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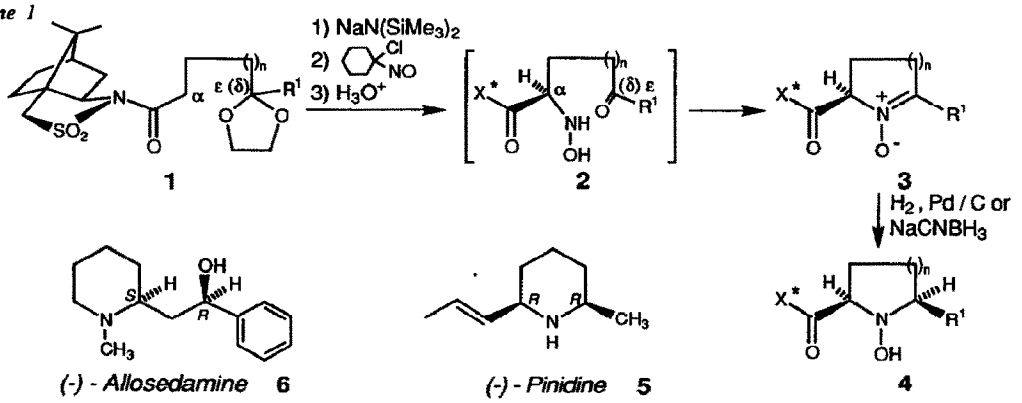
Diastereo- and Enantioselective Syntheses of (-)-Coniine, (-)-Solenopsin A, (-)-Solenopsis fugax venom and (-)-Xenovenine via Deoxygenative Decarboxylation of 2-Carbonylsultam-Substituted N-Hydroxy-Piperidines and -Pyrrolidines [1)]

Wolfgang Oppolzer*, Christian G. Bochet and Eric Merifield
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

Abstract: Heating cyclic 2-carbonylsultam-substituted *N*-hydroxylamines **4** with NaH yields sultam auxiliary **8** and imines **10**, which are trapped *in situ* either by *i*-Bu_2AlH or organocerium reagents to give enantiomerically pure 2-mono- or *trans*-2,6(2,5)-disubstituted piperidines (pyrrolidines) **11** or **12**.

During the last years, increasing attention has been paid to the construction of piperidine and pyrrolidine alkaloids in enantiomerically pure form. [2)] In this context, we have recently reported the use of chiral cyclic nitrones **3** and **ent-3** as key intermediates for the syntheses of (-)-pinidine (**5**) [3)] and (-)-allosedamine (**6**), [4)] respectively (Scheme 1).

Scheme 1



We present here an extension of this strategy based on the ready availability of *N*-hydroxy-piperidines or -pyrrolidines **4** by diastereoselective reduction of nitrones **3** which, in turn, were prepared by asymmetric electrophilic α-hydroxyamination [5)] of chiral *N*-(ε/δ-ketoacyl)sultam acetals **1** [6)] (Table 1).

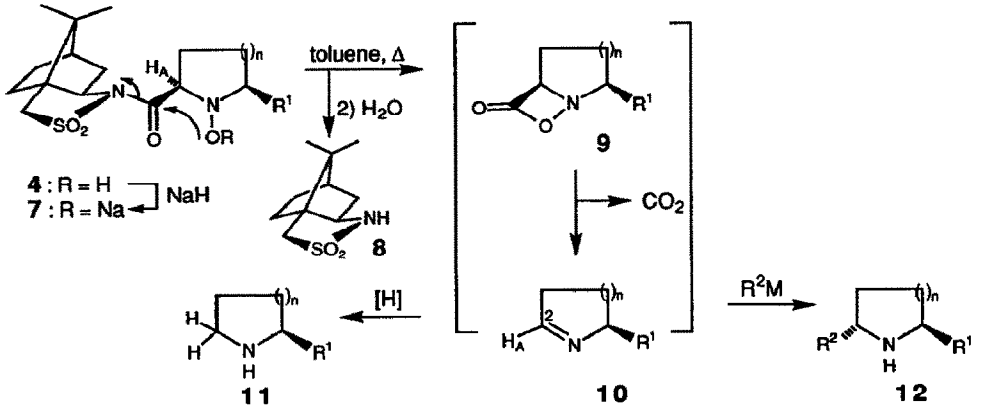
Table 1: Conversion of Chiral *N*-(ε/δ-Ketoacyl)sultam Acetals into *N*-Hydroxy-Piperidines and -Pyrrolidines: **1 → 3 → 4**.

