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Enantioselective Synthesis of *cis*- and *trans*-3,5-Disubstituted Piperidines. Synthesis of 20*S*- and 20*R*-Dihydrocleavamine

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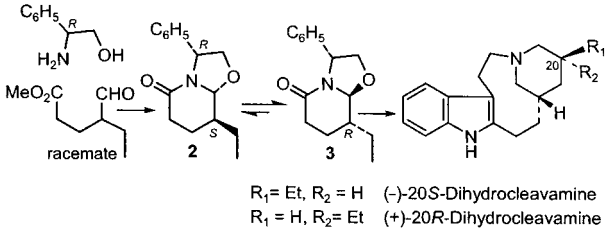
ABSTRACT



Diastereoselective alkylation at the carbonyl α-position of chiral nonracemic lactams 2 and 3, the former prepared by cyclocondensation of (*R*)-phenylglycinol with a racemic γ-substituted δ-oxoester in a process that involves a dynamic kinetic resolution and the latter by a subsequent equilibration, provides access to enantiopure *cis*- and *trans*-3,5-disubstituted piperidines. The usefulness of the approach is illustrated with the synthesis of the alkaloids 20*S*- and 20*R*-15,20-dihydrocleavamine.

Chiral nonracemic bicyclic lactams derived from phenylglycinol have proven to be versatile building blocks for the enantioselective synthesis of enantiopure piperidines with a variety of substitution patterns: 2- and 3-substituted, cis and trans 2,3-, 2,4-, 2,6-, and 3,4-disubstituted, as well as 2,3,4- and 3,4,5-trisubstituted and 2,3,4,5-tetrasubstituted.[1] Most of these targets were selected because they are naturally occurring products (or synthetic precursors) or because of their biological activities.

We report here a synthetic entry to enantiopure *cis*- and *trans*-3,5-disubstituted piperidines. The key steps of the synthesis, involving the generation of the stereogenic centers at the piperidine β and β′ positions, are (i) the cyclocondensation of a racemic γ-substituted δ-oxoester with (*R*)-phenylglycinol in a process that involves a dynamic kinetic resolution (DKR) and (ii) the stereoselective alkylation at the carbonyl α-position of the resulting bicyclic δ-lactam. We illustrate the potential and usefulness of this approach with the enantioselective synthesis of the diastereomeric indole alkaloids (−)-20*S*- and (+)-20*R*-15,20-dihydrocleavamine.

The enantiopure ethyl-substituted bicyclic lactam **2** was obtained[2] in 70% yield by cyclocondensation of racemic aldehyde ester **1** with (*R*)-phenylglycinol under neutral conditions, followed by column chromatography of the

(1) For reviews, see: (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun*. **1997**, 1−8. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843−9873. For recent work, see: (c) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc*. **1995**, *117*, 5399−5400. (d) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084−7085. (e) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091−3094. (f) Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931−8952. (g) Dwyer, M. P.; Lamar, J. E.; Meyers, A. I. *Tetrahedron Lett*. **1999**, *40*, 8965−8968. (h) 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*, 3074−3084. (i) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett*. **2001**, *3*, 611−614. (j) Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett*. **2001**, *3*, 3257−3260. (k) Amat, M.; Cantó, M.; Llor, N.; Bosch, J. *Chem. Commun*. **2002**, 526−527. (l) Amat, M.; Pérez, M.; Llor, N.; Bosch, J. *Org. Lett*. **2002**, *4*, 2787−2790. (m) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem*. **2002**, *67*, 5343−5351. (n) Amat, M.; Cantó, M.; Llor, N.; Ponzo, V.; Pérez, M.; Bosch, J. *Angew. Chem., Int. Ed*. **2002**, *41*, 335−338. (o) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem*. **2003**, *68*, 1919−1928.

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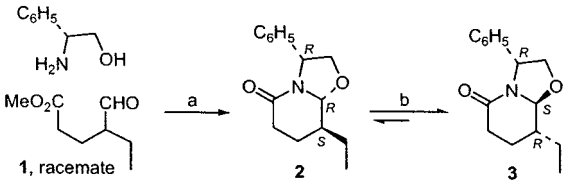
resulting 4:1 diastereomeric mixture of lactams **2** and **3** (Scheme 1). Interestingly, when the above crude mixture was

Scheme 1. Stereocontrolled Generation of Enantiopure Bicyclic γ-Substituted δ-Lactams[a]



[a] Reagents and conditions: (a) Et_2O, anhyd Na_2SO_4, 0 °C, 1 h, then 70 °C, 10−15 mmHg, 79% (**2**/**3** ratio 89:11); (b) 3 N MeOH−HCl, 25 °C, 24 h, quantitative (**2**/**3** ratio 3:7).

