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Conjugate Addition of Organocuprates to Chiral Bicyclic δ-Lactams. Enantioselective Synthesis of *cis*-3,4-Disubstituted and 3,4,5-Trisubstituted Piperidines

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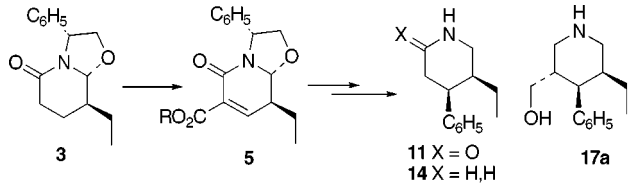
ABSTRACT



Chiral nonracemic bicyclic lactam 3, easily accessible by cyclodehydration of (*R*)-phenylglycinol and racemic methyl 4-formylhexanoate, was converted to the unsaturated lactams 5, which undergo the stereoselective conjugate addition of lower order cyanocuprates to ultimately lead to enantiopure *cis*-3,4-disubstituted and 3,4,5-trisubstituted piperidines.

A large number of piperidine-containing compounds, either natural or synthetic, are biologically and medicinally interesting.[1] As a consequence, the development of new methods for the enantioselective synthesis of piperidine derivatives by stereoselective introduction of substituents at the carbon positions of the heterocycle constitutes an area of current interest.[2] In this context, chiral nonracemic bicyclic lactams derived from phenylglycinol have proven to be versatile building blocks for the synthesis of diversely substituted enantiopure piperidines, giving access to 2-[3] and 3-substituted[4] and *cis*-2,4-,[5] *cis*-2,6-,[6] *trans*-2,6-,[7] and *trans*-3,4-disubstituted[8] piperidines.[9] In a further application of (*R*)-

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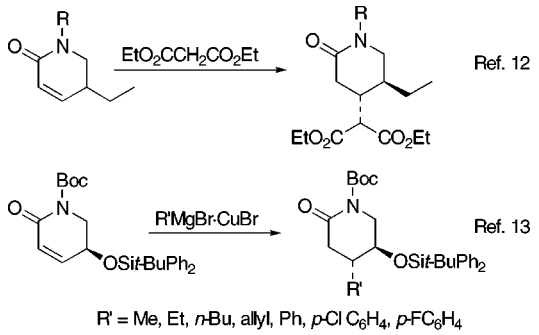
phenylglycinol-derived lactams, we present here a synthetic route for the preparation of enantiopure *cis*-3,4-disubstituted piperidines and open up a route to more complex enantiopure 3,4,5-trisubstituted piperidines.

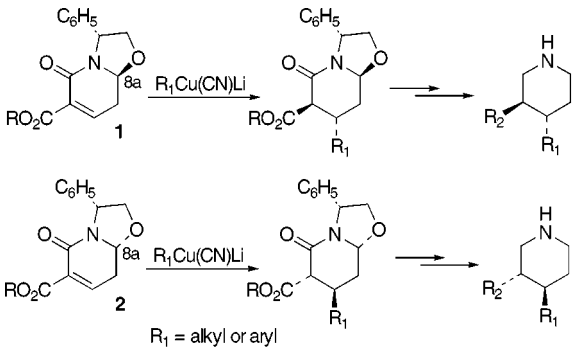
The conjugate addition of carbon nucleophiles to γ-substituted α,β-unsaturated γ-lactams (2-pyrrolidones), either simple[10] or bicyclic,[11] is a well-documented reaction that has been reported to stereoselectively give *trans*-4,5-disubstituted 2-pyrrolidones. In contrast, the addition of stabilized anions[12] and organocuprates[13] to γ-substituted α,β-unsaturated δ-lactams (2-piperidones) has been scarcely used as a method for the stereoselective synthesis of piperidine derivatives. In the few reported examples, all of them dealing with simple unsaturated δ-lactams, the 1,4-addition also leads to the *trans* isomers as a consequence of either the thermodynamic control (from β-carbonyl enolates) or the kinetic axial attack of the nucleophile (from copper derivatives) upon a conformation in which the γ-substituent is pseudoaxial in order to avoid A$^{(1,2)}$ strain with the olefinic hydrogen atom (Scheme 1).[14]