Series	Ring Size	R^1	Yield (%) of Nitrone **3**	Reducing Agent	Yield (%) of Hydroxylamine **4**
a	n=2	$n\text{-}C_{11}H_{23}$	70	H_2, Pd/C	90
b	n=2	$n\text{-}C_3H_7$	72	H_2, Pd/C	92
c	n=1	$n\text{-}C_7H_{15}$	64	$NaCNBH_3$	97

Hence, successive treatment of acylsultams 1 with sodium hexamethyldisilazide, 1-chloro-1-nitrosocyclohexane and 1N aq. HCl [3] provided the expected diastereomerically pure nitrones 3 [9] in 64 to 72% yield (Table 1). Palladium catalyzed hydrogenation of the C,N double bond in 3a and 3b took place from the less hindered face [3] giving the *cis*-2,6-disubstituted *N*-hydroxypiperidines 4a [9] and 4b [9] as single stereoisomers (90 and 92%); only 5% of *N,O*-hydrogenolysis was observed. Reduction of trihydropyrrol-*N*-oxide 3c did not take place under these conditions, but proceeded readily with sodium cyanoborohydride (1.2 mol-equiv.) in MeOH at pH= 3 yielding *N*-hydroxypyrrolidine 4c [9] (97%).

With key precursors 4 in hand, we pursued the idea of removing the acylsultam substituent with simultaneous *N,O*-cleavage (Scheme 2). Although unprecedented, it seemed plausible that an internal 'transesterification' 7 → 9 (with recovery of auxiliary 8) followed by a spontaneous decarboxylation of transient oxazetidin-4-one 9 would lead to cyclic imines 10. [10] Hydride or organometal additions to the non-isolated imines 10 could yield C(2)-monosubstituted or C(2,6)/C(2,5)-disubstituted piperidines/pyrrolidines 11 or 12.

Scheme 2



Indeed, heating a 0.02 M solution of *N*-hydroxypiperidine 4a in toluene with NaH (2 mol-equiv.) under Ar at reflux for 2 h, followed by stirring of the reaction mixture with *i*-Bu_2AlH (1.4 mol-equiv.) at 0°C for 2 h, addition of sat. aq. NH_4Cl, extraction (AcOEt) and flash chromatography (FC) provided sultam 8 (90%) and the more polar piperidine 11a (68%, $[\alpha]_D$ = -2.13 (c=1, $CHCl_3$), Table 2, entry 1).

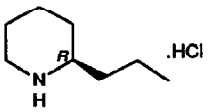
Table 2: Deoxygenative Decarboxylation of Cyclic 2-Carbonylsultam-Substituted *N*-Hydroxylamines / Imine Trapping: 4 → 8 + 10 → 11 or 12

	N - Hydroxylamine					Piperidine / Pyrrolidine			
Entry		Ring Size	R^1	Trapping Agent	Yield (%) Sultam 8	Ratio *trans/cis*		R^2	Yield (%) from 4
1	4a	n=2	*n*-$C_{11}H_{23}$	*i*-Bu_2AlH	90	-	11a	-	68
2	4b	n=2	*n*-C_3H_7	*i*-Bu_2AlH	83	-	11b	-	56
3	4a	n=2	*n*-$C_{11}H_{23}$	MeLi/$CeCl_3$	80	>99:1	12a	CH_3	54
4	4c	n=1	*n*-C_7H_{15}	*i*-Bu_2AlH	93	-	11c	-	64
5	4c	n=1	*n*-C_7H_{15}	*n*-BuLi/$CeCl_3$	63	93:7	12c	*n*-C_4H_9	60
6	4c	n=1	*n*-C_7H_{15}	3-ButenylMgBr/$CeCl_3$	79	>99:1	12d	3-Butenyl	48

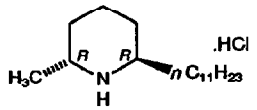
To test the intramolecularity of the deoxygenative decarboxylation **4a** → **10a**, a 0.036 M solution of **4a** in d_8-toluene was deprotonated with NaH (2 mol-equiv.) within a NMR-tube under Ar and the mixture was heated at 50°C. Monitoring the disappearance of the H_A-signal of sodium salt **7a** (δ=4.05 ppm, broad *d*, *J*=12 Hz), using the residual toluene signals as a reference, indicated clean first-order kinetics, $k_1 = 2.1 \times 10^{-2}$ min^{-1}. As expected, no trace of oxazetidin-4-one **9a** was discernible by these measurements, which, on the other hand, showed the appearance of a broad singlet at δ=7.6 ppm corresponding to H_A of imine **10a**. This signal increased to a maximum intensity, which corresponded to only ~0.6 H, probably due to a partial trimerization/polymerization of the imine.

