on the enantioselective synthesis of insect pheromones and defense compounds.

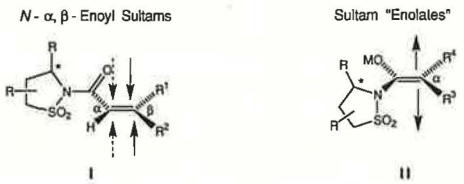
To construct these chiral molecules with the correct absolute configuration we employed the enantiomerically pure sultam auxiliaries **1** and **2** (scheme 1).

The antipodal auxiliaries (–)-**1** and (+)-**1**, readily available from (+)- and (–)-camphorsulphonic acid and manufactured on a 100 kg-scale, rank today among the most efficient, versatile and reliable sources of chirality[2]. More recently, we prepared the related toluenesultams **2** by an unusual asymmetrically catalyzed imine hydrogenation[3]. Both types of sultam moieties provide high π-facial discrimination in various reactions of their *N*-enoyl or enolate derivatives **I** or **II** (scheme 2).

SCHEME 1



SCHEME 2



Thus, *O*-metallated *N,O*-ketene acetals **II** react with a broad range of electrophiles with efficient generation of one or two stereogenic centres. This is highlighted by the asymmetric synthesis of either *syn*-aldols **4**[4] or *anti*-aldols **5**[5] through aldolizations of the **same** boryl enolate **3** with aromatic, conjugated and aliphatic aldehydes (scheme 3).

Thus, $TiCl_4$ specifically inverts the enolate topicity of **3** in the aldol condensation, which is

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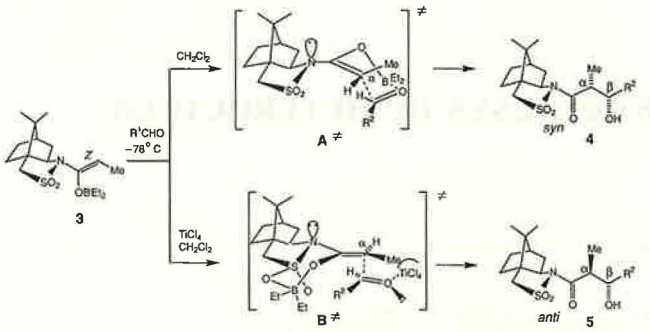
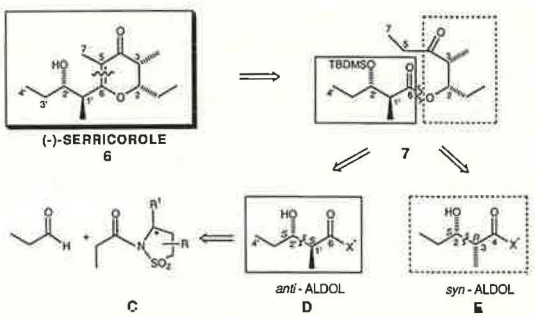
(**) Work supported by the Swiss National Science Foundation, Sandoz Pharma Ltd., Basel, and Givaudan-Roure AG, Dübendorf.

SCHEME 3



consistent with the «open» transition state $\mathbf{B}^{\neq}$ as compared to the «closed» transition state $\mathbf{A}^{\neq}$ in the absence of $TiCl_4$. This unique stereodivergent protocol lends itself perfectly to the synthesis of (–)-serricorole, **6** (scheme 4), a sex pheromone of the cigarette beetle (*Lasioderma serricorne* F.).

SCHEME 4



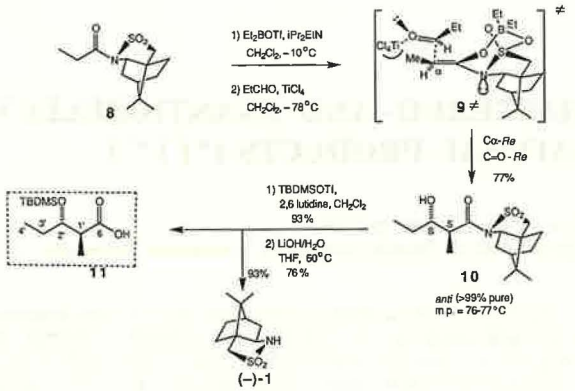
Our strategy centres on the intramolecular condensation **7** → **6** which has been reported by Mori *et al.*[6] to proceed in low yield. Nevertheless, β-acyloxy ketone **7** appeared to us as being a very attractive key intermediate, since it should be readily accessible from stereochemicaly pure *'anti'*- and *'syn'*-aldols **D** and **E**. These segments, in turn, are easily prepared by aldol condensation of propionaldehyde with chiral *N*-propionylsultams **C**, which can be directed either in an *'anti'*- (**C**→ **D**) or *'syn'*-sense (**C** → **E**).

