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Chiral Precursors for the Synthesis of Enantiomerically Pure Piperidines. Total Synthesis of (*R*)-(-)-Coniine.

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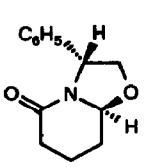
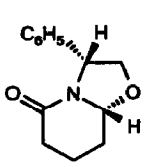
Abstract: The preparation of chiral *cis*- and *trans*-oxazolopiperidones **1**, **2**, and **3** by alternative procedures and an efficient synthesis of the piperidine alkaloid (*R*)-(-)-coniine from *trans*-**1** is reported.

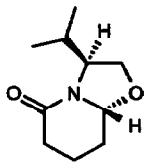
The development of synthetic methods for the preparation of optically active piperidine derivatives constitutes an area of current interest due to the presence of this heterocyclic nucleus in a large number of biologically active natural compounds. With the aim of finding a versatile chiral precursor for the elaboration of enantiomerically pure substituted piperidines we decided to investigate the synthetic utility of oxazolopiperidones **1-3**. The interest of these chiral lactams lies in several aspects: (*i*) they are precursors of N-acyliminium ions,[1] thus allowing the introduction of a substituent at the piperidine C-6 position, (*ii*) the amide carbonyl group allows the alkylation at the piperidine C-3 position,[2] and (*iii*) this carbonyl group can be further elaborated making possible the introduction of a substituent at C-2. During the course of our studies, Royer and Husson[3] reported the synthesis of lactams **1**. This fact prompted us to present our results in this area.[4]



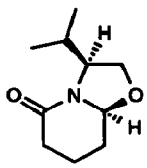
trans-**1**



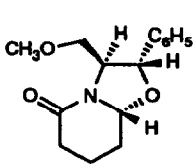
cis-**1**



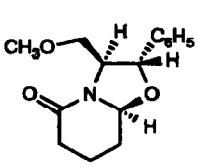
trans-**2**



cis-**2**



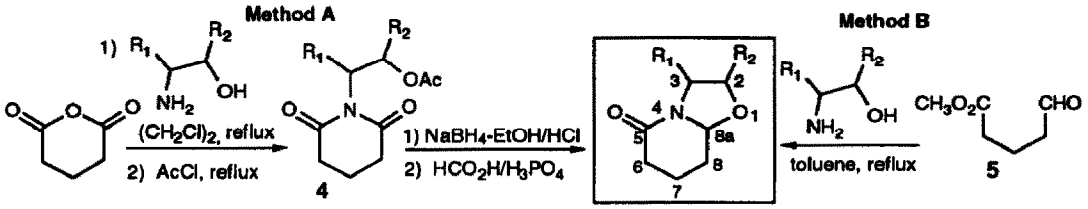
trans-**3**



cis-**3**

Two alternative procedures were studied for the preparation of chiral lactams **1**, **2**, and **3**. Condensation of glutaric anhydride (1.5 equiv) with (*R*)-(-)-phenylglycinol ($(CH_2Cl)_2$, reflux, and then AcCl, reflux), followed by reduction ($NaBH_4$, EtOH, HCl)[5] of the corresponding imide **4** (R_1=C_6H_5, R_2=H) and further acid treatment (1:1 85% HCO_2H-85% H_3PO_4, 24 h, rt) of the resulting mixture of 6-hydroxy- and 6-ethoxylactams (Method A) afforded oxazolopiperidone **1** in 47% overall yield as a 7:3 diastereomeric mixture of *trans*-**1** and *cis*-**1**,[6] respectively.[7] The relative stereochemistry of H-3/H-8a in lactams **1** was inferred by means of 1D n.O.e. difference experiments. Presaturation of one of the H-2 protons in *cis*-**1**

resulted in the simultaneous enhancement of H-3 and H-8a signals, while irradiation of each H-2 protons in *trans*-**1** resulted in alternative enhancements of the signals corresponding to H-3 and H-8a. Following a similar procedure, lactam **2** was prepared in 62% overall yield as a single epimer *trans*-**2**[8] from glutaric anhydride and (*S*)-(+)-valinol. However, all attempts to prepare lactams **3** following the above procedure were unsuccessful since, although the corresponding imide **4** (R_1=CH_3OCH_2, R_2=C_6H_5) could be prepared in low yield (35%) from glutaric anhydride and (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol,[9] further reduction and acidic treatment did not afford the desired compound **3**.

