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Stereodivergent Synthesis of Enantiopure *cis*- and *trans*-3-Ethyl-4-piperidineacetates

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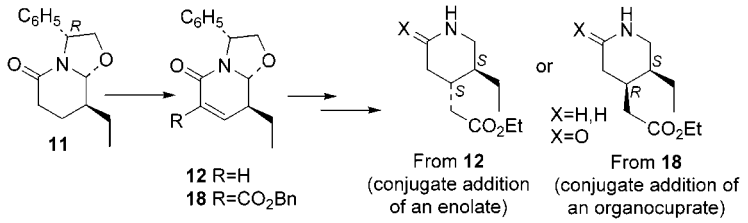
ABSTRACT



Starting from a common chiral bicyclic lactam 11, enantiopure *trans*- or *cis*-3-ethyl-4-piperidineacetate derivatives are obtained by conjugate addition of an enolate or a cuprate to the unsaturated lactams 12 or 18, respectively.

cis- and *trans*-3-ethyl-4-piperidineacetates (and 4-piperidineethanols) are structural moieties of monoterpenoidal origin present in a variety of benzo[*a*]- and indolo[2,3-*a*]-quinolizidine alkaloids[1] (Figure 1). Many syntheses of these

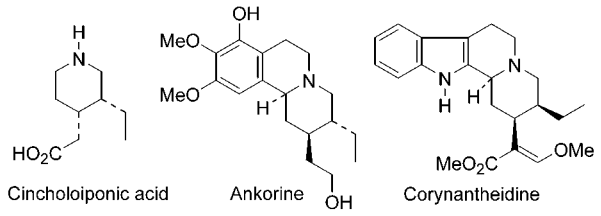


Figure 1.

alkaloids involve the use of *cis*- or *trans*-3-ethyl-4-piperidineacetates, or their 6-oxo derivatives, as crucial intermediates.[2] Additionally, the ester group provides synthetic access to the more complex emetine, tubulosine, ochrolifuamine, and related alkaloids.[3] 3-Ethyl-4-piperidineacetic esters, in particular ethyl cincholoiponate, are accessible in enantiopure form by degradation of secologanine[4] and cinchonine,[5] thus allowing the development of enantioselective routes to the above-mentioned alkaloids. However, there are very few methods for the enantioselective synthesis of *cis*- and *trans*-3-ethyl-4-piperidineacetate derivatives.[6]

In this paper we report the enantioselective synthesis of both *cis*- and *trans*-3-ethyl-4-piperidineacetate derivatives by stereocontrolled conjugate addition to (*R*)-phenylglycinol-derived unsaturated bicyclic lactams. The potential of bicyclic lactams derived from chiral amino alcohols as building

(1) (a) Brown, R. T. In *Indoles, The Monoterpenoid Indole Alkaloids*, Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Series Eds.; John Wiley and Sons: New York, 1983; Vol. 25; Part 4, Chapter 3. (b) Lounasmaa, M.; Tolvanen, A. In *Monoterpenoid Indole Alkaloids*, Saxton, J. E., Ed. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Series Ed.; John Wiley and Sons: Chichester, 1994; Vol. 25; Supplement to Part 4, Chapter 3.

(2) For reviews, see: (a) Fujii, T.; Ohba, M. *Heterocycles* **1988**, *27*, 1009. (b) Fujii, T.; Ohba, M. *Heterocycles* **1998**, *47*, 525.

(3) (a) Kametani, T. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; ; John Wiley and Sons: New York, 1977; Vol. 3, pp 1−273. (b) Wiegrebe, W.; Kramer, W. J.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 397.

(4) Brown, R. T.; Leonard, J. *Tetrahedron Lett.* **1978**, 1605.

(5) (a) Kaufmann, A.; Rothlin, E.; Brunschweiler, P. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 2299. See also: (b) Fujii, T.; Ohba, M. *Chem. Pharm. Bull.* **1985**, *33*, 583.

(6) The *trans* isomers are accessible by intramolecular Michael addition: Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 517.

