CHEMISTRY LETTERS, pp. 223-228, 1977. Published by the Chemical Society of Japan

ASYMMETRIC SYNTHESIS OF PIPERIDINE DERIVATIVES: AN APPLICATION TO SYNTHESIS OF (S)-(-)-SEDAMINE AND (S)-(-)-ALLOSEDAMINE[1]

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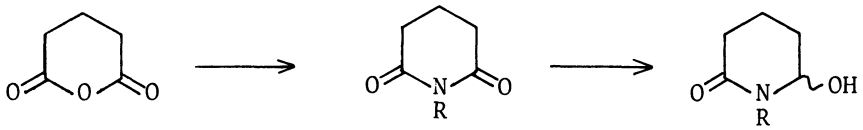
(S)-(+)-2-oxo-6-piperidineacetic acid was synthesized by a novel route involving an asymmetric cyclization process. Its absolute configuration was determined by converting it to (S)-(-)-sedamine and (S)-(-)-allosedamine, piperidine alkaloids.

While there have been serious studies on the biomimetic cyclization,[2] the asymmetric approach to this problem has few examples.[3] Searching for systems which would give chiral six-membered heterocycles in biomimetic processes, we tried to extend the previously developed[4] Wittig-type condensation carried out on chiral five-membered ω-carbinollactams to chiral six-membered ones. This communication concerns with the synthesis of (S)-(+)-2-oxo-6-piperidineacetic acid (8) by the asymmetric intramolecular Michael reaction and the subsequent conversion of 8 to (S)-(-)-sedamine (1)[5] and (S)-(-)-allosedamine (2),[6] piperidine alkaloids.

Treatment of glutaric anhydride with (R)-(+)-α-phenylethyl amine at 250°C for 5 hr afforded the optically active imide 3 [mp 119.5-121.0°C, $[\alpha]_D^{26}$+142.6° (C=1.0, EtOH)]. The imide 3 was then reduced with sodium borohydride to give the 6-hydroxy lactam (4).[7] Reaction of 4 with methyl diethylphosphonoacetate and sodium hydride in THF at room temperature for 20 min did not give the cyclized ester 6b, but gave the optically active



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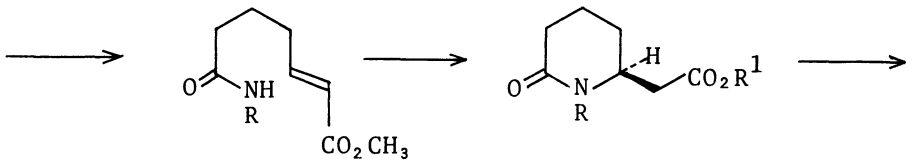
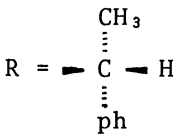
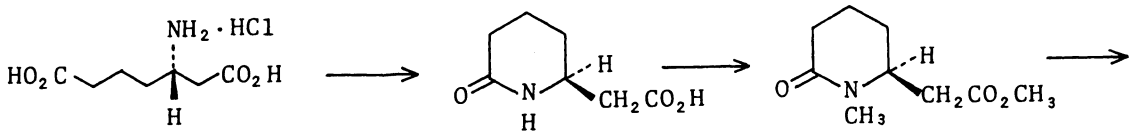


5 6a R^1= H
6b R^1= CH_3



trans-olefinic ester 5 [mp 60-61°C, $[\alpha]_D^{28}$+69.5° (C=1.0 EtOH), nmr (in $CDCl_3$, δ from TMS): 5.76 (d, 1H, J=16.0 Hz, $-CH_2-CH=C\underline{H}-CO_2CH_3$), 6.90 (dt, 1H, J=16.0, 6.4 Hz, $-CH_2-C\underline{H}=CH-CO_2CH_3$)]. The resulting ester 5 is suitable for synthesizing optically active piperidine derivatives by applying asymmetric intramolecular Michael addition of a chiral amide anion onto the double bond of an unsaturated ester[8] and then by removing the chiral conrolling α-methylbenzyl group.



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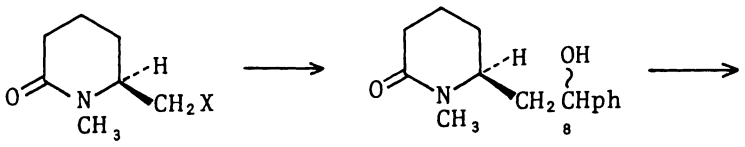

10a X=CH_2OH
10b X=CHO

11

1 2

Cyclization of 5 with KO^{t}Bu in chlorobenzene-THF (4:1) at -54°C for 12 hr gave a mixture of the ester 6b and the minor diastereomer at C-6 in 61% yield and 39% diastereomer excess for 6b.[9] Hydrolysis of the above mixture of 6b and its diastereomer and subsequent recrystallization from a mixture of DMF-MeOH afforded 6a [64% diastereomer excess at C-6, mp 158-160°C, $[\alpha]_D^{25}$+85.3° (C=1.0, EtOH)].

The absolute configuration at C-6 in 6a was determined as S by converting 6a to natural (S)-(-)-sedamine (1) and (S)-(-)-allosedamine (2) whose absolute configurations are known.[10]

The acid 6a in 64% diastereomer excess was treated with 6N-HCl under reflux for 2 hr to give (S)-(+)-β-aminopimelic acid hydrochloride (7) in 94% yield [mp 137-139.5°C, $[\alpha]_D^{24}$+10.7° (C=1, Water)]. Cyclization of 7 in pyridine under reflux for 1.5 hr afforded (S)-(+)-2-oxo-6-piperidineacetic acid (8) in 90% yield [mp 132-134°C $[\alpha]_D^{24}$+11.3° (C=1, EtOH)] which is a potential intermediate in the synthesis of a compound containing a chiral center next to N-atom in piperidine ring. Methylation of 8 with methyl iodide and sodium hydride in DMF gave (S)-(-)-9 in 71% yield, which was reduced with sodium borohydride to yield (S)-(+)-2-oxo-6-piperidineethanol (10a) in 86% yield [$[\alpha]_D^{27}$+3.2° (C=2.2, EtOH)]. Treatment of (S)-(+)-10a with dipyridine-chromium oxide in methylene-chloride gave the aldehyde 10b in 58% yield. Addition of phenylmagnesium bromide to (S)-10b in THF-Et_2O gave 11 as a mixture of diastereomers [the ratio of the above diastereomers at C-8 is ca. 1:1 by nmr assay] in 55% yield. Reduction of 11 with lithium aluminum hydride in Et_2O-THF, followed by alumina chromatography (C_6H_6-Et_2O) afforded (S)-(-)-sedamine (1) in 16% yield [mp 85-87°C (from pentane-Et_2O), $[\alpha]_D^{27}$-53.6° (C=0.28, MeOH), ms; m/e a19 (M^+), 98 (base peak)], and (S)-(-)-allosedamine (2) in 15% yield [mp 79-80°C (from pentane), $[\alpha]_D^{28}$-26.1° (C=0.27, MeOH), ms; m/e 219 (M^+), 98 (base peak)]. The synthetic 1 and 2 gave identical IR spectra (in CCl_4) with those of the reported racemic compounds[11] and showed identical TLC mobilities on alumina with authentic samples.[12]

Acknowledgement.

We are indebted to Miss. T. Seki for her excellent technical assistance. We are also grateful to Drs. T. Noguchi and S. Tsunoda for their encouragement and support.

References and Notes

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12. We are indebted to Prof. H. C. Beyerman for providing us samples of racemic sedamine and natural allosedamine.

(Received November 13, 1976)