To prepare the *'anti'*-aldol segment C(4')-C(6), *N*-propionylsultam **8** was treated with *in situ* prepared diethylboryl triflate/ethyldiisopropylamine (scheme 5).

$TiCl_4$-mediated condensation of the resulting crude *O*-boryl-*N,O*-ketene acetal with propionaldehyde at –78 °C gave pure *'anti'*-aldol **10** in 77% yield after crystallization. *O*-Silylation of **10** (93%) and saponification with LiOH provided recovered auxiliary (–)-**1** (93%) and pure *S,S*-carboxylic acid **11** (76%).

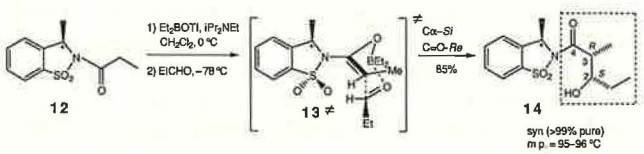
We then proceeded to assemble the C(2)-C(4) segment. The corresponding crystalline *'syn'*-aldol **E** was easily obtained from the same propionylbornanesultam **8** *via* conventional borylenolate/propionaldehyde condensation (in the absence

SCHEME 5



of a Lewis acid)[4]. However, in view of our intention to displace the auxiliary group ultimately by a C-nucleophile [to introduce the C(5)/C(7)-segment, *vide infra*] we employed the more readily removable toluenesultam auxiliary (scheme 6).

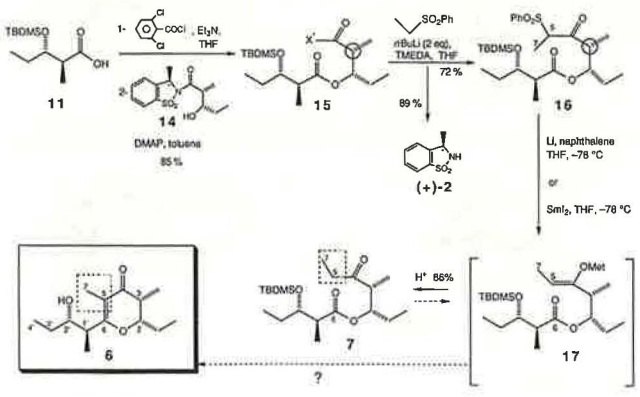
SCHEME 6



Thus, successive treatment of propionyltoluenesultam **12** with (*in situ* prepared) diethylboryl triflate/ethyldiisopropylamine at 0 °C and propionaldehyde at –78 °C yielded pure *'syn'*-aldol **14** (85% after crystallization).

To couple the C(2)-C(4) and C(4')-C(6) segments, aldol **14** was *O*-acylated with the mixed anhydride derived from carboxylic acid **11** and 2,6-dichlorobenzoyl chloride/NEt_3 which furnished ester **15** in 85% yield after crystallization (scheme 7).