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blocks for the enantioselective synthesis of diversely substituted piperidine derivatives has previously been demonstrated.[7]

In this context, in recent work we have established that unsaturated lactams **A** (X = CO_2Bn) and **B** (X = CO_2Bn, R = H or Et), which differ in the configuration at the C-8a stereocenter, undergo conjugate addition of *cyanocuprates* with opposite facial selectivity.[8] This result was explained by considering that the conformation of the piperidine ring differs in lactams **A** and **B** and that the attack of the nucleophile takes place, under stereoelectronic control, axial to the electrophilic carbon of the conjugated double bond (Figure 2). This has led to the enantiodivergent synthesis of

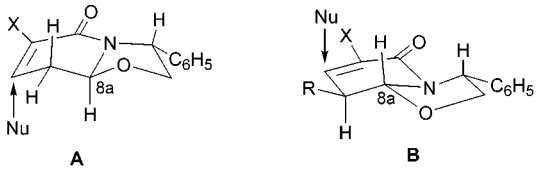
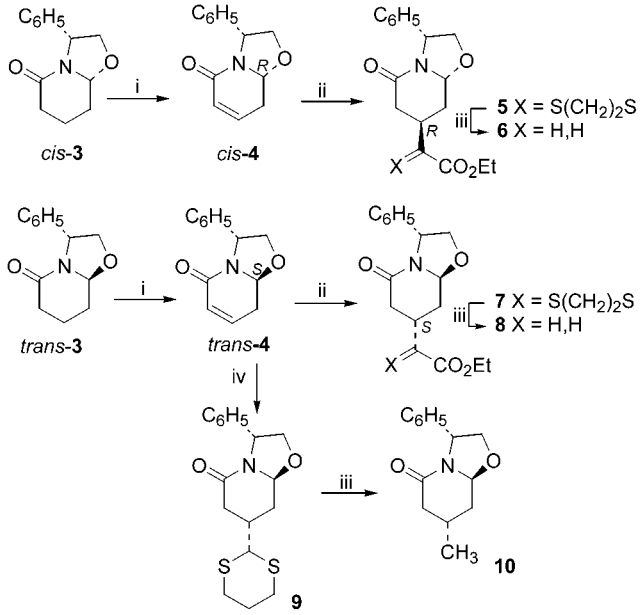


Figure 2. Stereoelectronic control.

both enantiomers of the antidepressant drug paroxetine starting from the epimeric lactams **A** and **B** (X = CO_2Me, R = H) derived from the same chiral inductor, (*R*)-phenylglycinol.[8a] Interestingly, when R = Et, the additions to **B** stereoselectively lead to the C-7/C-8 *cis* isomers, thus providing a synthetic entry to enantiopure *cis*-3-alkyl-4-arylpiperidines.[8b] This stereochemical outcome contrasts with the usual stereoselectivity of conjugate additions to γ-substituted α,β-unsaturated δ-lactams, in which the *trans* isomers are formed.[9]

The conjugate addition of stabilized anions to α,β-unsaturated carbonyl compounds differs from the cuprate additions in that it is a reversible process. As a consequence, thermodynamic control operates, which can have stereochemical implications. For this reason, we decided to investigate if the conjugate addition of stabilized anions to the diastereomeric lactams *trans*-**4** (**A**, X = H) and *cis*-**4** (**B**, X = H, R = H), lacking the ethyl substituent, takes place with the same stereoselectivity as the addition of cuprates to the related *trans* and *cis* lactams **A** (X = CO_2Bn) and **B** (X = CO_2Bn, R = H or Et) mentioned above. The required nonactivated[10] unsaturated lactams **4** were prepared in excellent yield by treatment of the corresponding saturated lactams **3** with KH and methyl phenylsulfinate, followed by heating of the resulting sulfoxides in toluene solution (Scheme 1). As we have already reported,[8a] both *cis*- and

Scheme 1. Conjugate Addition of Enolates to Phenylglycinol-Derived α,β-Unsaturated δ-Lactams[a]



[a] Reagents and conditions: (i) KH, $C_6H_5SO_2Me$, THF, reflux, then Na_2CO_3, toluene, reflux, 86%; (ii) ethyl 1,3-dithiolane-2-carboxylate, LDA, THF, HMPA (from *cis*-**4**), 60% (**5**), 72% (**7**); (iii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, 1:3 THF−MeOH, 79% (**6**), 71% (**8**), 93% (**10**); (iv) 1,3-dithiane, *n*-BuLi, THF, 71%.

trans-**3** are easily accessible by cyclodehydration of methyl 5-oxopentanoate with (*R*)-phenylglycinol, the former being the kinetic product and the latter the more stable isomer.