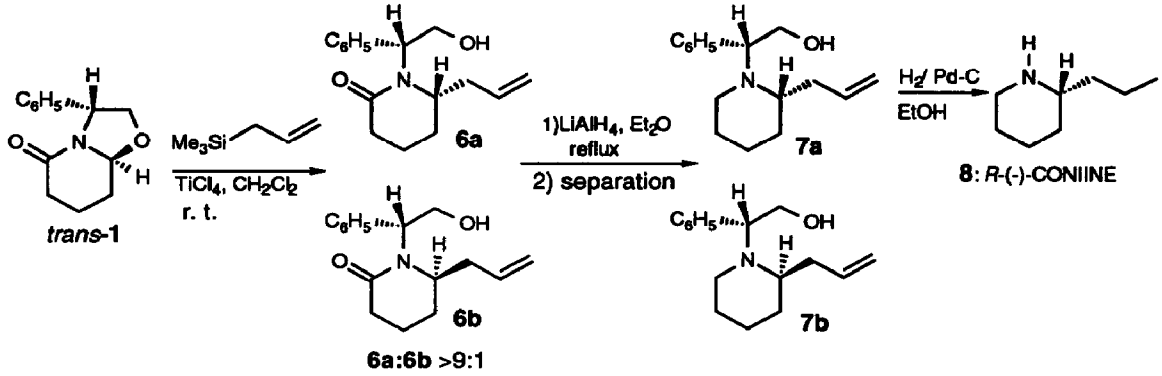


	Method A		Method B	
Compound	overall yield (%)	cis:trans ratio	overall yield (%)	cis:trans ratio
1	47	3:7	25	1:0
2	62	0:1	33	9:1
3	0	-	33	3:1

The second, more straightforward procedure we tried for the synthesis of **1-3** was the cyclodehydration method reported by Meyers,[2] consisting in the condensation of an amino alcohol with a keto acid (Method B). Thus, (*R*)-(-)-phenylglycinol, (*S*)-(+)-valinol or (1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol were treated with methyl 5-oxopentanoate[10] (**5**) in refluxing toluene, with azeotropic removal of water. As expected for this kind of reactions in which an aldehydic ester instead of a keto ester is used, the yields were only moderate (see Table). However, by this method lactams **3** could be prepared in 33% yield as a 3:1 epimeric mixture at C-8a, *cis*-**3** and *trans*-**3**[11] respectively. Interestingly, lactam **1** was formed as a single stereoisomer, *cis*-**1**, while **2** was obtained as a 9:1 mixture of epimers *cis*-**2**[12] and *trans*-**2**, respectively. The reverse stereochemical result obtained in each method (A and B) can be explained by considering that the H-3/H-8a *trans* lactams **1** and **2** are thermodynamically more stable than the corresponding epimers *cis*-**1** and *cis*-**2**. This was corroborated since treatment of pure isomer *cis*-**1** under acidic conditions (TFA 10 equiv, CH_2Cl_2, 64 h, rt) led to a 86:14 mixture of *trans*-**1** and *cis*-**1**, respectively. The same result was obtained when pure *trans*-**1** was subjected to the above conditions. Similarly, pure *trans*-**2** and *trans*-**3** were obtained from the corresponding *cis* isomers after acid treatment (TFA 10 equiv, CH_2Cl_2, rt). Therefore, in method A both epimers equilibrate during the final acid cyclization affording a mixture in which the most stable *trans* bicyclic lactam predominates. However, in method B the observed stereochemical result can be rationalized taking into account that the initially formed 2,4-disubstituted oxazoline adopts the most stable[13] *cis* configuration, which is maintained after the subsequent intramolecular N-acylation leading to bicyclic lactams **1** or **2** under non acidic conditions.

In order to initially explore the behaviour of chiral lactams **1** and **2** in asymmetric α-amidoalkylation reactions, we studied their allylation with allylic silanes in the presence of a Lewis acid. Thus, when lactam

trans-**1** was treated with allyltrimethylsilane and $TiCl_4$ in CH_2Cl_2 at room temperature for 4 h, an epimeric mixture of 6-allyl-2-piperidones (**6a**:**6b** > 9:1 calculated by 500 MHz ^{1}H-NMR) was obtained in 91% yield.[14] However, when the epimer *cis*-**1** was subjected to the same reaction conditions, the reaction was slower and, after 25 h at room temperature, compounds **6** were formed in only 45% yield. Variable amounts of *trans*-**1**, resulting from the epimerization of the starting material *cis*-**1**, were also formed. The stereochemical outcome in the formation of **6** from *cis*-**1** was identical to that found from *trans*-**1**. Lactam *trans*-**2** also reacted slowly with allyltrimethylsilane and $TiCl_4$ in CH_2Cl_2 (76% of the corresponding 6-allyl-2-piperidone was formed after 22 h at room temperature).