SCHEME 7



To introduce the remaining C(5)-C(7) segment, the sultam moiety of **15** was displaced with dilithiated ethyl phenyl sulphone. Thus, deprotona-

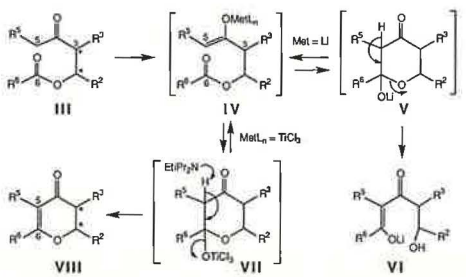
tion of ethyl phenyl sulphone with BuLi/TMEDA (2 mol-equiv.) at 0 °C in THF, addition of acyltoluenesultam **15** at –78 °C and stirring the mixture at –78 °C for 3 h gave sultam auxiliary (+)-**2** (89%) and keto sulphone **16** (72%) as a 93:7 mixture of C(5)-epimers. It is remarkable that the $MeCLi_2SO_2Ph$ reagent selectively attacks the C(4)-imide-carbonyl group in preference to the C(6)-ester-carbonyl group and without epimerization at C(3) or C(1').

Reductive cleavage of the β-keto sulphone **16** was initially expected to yield the dihydropyranone ring of **6** directly *via* a spontaneous cyclization of the regioselectively generated enolate **17**. Desulphonation of **16** with lithium naphthalenide and aqueous workup gave ethyl ketone **7** in 84% yield, but to our disappointment, not even a trace of dihydropyranone. All further attempts to cyclize the transient enolate **17**, including transmetallation of **17**, Met = Li, with $TiCl_4$, $Ti(OiPr)_3Cl$, $CeCl_3$, Me_2AlCl and $ZnCl_2$ failed. Reduction of **16** with SmI_2 also yielded the acyclic ketone **7** (84-86%) but no dihydropyranone.

With ketone **7** in hand, we then tried to reproduce the reported cyclization conditions **7**→**6**[6]. Deprotonation of **7** with LiHMDS (2 mol-equiv.) in THF/TMEDA at –78 °C to 0 °C under Ar, pouring of the mixture into a 10% solution of chloroacetic acid in THF/H_2O (1:1), stirring for 20 h at r.t., workup and desilylation gave at best a 4% yield of serricorole, **6**, together with its C(3)-epimer (4%). Systematic exploration of various reaction conditions led to the following cyclization protocol. A 0.02 *M* solution of ketone **7** in CH_2Cl_2 was treated with $TiCl_4/EtN(iPr)_2$ (8 mol-equiv.) at –78 °C (1 h) and then at 0 °C (20 h). Workup and desilylation of the crude cyclization product (HF/MeCN, 0 °C) provided pure (–)-serricorole, **6**, in 67% yield (from **7**). In summary, pure (–)-serricorole, **6**, has been prepared from propionylsultam **8** by an 8-step sequence in 23% overall yield (scheme 8)[7].

Hence, all four stereocentres of **6** were perfectly controlled *via* sultam-directed *'syn'*- or *'anti'*-aldolizations. The cleavage of an *N*-acylsultam using a lithiated alkyl sulphone as a C-nucleophile (**15**→**16**) represents a general approach to chiral alkyl ketones[8]. A convenient and efficient route to optically pure, polysubstituted γ-dihydropyranones by Ti-mediated cyclization of β-acyloxy ketones is exemplified by the key step **7**→**6**[9]. The decisive role of $TiCl_4$ in this cyclocondensation of acyloxy ketones **III** may be rationalized as follows (scheme 9)[9].