The introduction of an acetate chain at the piperidine 4-position of *cis*-**4** was accomplished by conjugate addition of the enolate derived from ethyl 1,3-dithiolane-2-carboxylate,[11] followed by desulfurization of the resulting dithioacetal **5** with Ni boride. Piperidineacetate **6** was obtained as a single stereoisomer detectable by spectroscopic methods. However, all attempts to induce the conjugate addition of the sodium salt of dimethyl malonate failed,[12] the corresponding pyridone being the only isolable product under forcing conditions. A similar two-step sequence from lactam *trans*-**4** led to ester **8**, again as a single stereoisomer.[13] It is worth mentioning

(7) For reviews, see: (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (b) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; Mclaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.

(8) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611.

(9) For the addition of organocuprates, see: (a) Fleming, I.; Reddy, N. L.; Takaki, K.; Ware, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 1472. (b) Herdeis, C.; Kaschinski, C.; Karla, R.; Lotter, H. *Tetrahedron: Asymmetry* **1996**, *7*, 867. For the addition of stabilized anions, see: (c) Battersby, A. R.; Turner, J. C. *J. Chem. Soc.* **1960**, 717. (d) Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799. (e) Fujii, T.; Ohba, M.; Sakaguchi, J. *Chem. Pharm. Bull.* **1987**, *35*, 3628.

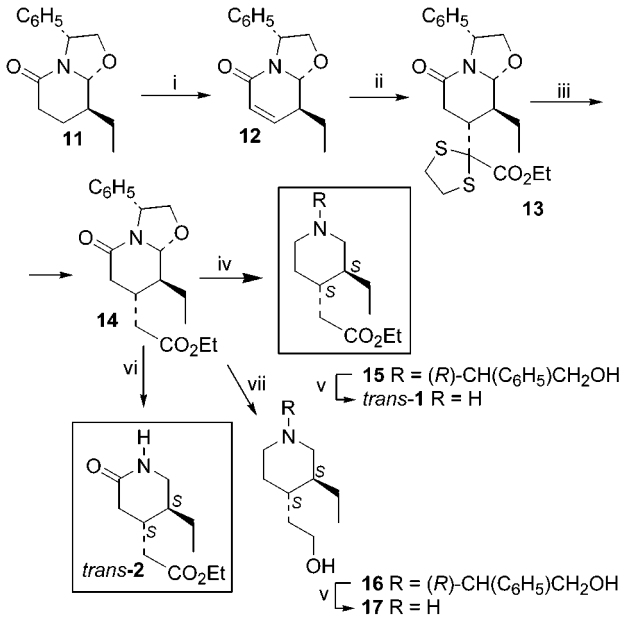
(10) Attempted conjugate addition of the enolates derived from $CH_2(CO_2Me)_2$, $MeCOCH_2CO_2Me$, or $CH_3S(O)CH_2CO_2Me$ to the more activated unsaturated lactam **A** (X = CO_2Bn) under a variety of conditions resulted in failure, the only identifiable product being the 2-pyridone formed by the opening of the oxazolidine ring promoted by the abstraction of an acidic C-8 proton.

(11) Hermann, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2599.

(12) For a similar result, see: Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Sniekus, V. *Tetrahedron Lett.* **1980**, *21*, 4823.

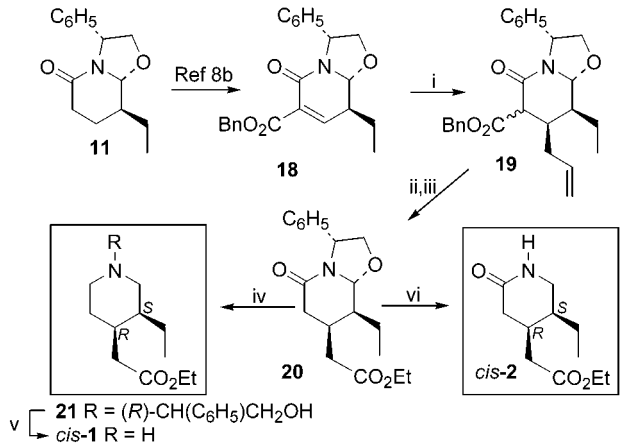
(13) Ester **8** was also prepared, although in lower overall yield, by conjugate addition of the enolate derived from $MeSCH_2CO_2Et$ to *trans*-**4** (32%) followed by desulfurization (93%).