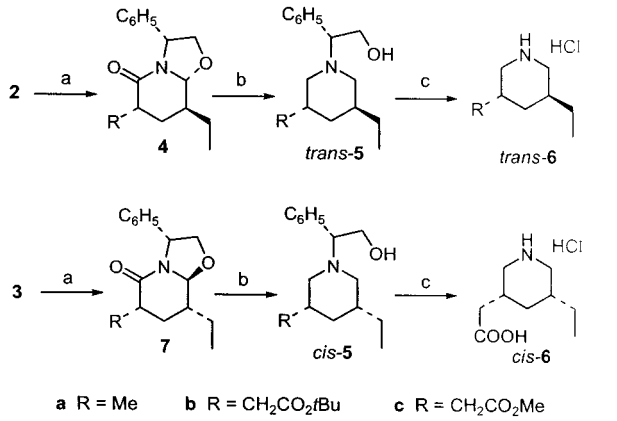
treated under acidic conditions a reversal in the ratio of isomeric lactams **2** and **3** was observed, and lactam **3** could be easily isolated in 60% overall yield after chromatographic purification.

To gain access to 3,5-disubstituted piperidines we explored the stereochemical outcome of the alkylation of the enolates derived from the above lactams **2** and **3**. Although the alkylation at the carbonyl α-position of bicyclic γ- and δ-lactams derived from amino alcohols has received considerable attention from both the synthetic and theoretical standpoint,[3] the observed stereoselectivities are difficult to rationalize and, to our knowledge, there are no precedents of such alkylations from δ-lactams with the substitution pattern present in **2** or **3**.

Generation of the enolate of **2** with lithium hexamethyldisilazide followed by alkylation with methyl iodide took place with moderate facial diastereoselectivity to give a 7:3 mixture of the *endo* alkylation product **4a**, in which the piperidine β and β' substituents are trans, and the *exo* epimer in 94% overall yield (Scheme 2). A much better result from the stereochemical standpoint was obtained from lactam **3**, which underwent *exo* alkylation with excellent yield (84%) and high stereoselectivity to give lactam **7a**, bearing cis substituents at the piperidine β and β' positions. Only very minor amounts (<5%) of the corresponding *endo* epimer were detected. The alkylated product **4a** was converted to piperidine *trans*-**6a** by borane reduction followed by catalytic debenzylation of the resulting 3,5-dialkylpiperidine *trans*-**5a**. A similar borane reduction from lactam **7a** gave 3,5-dialkylpiperidine *cis*-**5a**.

The cis−trans relationship between the substituents at the β and β' positions of the piperidine ring in lactams **4a** and **7a**, as well as in piperidines **5a**, was deduced by ^{13}C NMR from the upfield chemical shift of the piperidine β and β' carbons observed in the trans isomers as compared with the

Scheme 2. Enantioselective Synthesis of *cis*- and *trans*-3,5-Disubstituted Piperidines[a]



[a] Reagents and conditions: (a) LiHMDS, −78 °C, 1 h, then MeI or $BrCH_2CO_2tBu$, −78 °C, 2 h, 66% (**4a**, 70% **4b**), 80% (**7a**), 60% (**7b**); (b) 1 M BH_3−THF, −78 °C, rt, 53% (*trans*-**5a**), 77% (*trans*-**5b**), 47% (*cis*-**5a**), 57% (*cis*-**5b**); (c) MeOH−HCl, then H_2/$Pd(OH)_2$, 75% (*trans*-**6a**), 86% (*trans*-**6c**), 78% (*cis*-**6**).

respective cis epimers, as a consequence of γ-gauche effects. The same criterion was used in the **b** series (see below).

In this manner, as a consequence of the different facial stereoselectivity in the above alkylations, it is possible to prepare either trans or cis enantiopure 3,5-dialkylpiperidines. It is simply a matter of using either the kinetic lactam **2**, formed through a dynamic kinetic resolution during the cyclocondensation process, or the most stable isomer **3**, formed by a subsequent equilibration.