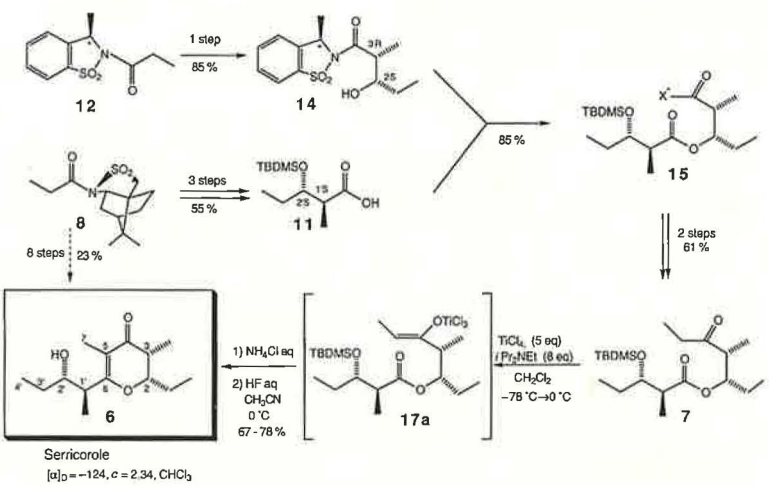
SCHEME 9



Coordination of Ti(IV) with the ester carbonyl group should accelerate the cyclization of enolates **IV**, Met = Ti(IV) to give tetrahedral intermediates **VII** which undergo irreversible elimination to the dihydropyranone products **VIII** by facile departure of $OTiCl_3$. The poor yields of serricorole **6** previously obtained by successive treatment of acyloxy ketone **7** with lithium hexamethyldisilazide and aqueous acid[6] may be ascribed to a tetrahedral intermediate **V** which eliminates with departure of the endocyclic oxygen atom rather than with departure of the poor lithium alkoxide leaving group. Resulting 1,3-diketone enolate **VI** could undergo various side reactions prior to its acid promoted conversion to **VIII**.

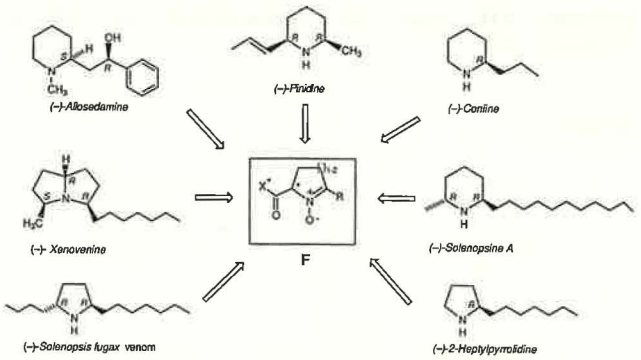
In the following part of this account let us direct our attention towards a new and versatile approach to enantiomerically pure piperidines and pyrrolidines. Piperidine and pyrrolidine nuclei are common structural elements of numerous naturally

SCHEME 8



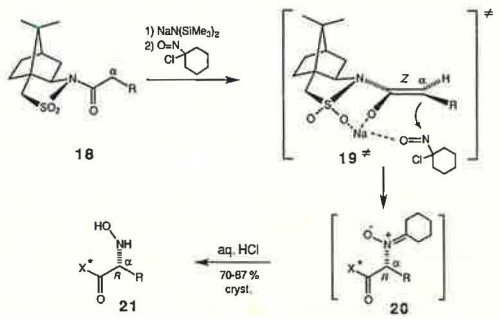
occurring alkaloids. We describe here the use of chiral cyclic nitrones **F** (and **ent-F**) as a platform to construct these ring systems in enantiomerically pure form (scheme 10).

SCHEME 10



Our approach to nitrones **F** relies on the previously developed ~100% diastereoface selective C-N bond formation when enolates of *N*-acylsultams **18** were reacted with the unconventional electrophile 1-chloro-1-nitrosocyclohexane (scheme 11)[10].

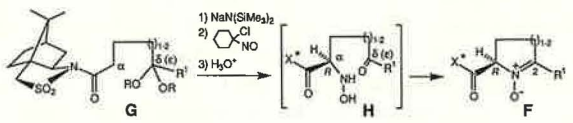
SCHEME 11



Hydrolysis of the resulting nitrones **20** and N,O-cleavage of hydroxylamines **21** provided various optically pure α-amino acids in excellent yields.

En route to nitrones **F**, chiral *N*-acylsultams **G** carrying a protected carbonyl group in the ε-position were similarly treated with sodium hexamethyldisilazide/1-chloro-1-nitrosocyclohexane (scheme 12).

SCHEME 12



Acidic hydrolysis of the resulting, non-isolated nitrone-acetals prompted deprotection and spontaneous condensation of the carbonyl and *N*-hydroxylamine units in **H**.