Scheme 2. Synthesis of Enantiopure *trans*-3-Ethyl-4-piperidineacetate Derivatives[a]



[a] Reagents and conditions: (i) KH, $C_6H_5SO_2Me$, THF, reflux, then Na_2CO_3, toluene, reflux, 81%; (ii) ethyl 1,3-dithiolane-2-carboxylate, LDA, THF, 52%; (iii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, 1:3 THF−MeOH, 66%; (iv) BH_3−THF, 61%; (v) H_2, Pd-C, MeOH, 73%; (vi) Ca, liq NH_3, then Et_3SiH, TFA, 53%; (vii) $AlCl_3$, $LiAlH_4$, THF, 63%.

Scheme 3. Synthesis of Enantiopure *cis*-3-Ethyl-4-piperidineacetate Derivatives[a]



[a] Reagents and conditions: (i) $(C_6H_5)_3(CH_2{=}CHCH_2)Sn$, C_6H_5Li, CuI, TMSCl, LiCl, THF, 86%; (ii) O_3, 1:1 CH_2Cl_2−MeOH, Me_2S, then PDC, DMF, then TMSCl, EtOH, 67%; (iii) H_2, 10% Pd/C, then toluene, reflux 82%; (iv) BH_3−THF, 66%; (v) H_2, Pd/C, MeOH, 70%; (vi) Ca, liq NH_3, then Et_3SiH, TFA, 35%.

that the initially formed dithioacetal **7** was recovered unchanged after treatment with LHMDS under equilibrating conditions. The absolute configuration of the new stereogenic center generated in the conjugate addition step, *R* in the addition to *cis*-**4** but *S* in the addition to *trans*-**4**, was deduced by comparing the spectroscopic data of **6** and **8** with those of the respective C-7 epimers, which had been obtained by a different procedure.[14] Additionally, the facial selectivity of the conjugate addition of stabilized anions to *trans*-**4** was confirmed since the addition of the lithium salt of 1,3-dithiane led to a single dithioacetal, **9**, which was desulfurized to **10**, a lactam of known configuration.[8a]

Next we investigated if the presence of a substituent at the γ-carbon of the α,β-unaturated carbonyl system had any influence on the stereoselectivity of the addition of stabilized anions. Accordingly, operating as in the above deethyl series, unsaturated lactam **12** was prepared in excellent yield from **11**, which, in turn, was easily accessible[14] by cyclodehydration of (*R*)-phenylglycinol with racemic methyl 4-formylhexanoate, in a process involving a dynamic kinetic resolution. The conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate to unsaturated lactam **12** took place again with high facial selectivity to give a single product **13**, which was desulfurized to ester **14** by treatment with Ni boride (Scheme 2). The *S* configuration of the stereogenic center at the piperidine 4-position was established by comparing the NMR data and [α] value of ester **14** with those of the same ester previously prepared by an alternative procedure.[14] The different facial selectivity of the above conjugate addition with respect to the analogous addition to *cis*-**4** deserves comment as it reveals that the ethyl substituent exerts a dramatic influence on the stereochemical course of the conjugate addition of enolates. This result can be accounted for by considering that the addition of enolates is a reversible process that, starting from **12**, leads to the thermodynamically more stable 3,4-*trans* isomer.

The synthetic usefulness of lactam **14** is illustrated by its conversion to (3*S*,4*S*)-3-ethyl-4-piperidineacetate *trans*-**1**, the corresponding 6-oxo derivative *trans*-**2**, and *trans*-3-ethyl-4-piperidineethanol **17**. Thus, treatment of **14** with borane brought about both the reduction of the lactam carbonyl group and the reductive cleavage of the oxazolidine ring to give piperidine **15**, which was debenzylated to *trans*-**1**. Alternatively, hydrogenolysis of the C−N bond of **14** with Ca in liquid NH_3, followed by treatment of the resulting oxylactams with Et_3SiH in TFA afforded lactam *trans*-**2**. Finally, $LiAlH_4$ reduction of **14** followed by debenzylation led to piperidineethanol **17**.