Scheme 1. Conjugate Additions to Simple γ-Substituted α,β-Unsaturated δ-Lactams



Recently, we have studied the conjugate addition of lower order cyanocuprates to the diastereomeric (*R*)-phenylglycinol-derived α,β-unsaturated lactams depicted in Scheme 2 and demonstrated that the configuration of the stereocenter at the angular position (C-8a) determines if the attack of the nucleophile takes place on the *si* or the *re* face of the electrophilic carbon of the conjugated double bond. These conjugate additions constitute the key step of an enantiodivergent synthesis of both enantiomers of the antidepressant drug paroxetine (a *trans*-3,4-disubstituted piperidine).[8]

Scheme 2



In this paper we want to disclose the effect that a substituent at the γ position of the unsaturated bicyclic lactam **2** has on the stereoselectivity of the conjugate addition of organocuprates and report a method for the enantioselective synthesis of *cis*-3,4-disubstituted and 3,4,5-trisubstituted piperidines. The required unsaturated lactams **5** were prepared, via the selenides **4**, from the enantiopure bicyclic lactam **3**, which was easily accessible by cyclodehydration of (*R*)-phenylglycinol and racemic methyl 4-formylhexanoate.[15] The alkoxycarbonyl group not only enhances the reactivity of the conjugated system, thus allowing the subsequent conjugate addition of an organocuprate, but also can later be manipulated to ultimately lead to 3,4,5-trisubstituted piperidines. Thus, sequential treatment of **3** with 2.2 equiv of LHMDS, the appropriate chloroformate, and PhSeCl, followed by ozonolysis of the resulting selenides under neutral conditions, led to the unsaturated lactams **5a** and **5b** (Scheme 3). Addition of lithium methyl- or phenylcyanocuprate to these lactams at low temperature stereoselectively afforded compounds **6a,b** and **7a,b** as mixtures of epimers at the isomerizable stereocenter adjacent to the ester and lactam carbonyl goups (approximate ratio of CO_2R α:β isomers, 7:3 for **6** and 4:1 for **7**).[16] The high facial stereoselectivity of the conjugate addition was confirmed after removal of the benzyloxycarbonyl substituent. Thus, hydrogenolysis of the benzyl esters **6a** and **7a** by treatment with hydrogen in the presence of Pd−C, followed by

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(14) The same *trans* relative stereochemistry is obtained in the conjugate addition to γ-substituted α,β-unsaturated δ-lactones: Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N.; Hosoya, K. *Tetrahedron Lett.* **1990**, *31*, 7623. See also refs 10g and 13b.

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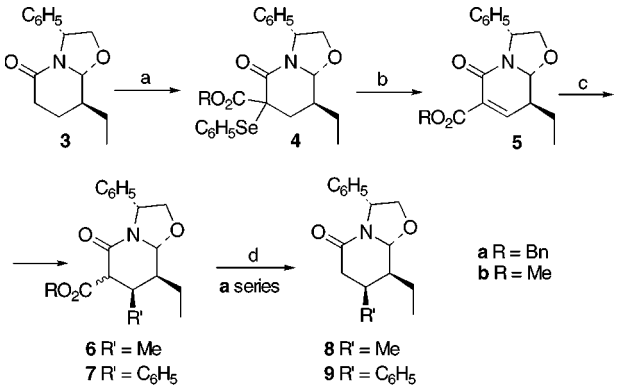
(16) All yields are from material purified by column chromatography. Satisfactory spectral (IR, ^{1}H and ^{13}C NMR), analytical, and/or HRMS data were obtained for all new compounds.