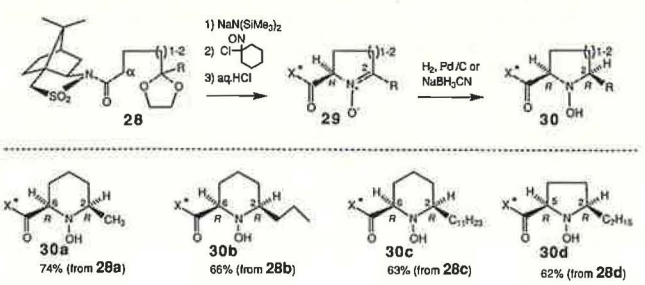
This concept may be exemplified by an asymmetric synthesis of (–)-allosedamine, **27** (scheme 13)[11].

Successive treatment of *N*-acylsultam **22** with $NaN(TMS)_2$, 1-chloro-1-nitrosocyclohexane and aq. HCl furnished crude tetrahydropyridine-1-oxide **23**. Non-purified nitrone **23** underwent an about 100% *exo*-selective 1,3-dipolar addition to styrene with 96.5% preference at the face opposite to the C(6)-substituent (cfr. transition state **24**#) giving cycloadduct **25** in 70% overall yield from **22**. Key cycloadduct **25** was then transformed into alkaloid **27** *via* *N*-methylation and the interesting zinc promoted N/O-cleavage-decyanation step **26**→**27**.

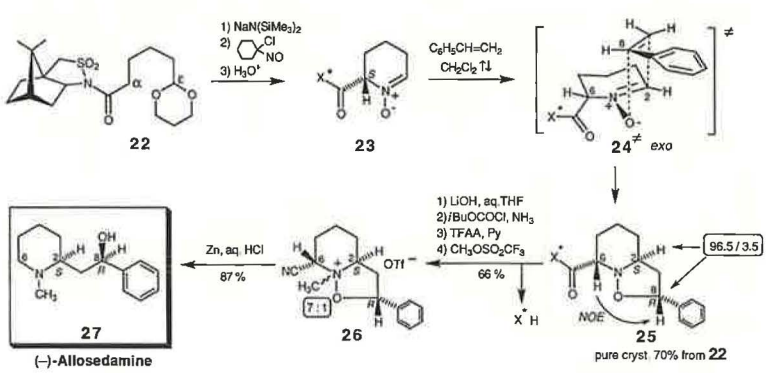
Nitrones **F** (and **ent-F**) display high facial discrimination not only in cycloadditions but also in other reactions. For instance, in the reduction of tetrahydropyridine-1-oxides and 1-pyrroline-1-oxides, **29** (with H_2/Pd and $NaBH_3CN$, respectively) a hydrogen atom was exclusively delivered at the C(2)-face opposite to the acyl substituent (scheme 14).

Thus, a series of *cis*-disubstituted *N*-hydroxypiperidines, **30a-c**, and *N*-hydroxypyrrolidine **30d** were readily prepared.

SCHEME 14

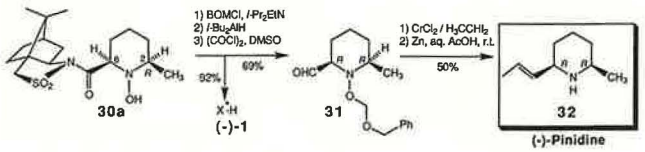


SCHEME 13



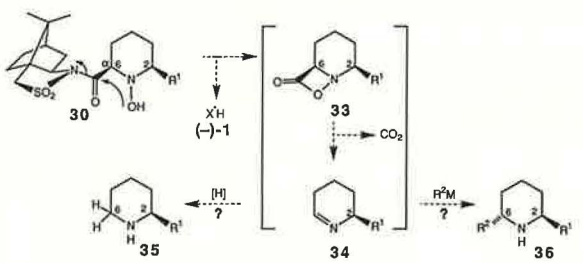
Modification of the acyl substituent in compounds **30** offers a convenient route to 2,6-disubstituted piperidines (and to 2,5-disubstituted pyrrolidines) as exemplified by the conversion of **30a** into (–)-pinidine, **32** (scheme 15)[12].

