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Stereoselective Synthesis of (R)-7-Pentylhexahydroazepine-2-thione: Formal Precursor of (-)-Perhydrohistrionicotoxin

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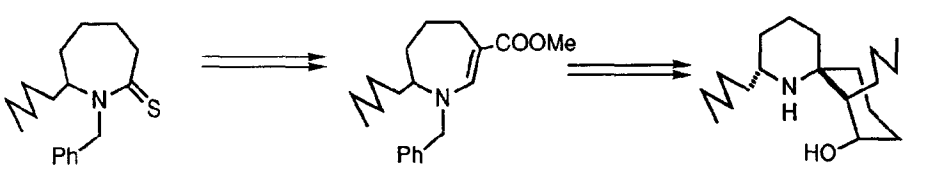
Abstract: The (R)-7-pentylthiocaprolactam **1**, a formal precursor of (-)-perhydrohistrionicotoxin **2** is synthetized in four steps using asymmetric alkylation of cyclohexanone. Metalation and alkylation of (R)-imine **3** afford after hydrolysis (R)-2-pentylcyclohexanone **4** with high stereoselectivity (e.e.=78%). The Beckmann type rearrangement of the optically enriched ketone **4** proceeds without racemization. The resulting 7-pentylcaprolactam **6** was transformed in two steps to the (R)-benzylthiolactam which was purified by recrystallization to give optically pure compound **1** (e.e.>95%).

In a previous work,[1] we reported a new stereoselective route to the polyfunctionalized piperidinic compounds utilizing a ring contraction of seven membered heterocyclic enamines easily accessible from the thiolactam (±)-**1**. We also demonstrated a synthetic potential of this reaction by applying it to the total synthesis of perhydrohistrionicotoxine (±)-**2**. Here, we wish to report the preparation of the optically active thiolactam (R)-**1** which is a formal precursor of (-)-perhydrohistrionicotoxin.[2-4]

Scheme1

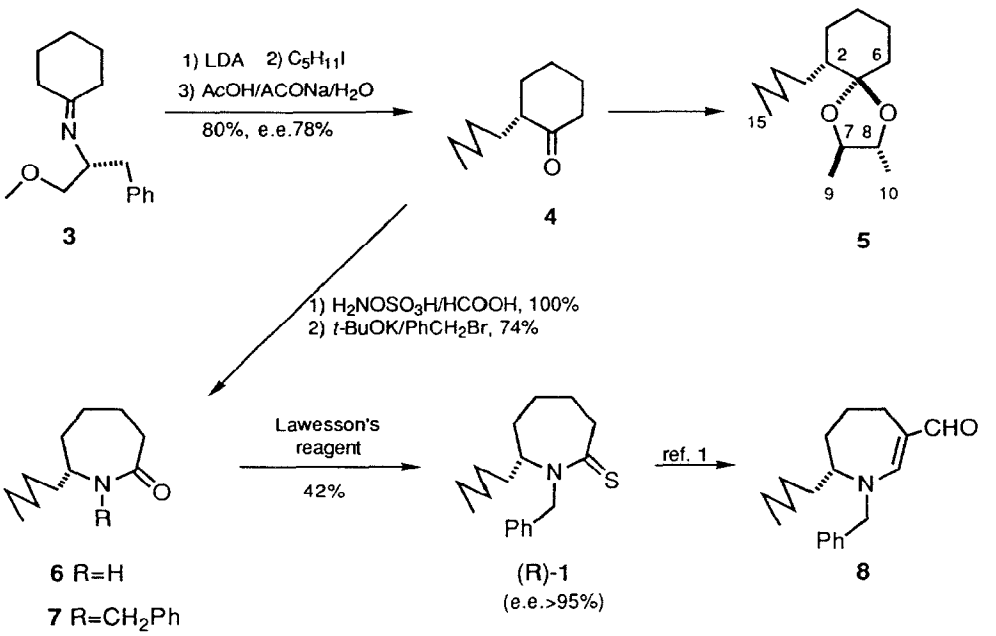


1 **2**
Perhydrohistrionicotoxin

Searching in the literature, we have found few method to prepare optically active lactams[5]. As several enantioselective alkylation methods of cyclohexanone are described in the literature,[6] the Beckmann-type rearrangement of chiral cyclic ketones provides a versatile method for the preparation of optically active lactams.

The optically active 2-pentylcyclohexanone has never been prepared to our knowledge. We adapted Meyer's method for this purpose.[6a]

Scheme 2



The treatment of (R)-imine **3** by LDA followed by pentyl iodide afforded (R)-2-pentylcyclohexanone **4** (e.e.=78±5%). The alkylation occurs predominantly from the *re* face of lithioenamine intermediate. The enantiomeric excess of the resulting ketone was determined using the Wynberg method[7] by ^{13}C NMR analysis of chiral acetal **5**, prepared with (2R,3R)-butanediol following the procedure described in Meyers'paper.[6a,8]

Subsequently, the ketone **4** was converted by Beckmann type reaction using Olah-Fung reagent[9] to yield an isomeric mixture of 3- and 7-pentylcaprolactams (about 1/9 ratio) which were separated after N-benzylation. In these two steps, no significant amount of racemization was observed. The optical purity of benzyllactam **7** was found to be almost identical (e.e.=74±5%) to the ketone **4** by ^1H-NMR analysis using chiral shift reagent [Eu(hfc)$_3$].