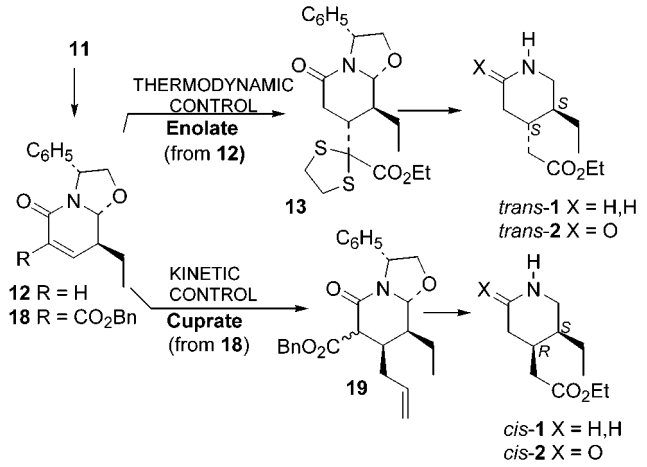
The potential of lactam **11** in the enantioselective synthesis of 3-ethyl-4-piperidineacetate derivatives was further demonstrated as this lactam also provides easy access to these derivatives in the *cis* series. After conversion of **11** into the unsaturated lactam **18** via a selenide,[8b] conjugate addition of an allyl group via a copper derivative took place under stereoelectronic control (see Figure 1; **B**, X = CO_2Bn, R = Et), *cis* with respect the ethyl substituent, to give **19** (Scheme 3). Although the conjugate addition of an aryl group to **18** has been reported to take place in good yield (80%) via a lower order cyanocuprate, the use of lithium methylcyanocuprate results in lower yield (38%).[8b] After considerable experimentation, the best conditions for the introduction of

(14) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 335.

the allyl substituent were found by using stoichiometric allylcopper, generated in situ by treatment of allyltriphenyltin with phenyllithium and CuI, in the presence of TMSCl/LiCl. Under these conditions, compound **19** was isolated in 86% yield as a 83:17 mixture of C-6 epimers. The allyl substituent of **19** was efficiently converted into the acetate chain by ozonolysis, followed by oxidation of the resulting aldehyde, and esterification. Subsequent removal of the benzyloxycarbonyl substituent by hydrogenolysis afforded ester **20**, which was then converted to enantiopure 3-ethyl-4-piperidineacetate *cis*-**1** and lactam *cis*-**2** as in the above *trans* series.

In conclusion, the conjugate addition of enolates to the phenylglycinol-derived unsaturated lactams *trans*-**4** (**A**, X = H) and *cis*-**4** (**B**, X = R = H) occurs with the same stereoselectivity as the addition of cuprates to the related *cis* and *trans* lactams **A** (X = CO_2Bn) and **B** (X = CO_2Bn, R = H or Et), respectively, the configuration of the new stereocenter generated in the process being determined by the configuration of C-8a. However, the presence of an ethyl substituent at C-8, as exists in lactam **12**, changes the stereoselectivity of the enolate addition. This result is of interest because, starting from a common lactam **11**, enantiopure 3-ethyl-4-piperidineacetate derivatives are easily accessible in either the *cis* or *trans* series. Kinetically controlled conjugate addition of an allylcopper reagent to the unsaturated lactam **18**, which incorporates an additional activating alkoxycarbonyl group, leads to the *cis* isomers, whereas thermodynamically controlled conjugate addition of an enolate to unsaturated lactam **12** leads to the *trans* isomers (Scheme 4). Taking into account that both enantiomers of phenylglycinol are commercially available, the routes reported here can provide access to *cis*- and *trans*-3-ethyl-4-piperidineacetate derivatives in both enantiomeric series.

Scheme 4. Stereodivergent Synthesis of *cis*- and *trans*-3-Ethyl-4-piperidineacetate Derivatives



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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of *cis*-**1**, *trans*-**1**, *cis*-**4**, *trans*-**4**, **6**, **8**−**10**, **12**, **14**−**17**, **19**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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