SCHEME 15



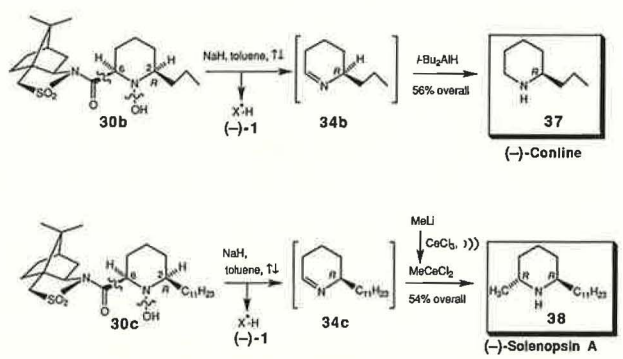
We then pursued the more challenging idea of removing the C(6)-substituent with simultaneous N/O-cleavage. Although unprecedented, it seemed plausible that an internal 'transesterification' **30**→**33** (with recovery of the auxiliary) followed by a spontaneous decarboxylation of oxazetidin-4-one **33** would lead to cyclic imines **34** (scheme 16).

SCHEME 16



Indeed, heating *N*-hydroxypiperidine **30b** with NaH in toluene under reflux, followed by addition of *i*-Bu_2AlH provided the C(2)-monosubstituted, optically pure alkaloid (–)-coniine, **37**, in 56% overall yield (scheme 17)[13].

SCHEME 17

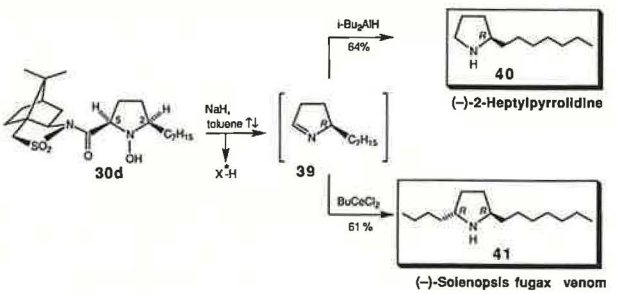


For the introduction of a carbon substituent at C(6) of imines **34** organocerium reagents, prepared by ultrasonication of $CeCl_3$/RLi 1:1-mixtures in THF, appeared to be most suitable.

Hence, applying this novel deoxygenative decarboxylation protocol to *N*-hydroxypiperidine **30c** and trapping of the transient imine **34c** with (*in situ* prepared) «$MeCeCl_2$» furnished the *C*(2,6)-*trans*-disubstituted piperidine (–)-solenopsin-A (**38**, 54% overall) with none of its *cis*-isomer (scheme 17)[13].

Extension of the «oxazetidin-4-one route» to the flexible preparation of enantiomerically pure pyrrolidines is straightforward as demonstrated in scheme 18.

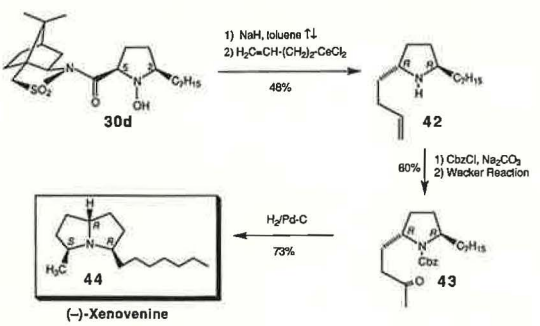
SCHEME 18



Thus, *N*-hydroxypyrrolidine **30d** was smoothly transformed into (–)-2-heptylpyrrolidine, **40**, as well as into *trans*-disubstituted (–)-solenopsis fugax venom **41**[13].

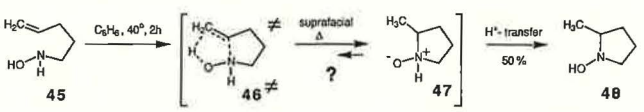
Similar addition of the organocerium nucleophile obtained from 3-butenylmagnesium bromide and $CeCl_3$ to imine **39** yielded *trans*-disubstituted pyrrolidine **42**. *N*-Benzyloxycarbonylation of **42**, Wacker oxidation and stirring of the resulting methyl ketone **43** with Pd/C in MeOH under H_2 gave the pyrrolizidine alkaloid (–)-xenovenine, **44** (scheme 19).