Scheme 3. Conjugate Addition to Bicyclic γ-Substituted α,β-Unsaturated δ-Lactams Derived from (*R*)-Phenylglycinol[a]



[a] Reagents and conditions: (a) LHMDS, $ClCO_2R$, PhSeCl, THF, −78 °C, 86% (**4a**), 89% (**4b**); (b) O_3, CH_2Cl_2, −78 °C; (c) R′Cu(CN)Li, THF, −78 °C. Yields from **4a**: 38% (**6a**), 80% (**7a**). Yields from **4b**: 40% (**6b**), 75% (**7b**). (d) H_2, Pd−C, 25 °C, then toluene, reflux, 72% (**8**), 82% (**9**).

decarboxylation of the resulting β-keto acids by heating in refluxing toluene, afforded lactams **8** and **9**, respectively, as single isomers.

The stereoselectivity in the attack of organocuprates to both the unsaturated lactams **5a,b** and the deethyl lactams **1** and **2** can be rationalized by considering that these lactams are conformationally rigid as a result of the presence of an amide bond in a bicyclic system, the conformation of the six-membered ring being determined by the configuration of C-8a. As a consequence, they adopt the pseudochair conformations depicted in Figure 1, which implies the

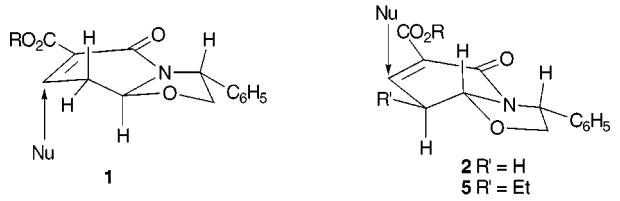


Figure 1. Stereoelectronic control in the conjugate addition to bicyclic α,β-unsaturated δ-lactams derived from (*R*)-phenylglycinol.

pseudoequatorial disposition of the ethyl substituent in **5a,b**. This was confirmed by ^{1}H NMR analysis since H-8a appears as a doublet with J = 10.8 Hz. A stereoelectronically preferred axial attack of the organocuprate at the electrophilic carbon, which occurs *cis* with respect to the ethyl substituent in **5a**,**b**, accounts for the resulting stereochemistry.

(17) For examples in the racemic series, see: (a) McErlane, K. M. J.; Casy, A. F. *Can. J. Chem.* **1972**, *50*, 2149. (b) Pridgen, L. N. *J. Org. Chem.* **1974**, *39*, 3059. (c) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324.

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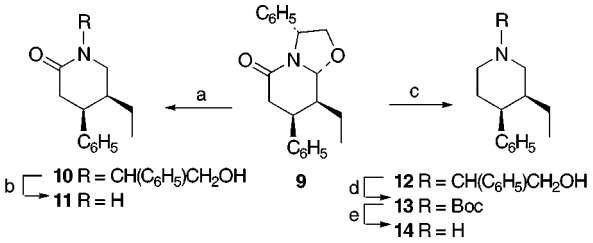
Oxazolopiperidone **9** was converted into *cis*-5-ethyl-4-phenyl-2-piperidone (**11**) by reductive cleavage of the C−O bond of the oxazolidine ring with triethylsilane and $TiCl_4$, followed by treatment of the resulting piperidone **10** with sodium in liquid ammonia (Scheme 4). Alternatively, alane

Scheme 4. Synthesis of Enantiopure *cis*-3,4-Disubstituted Piperidines[a]



[a] Reagents and conditions: (a) Et_3SiH, $TiCl_4$, CH_2Cl_2, reflux, 51%; (b) Na, liq NH_3, THF, −33 °C, 94%; (c) $AlCl_3$, $LiAlH_4$, THF, 25 °C, 89%; (d) H_2, $(Boc)_2O$, $Pd(OH)_2$, AcOEt, 25 °C, 73%; (e) TFA, CH_2Cl_2, 25 °C, 86%.