Sulfuration of the benzyllactam with Lawesson reagent[10] affords solid thiolactam (R)-**1** which after three recrystallizations gave constant specific optical rotation. The optical purity of this thiolactam (R)-**1** was found to be >95% by ^1H-NMR [Eu(hfc)$_3$] analysis of the enamino aldehyde **8**, prepared from **1** in three steps.

Experimental Section

General Procedure. All boiling points and melting points are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were taken on a Brucker AW80. ^{13}C spectra were taken on a Varian CFT20. The chemical shifts (δ values) are given in parts per million relative to TMS as an internal standard in $CDCl_3$ solutions. GC analysis were carried out on a Girdel 30 apparatus with column filled with 2.5% SE30/chromosorb. All compounds reported below showed the same spectral properties as those described for the racemic series in ref 1.

(R)-2-Pentylcyclohexanone (4). The title compound was obtained following the general procedure of Meyers et al reported in ref.6a. Starting from 6.1g (25.2 mmol) of imine **3**, we obtained 3.40g (20.2 mmol, 80%) of **4** after distillation (67-69°C/0.13 mmHg).

$[\alpha]_D^{25}$=-17.8 (c=5, MeOH); e.e.=78±5%.

Acetal **5** was obtained according to the method described in ref 6a with 85 and 78% yields respectively from the racemic and optically active ketones. The ^{13}C NMR of crude acetal prepared from racemic ketone shows several signal splittings. The diastereoisomeric purity of acetal obtained from optically active ketone was determined by the integration of C2 and C6 signals (d.e.=78%). The underlined signals below correspond to the major diastereomer obtained from optically active ketone above.

^{13}C NMR 110.3 and 110.1 (C1), 79.5 and 79.2 (C8), 77.7 and 77.6 (C7), 45.7 and 45.0 (C2), 37.3 and 36.7 (C6), 32.5 , 29.0 and 28.9, 28.2 and 28.1, 27.3, 24.9, 24.2 and 23.7 , 22.8, 17.9 (C9), 16.3 (C10), 14.1(C15).

(R)-7-Pentylhexahydroazepin-2-one (6). Following the procedure reported in ref 1, 1.55g (9.22 mmol) of ketone **4** was converted quantitatively to the lactam **6** which contains 11% (GC determination) of 3-pentyl isomer. The oily mixture obtained (1.71g) was used without further purification.

(R)-N-Benzyl-7-pentylhexahydroazepin-2-one (7). 3.1g (16.9 mmol) of lactam **6** was benzylated following the procedure reported in ref 1. 7-Pentylisomer was isolated by flash chromatography (Et_2O/petroleum ether=2/3) in 74% yield.

$[\alpha]_D^{25}$=+13.0 (c=6, MeOH); e.e.=74±5%.

The optical purity was determined by ^{1}H-NMR analysis using chiral shift reagent [Eu(hfc)$_3$]. When the europium salt was added to racemic-**7**, the doublet of the more deshielded proton of the benzylic CH_2 (δ5.05ppm, *gem*-coupled, J=-15Hz) became split into two doublets of equal intensity. Thus the same operation was repeated with optically enriched lactam **7** and the integration of split doublets afforded the ratio of two enantiomers (87/13).

(R)-N-Benzyl-7-pentylhexahydroazepin-2-thione [(R)-1]. Following the procedure reported in ref 1, 3.43g (12.5 mmol) of benzyllactam **7** was converted to the thiolactam **1**. Crude thiolactam {3.43g, 95%, $[\alpha]_D^{25}$=+65.8 (c=5, MeOH)} was recrystallized three times from pentane. The forth recrystallization gave no change of the specific optical rotation {42% yield; $[\alpha]_D^{25}$=+123.0 (c=5, MeOH): mp=59-61°C}. Anal. Calcd for $C_{18}H_{27}NS$: C, 74.68; H, 9.40; N, 4.84. Found: C, 74.34, H, 9.36, N, 4.86.

(R)-N-Benzyl-7-pentyl-[1H]-4,5,6,7-tetrahydroazepine-3-carbaldehyde 8. The title compound was obtained by the three step procedure described in ref 1. No enantiomeric enrichment occured during these steps, as we used only flash chromatography as purification method. The enantiomeric excess of the aldehyde **8** was found to be >95% by ^{1}H-NMR analysis using chiral shift reagent [Eu(hfc)$_3$]. While the

aldehyde proton singlet of racemic **8** became split upon addition of the europium salt, no detectable amount of the second signal has been observed in the case of the optically active enamino aldehyde **8**.

$[\alpha]_D^{25}$=+164 (c=5, MeOH)}.

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(8) The assignment of R-configuration to the ketone **4** is based on the two following criteria: 1) All alkylations in the Meyer's paper[6a] carried out on (S)-imine give the same *si* face selectivity. 2) The ^{13}C NMR analysis of the acetal **5** obtained from optically enriched ketone shows that the C2 and C6 of the major diastereomer are respectively more and less deshielded compared to those of the minor isomer, while the inversed tendency was reported for the acetals prepared from (S)-2-methyl, (S)-2-ethyl and (S)-2-propylcyclohexanone.[6a]

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