SCHEME 19



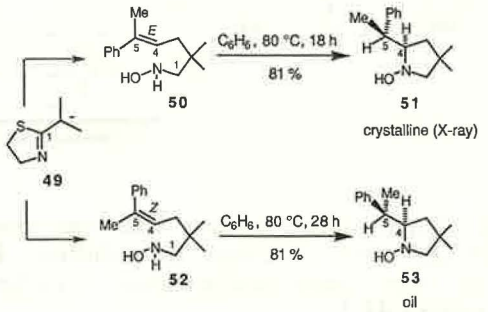
The second part of this account deals with the thermal cyclizations of *N*-4-alkenylhydroxylamines, such as the transformation **45**→**48**, first reported by House *et al.*[14a] and independently discovered by us[14b] (scheme 20).

SCHEME 20



Radical-chain[14a] and retro-Cope elimination pathways[15] 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 **50** and **52** cyclized smoothly in oxygen-free benzene at reflux to give *N*-hydroxypyrrolidines **51** and **53**, respectively, in 81% yield and without cross-contamination (scheme 21).

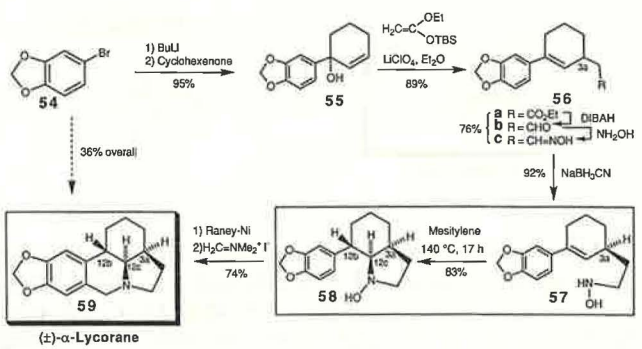
SCHEME 21



The configurations of the cyclization products **51** and **53**, unambiguously assigned by X-ray diffraction analysis of **51**, correspond to the expected suprafacial formation of the C(4)-N and C(5)-H bonds in the ring closure[16].

Having settled the mechanistic question in favour of a retro-Cope elimination we set out to exploit the newly found stereospecificity of alkenylhydroxylamine cyclizations in alkaloid synthesis. As depicted in scheme 22, (±)-α-lycorane, **59**, was synthesized in 36% overall yield from aryl bromide **54**.

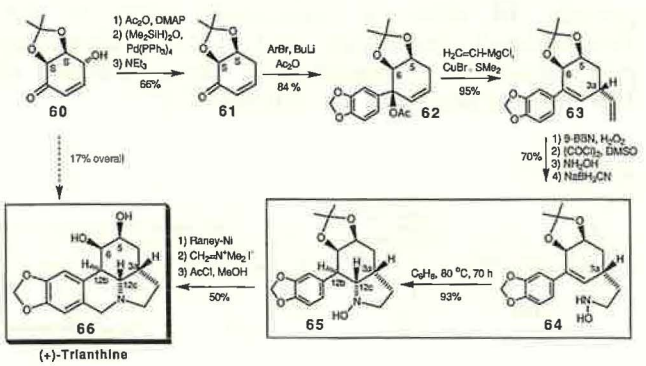
SCHEME 22



In the key step, heating of hydroxylamine **57** in mesitylene under Ar at 140 °C for 17 h provided the expected retro-Cope elimination product **58** as a single isomer in 83% yield[16].

A more ambitious example (scheme 23), the first enantioselective synthesis of (+)-trianthine [**66** = (+)-zephyranthine], starts with optically pure 4-

SCHEME 23



hydroxycyclohexenone, **60** (readily accessible *via* microbial oxidation of chlorobenzene[17]).

A novel deoxygenation **60**→**61**, followed by aryllithium-1,2-addition/*O*-acylation (**61**→**62**) and *anti*-selective S_N2'-substitution (**62**→**63**), secured the desired configuration at C(3a). Centre C(3a) then induced centres C(12b) and C(12c) with ~100% selectivity in the crucial retro-Cope elimination **64**→**65** (80°C/70h, 93% yield)[16].

It is a privilege to acknowledge the crucial contribution of my coworkers whose names appear in the references.

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