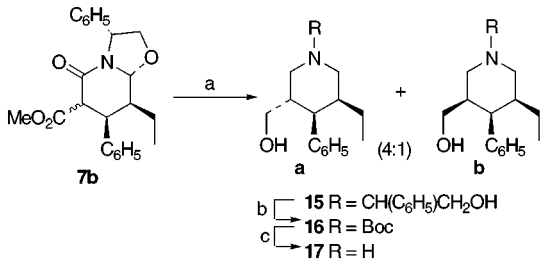
reduction of **9** afforded the *cis*-3,4-disubstituted piperidine **12**, which was subjected to hydrogenolysis in the presence of di-*tert*-butyl dicarbonate to give the *N*-Boc-protected piperidine **13**. Finally, treatment of **13** with TFA gave *cis*-3-ethyl-4-phenylpiperidine (**14**). Thus, the above route efficiently provides an enantioselective entry to *cis*-3,4-disubstituted piperidines, which are not easily accessible by alternative methods.[17] It is worth commenting that *cis*-3-alkyl-4-phenylpiperidines possess dopaminergic activity and are currently being investigated for the treatment of cocaine abuse.[18]

Alane reduction of the mixture of epimers **7b** brought about the cleavage of the C−O bond of the oxazolidine ring and the simultaneous reduction of the lactam and ester carbonyl groups to give a 4:1 epimeric mixture of *trans-trans* and *cis-cis* 3-piperidinemetanols, **15a**[19] and **15b**, respectively, which were transformed into the *N*-Boc-protected trisubstituted piperidines **16a** and **16b** by catalytic hydrogenation in the presence of di-*tert*-butyl dicarbonate (Scheme 5). Removal of the *N*-Boc protecting group of **16a** by treatment with TFA gave piperidine **17a**.

In summary, in contrast with the usual stereochemical outcome of conjugate additions to cyclic γ-substituted

(19) The configuration of **15a** was unambiguously confirmed by X-ray crystallography. The experiment was done on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-86) after applying Lorentz, polarization, and absorption (empirical PSI scan method; maximum and minimum transmission factors were 0.9737 and 0.9298, respectively) corrections. Full-matrix least squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and riding thermal parameters for H-atoms (positioned at calculated positions) converged to a *R* factor of 0.047 (calculated for the reflections with $I > 2\sigma(I)$). Crystal data: $C_{22}H_{29}NO_2$, monoclinic, space group *C*2, a = 16.570(4) Å, b = 10.150(4) Å, c = 11.597(2) Å, V = 1937.4(8) Å^3, μ (MoKα) = 0.073 mm^{-1}, D_c = 1.164 g/cm^3. Approximate dimensions: 0.7 × 0.5 × 0.18 mm^3. Data collection was up to a resolution of $2\theta = 56.8°$ producing 2659 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.133 and −0.147 e Å^{-3}.

Scheme 5. Synthesis of Enantiopure 3,4,5-Trisubstituted Piperidines[a]



[a] Reagents and conditions: (a) $AlCl_3$, $LiAlH_4$, THF, 25 °C, 64% (**15a**) and 16% (**15b**); (b) H_2, $(Boc)_2O$, $Pd(OH)_2$, AcOEt, 25 °C, 75% (**16a**), 62% (**16b**); (c) TFA, CH_2Cl_2, 25 °C, 55%.

unsaturated carbonyl compounds (in particular lactams), the conjugate addition to chiral bicyclic γ-substituted α,β-unsaturated lactams **5** stereoselectively leads to the *cis* isomers, thus providing an enantioselective route to *cis*-3,4-disubstituted piperidines. By appropriate manipulation of the activating alcoxycarbonyl group, the above route also provides easy access to enantiopure 3,4,5-trisubstituted piperidines bearing a functionalized one-carbon substituent at the β-position of the ring.

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Supporting Information Available: General procedure for the preparation of unsaturated lactams **5** from **3** and for the conjugate additions leading to **6** and **7**; copies of ^1H and ^{13}C NMR spectra of compounds **3**−**17**; complete X-ray crystallographic data for **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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