Subjecting hydroxylamine **4b** to slightly modified reaction conditions, furnished the hydrochloride of the hemlock alkaloid (-)-coniine (**11b**), [11] conveniently separated from sultam **8** by extraction (from CH_2Cl_2) with aq. HCl. Crystallization (CH_2Cl_2/hexane) provided **11b**.HCl (56% from **4b**) showing the expected properties (Figure 1), as well as an enantiomeric purity of 99.4% e.e. (by HPLC of its *N*-3,5-dinitrobenzoyl derivative using the chiral column *Daicel Chiralpak AD*).

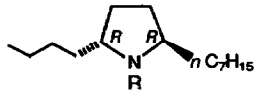
Figure 1



(-)-Coniine (**11b**.HCl)
M.p. 206-210°, lit.[11a] 209°
$[\alpha]_D^{20}$ = - 9.2, (c=0.8, EtOH)
lit.[11a] = - 5.8, (c=0.5, EtOH)



(-)-Solenopsin A (**12a**.HCl)
M.p. 148-149°, lit.[13f] 141-142°
$[\alpha]_D^{20}$ = - 8.9 (c=1.3, $CHCl_3$)
lit.[13f] = - 7.6 (c=0.5, $CHCl_3$)



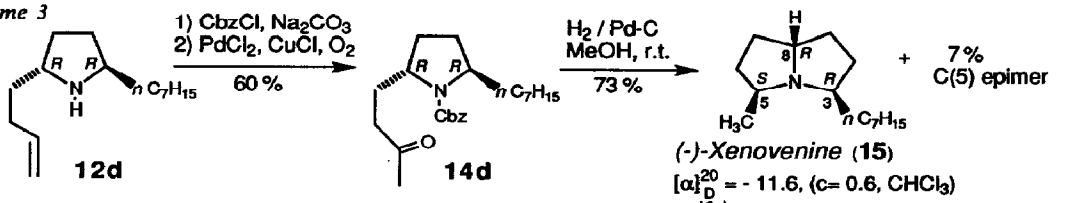
R=H: *(-)-Solenopsis fugax venom* (**12c**)
R=SO_2Ph : **13**
$[\alpha]_D^{20}$ = - 59.8, (c=0.9, CH_2Cl_2)
lit.[15c] = - 62.0, (c=1.0, CH_2Cl_2)

To introduce a carbon substituent at C(2) of imines **10**, we envisaged the addition of organocerium reagents, prepared by ultrasonication of $CeCl_3$/RLi 1:1-mixtures in THF at 0°. [12] Hence, heating *N*-hydroxypiperidine **4a** with NaH, followed by addition of *in situ* prepared "$MeCeCl_2$" (10 mol-equiv.) in THF (-78°, 3 h, then → r.t., 16 h) and workup with aq. Na_3EDTA provided the C(2,6)-*trans*-disubstituted piperidine alkaloid (-)-solenopsin A (**12a** [13], 54% from **4a**), identified as its hydrochloride salt (Figure 1). None of its *cis*-isomer was found in the reaction mixture.

Extension of the "oxazetidin-4-one route" to the flexible preparation of enantiomerically pure pyrrolidines was straightforward (Table 2, entries 4-6). Successive treatment of *N*-hydroxypyrrolidine **4c** with NaH and *i*-Bu_2AlH afforded (*R*)-2-heptylpyrrolidine **11c** [14] ($[\alpha]_D$= -15.5 (c=1.16, $CHCl_3$); lit.[14]: -15.7 ($CHCl_3$), 64% from **4c**). Intercepting transient imine **10c** with the "*n*-BuLi/$CeCl_3$ reagent" (11 mol-equiv.) furnished (-)-solenopsis fugax venom **12c** [15] ($[\alpha]_D$= -7.5 (c=0.7, MeOH), 60% from **4c**), easily separated from its minor (7%) 2,5-*cis*-isomer (FC) and characterized as its phenylsulfonamide **13** (Figure 1).

Similar addition of the organocerium nucleophile obtained from 3-butenylmagnesium bromide and $CeCl_3$ to imine **10c** yielded *trans*-disubstituted pyrrolidine **12d** [9] ($[\alpha]_D$= -4.9 (c=1.6, CH_2Cl_2), 48% from **4c**). *N*-Benzyloxycarbonylation of **12d**, Wacker oxidation, stirring of the resulting methyl ketone **14** with H_2/Pd-C in MeOH (1 atm., r.t., 20 h) and removal (FC) of the minor C(5)-epimer of **16** gave the pyrrolizidine alkaloid (-)-xenovenine **15** [16] (Scheme 3).

Scheme 3



(-)-Xenovenine (**15**)
$[\alpha]_D^{20}$ = - 11.6, (c= 0.6, $CHCl_3$)
lit.[16c] = - 11.5, (c= 0.5, $CHCl_3$)

Further applications and extensions of this novel tandem deoxygenative decarboxylation/imine trapping reaction are presently being explored in our laboratory.

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