Epimers **6a** and **6b** could not be separated by conventional column chromatography. However, separation was satisfactorily achieved after reduction with $LiAlH_4$, and piperidines **7a** and **7b** were isolated in 52% and 6% yields, respectively. Finally, the major isomer **7a** was subjected to catalytic hydrogenation in methanolic solution in the presence of 10% Pd-C to give 2-propylpiperidine **8**[15] whose hydrochloride showed identical data with those reported for (*R*)-(-)-coniine hydrochloride.[15c] The optical purity of (-)-coniine was also determined from the analysis of the ^{1}H-NMR (500 MHz) spectrum of the amide prepared by treatment of **8** with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[16]

It should be noted that the configuration of the new chiral center in the major isomer formed in the amidoalkylation is coincident with that resulting from related reactions from lactams having a chiral inductor derived from (*R*)-(-)-phenylglycinol or (*S*)-(-)-1-phenylethylamine on the amide nitrogen,[17] a stereochemical result that can be rationalized by considering a nucleophilic attack upon the less hindered face of the C=N bond of an N-acyliminium intermediate. This interpretation is in agreement with the fact that both epimers, *cis*-**1** and *trans*-**1**, afford the same epimeric ratio of **6a** and **6b**.

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2. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503.
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4. This work was presented in a preliminary form at the Eighth European Symposium on Organic Chemistry (ESOC-8), Sitges, Spain, August 1993.
5. Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.
6. *Trans*-**1**: ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 16.7 (C-7); 28.1 (C-8); 31.0 (C-6); 57.8 (C-3); 72.2 (C-2); 88.5 (C-8a); 126.0 (C-*o*C_6H_5); 127.5 (C-*p*C_6H_5); 128.7 (C-*m*C_6H_5); 139.6 (C-*i*C_6H_5); 169.0 (C=O); $[\alpha]_D$ -83.3° (CH_2Cl_2, *c* 0.6) (lit.[3] $[\alpha]_D$ -88° (CH_2Cl_2, *c* 0.6)). *Cis*-**1**: ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 17.6 (C-7); 28.0 (C-8); 30.8 (C-6); 58.7 (C-3); 73.7 (C-2); 88.9 (C-8a); 126.4 (C-*o*C_6H_5); 127.6 (C-*p*C_6H_5); 128.6 (C-*m*C_6H_5); 141.6 (C-*i*C_6H_5); 167.6 (C=O); $[\alpha]_D$ -45.9° (CH_2Cl_2, *c* 2.2) (lit.[3] $[\alpha]_D$ -51° (CH_2Cl_2, *c* 2.2)).
7. All new compounds gave satisfactory spectral data and elemental analysis.
8. This compound had been previously prepared in low overall yield (16%): Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.
9. Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.
10. Methyl 5-oxopentanoate (**5**) was prepared from δ-valerolactone by methanolysis followed by Swern oxidation.
11. *Trans*-**3** (oil): ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 17.0 (C-7); 28.3 (C-8); 31.3 (C-6); 59.1 (CH_3O); 61.6 (C-3); 70.2 (CH_2O); 79.8 (C-2); 88.1 (C-8a); 126.4 (C-*o*C_6H_5); 128.3 (C-*p*C_6H_5); 128.5 (C-*m*C_6H_5); 138.8 (C-*i*C_6H_5); 168.5 (C=O); $[\alpha]_D$ +4.7° (EtOH, *c* 1.0). *Cis*-**3** (oil): ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 17.1 (C-7); 28.1 (C-8); 30.5 (C-6); 58.8 (CH_3O); 60.0 (C-3); 70.1 (CH_2O); 80.2 (C-2); 86.1 (C-8a); 125.7 (C-*o*C_6H_5); 127.6 (C-*p*C_6H_5); 128.4 (C-*m*C_6H_5); 138.8 (C-*i*C_6H_5); 167.9 (C=O); $[\alpha]_D$ -87.6° (EtOH, *c* 1.0).
12. *Cis*-**2** (oil): ^{13}C-NMR ($CDCl_3$, 50.3 MHz) 14.9 (CH_3); 17.1 (C-7); 19.1 (CH_3); 25.1 (*C*H(CH_3)$_2$); 27.1 (C-8); 30.6 (C-6); 59.5 (C-3); 65.2 (C-2); 88.0 (C-8a); 167.5 (C=O).
13. Arséniyadis, S.; Huang, P. Q.; Morellet, N.; Beloeil, J.-C.; Husson, H.-P. *Heterocycles* **1990**, *31*, 1789.
14. At lower temperatures the reaction takes place slowly (after 7 h at -30°C only 25% of **6** was formed).
15. For previous asymmetric syntheses of coniine, see: (a) Archer, J. F.; Boyd, D. R.; Jackson, W. R.; Grundon, M. F.; Khan, W. A. *J. Chem. Soc. (C)* **1971**, 2560. (b) Aketa, K.-I.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1976**, *24*, 621. (c) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (d) Lathbury, D.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 114. (e) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (f) Kunz, H.; Pfrengle, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1067. (g) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525. (h) Wanner, K. T.; Wadenstorfer, E.; Kärtner, A.*Synlett* **1991**, 797. (i) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *Tetrahedron Lett.* **1992**, *33*, 7635. (j) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444. (k) Higashiyama, K.; Nakahata, K.; Takahashi, H. *Heterocycles* **1992**, *33*, 17. (l) Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.* **1992**, *33*, 3765. (m) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.
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