The above results prompted us to study similar alkylations using a bromoacetate ester to prepare 5-ethyl-3-piperidineacetate derivatives, which were envisaged as synthetic precursors of 20*R*- and 20*S*-dihydrocleavamine. These tetracyclic indole alkaloids,[4] embodying a 3,5-disubstituted piperidine moiety, differ in the configuration of the piperidine carbon bearing the ethyl substituent.

As could be expected from the above results, alkylation of the lithium enolates derived from lactams **2** and **3** with *tert*-butyl bromoacetate also took place with opposite diastereofacial selectivity to give the respective lactams **4b** (*endo* alkylation) and **7b** (*exo* alkylation) as the major products. Both the chemical yields and stereoselectivities were excellent (84%, 5:1 *endo*/*exo* ratio from **2**; 75%, 1:4 *endo*/*exo* ratio from **3**).

Treatment of lactams **4b** and **7b** with borane brought about both the reductive opening of the oxazolidine ring and the reduction of the lactam carbonyl to give the corresponding piperidines, *trans*-**5b** and *cis*-**5b**, which were converted to the 5-ethyl-3-piperidineacetic derivatives *trans*-**6c** and *cis*-**6** by catalytic debenzylation in methanol solution in the presence of HCl.

The synthesis of dihydrocleavamines from the above 5-ethyl-3-piperidineacetate derivatives required the introduction of the 2-(3-indolyl)ethyl chain on the piperidine nitrogen,

(2) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2237−2240.

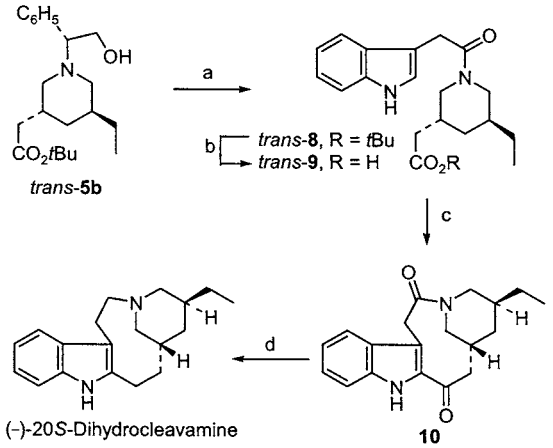
(3) (a) For reviews, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569 and ref 1b. See also: (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc*. **1998**, *120*, 7429−7438. (c) Ando, K.; Green, N. S.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc*. **1999**, *121*, 5334−5335. (d) Bailey, J. H.; Byfield, A. T. J.; Davis, P. J.; Foster, A. C.; Leech, M.; Moloney, M. G.; Müller, M.; Prout, C. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1977−1982. (e) Hughes, R. C.; Dvorak, C. A.; Meyers, A. I. *J. Org. Chem*. **2001**, *66*, 5545−5551. See also ref 1e.

(4) (a) Quirin, F.; Debray, M.-M.; Sigaut, C.; Thepenier, P.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1975**, *14*, 812−813. (b) van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737−748.

the closure of the nine-membered ring taking advantage of the acetate moiety at the piperidine 3-position, and the adjustment of the oxidation level of the resulting tetracyclic keto lactam.

In the event, debenzylation of *trans*-**5b** by hydrogenolysis with $Pd(OH)_2$ as the catalyst in the presence of the mixed anhydride of indole-3-acetic acid and pivalic acid[5] gave (83%) *N*-(indolylacetyl)piperidine *trans*-**8**, which was converted (95%) to the piperidineacetic acid *trans*-**9** by treatment with TFA (Scheme 3). The key cyclization of the acetate

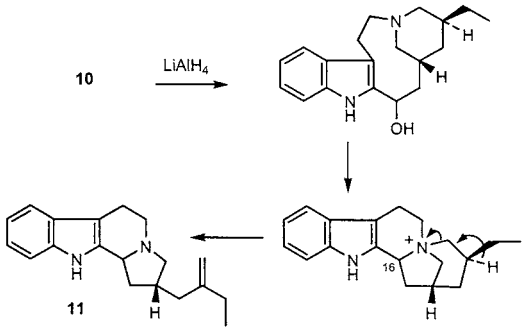
Scheme 3. First Enantioselective Total Synthesis of the Alkaloid (−)-20*S*-Dihydrocleavamine[a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$, then mixed anhydride of indole-3-acetic acid and pivalic acid, 83%; (b) TFA, rt, 15 min, 95%, (c) PPA, 90 °C, 30 min, 64%; (d) LAH, dioxane, rfx, 18 h, 34%.

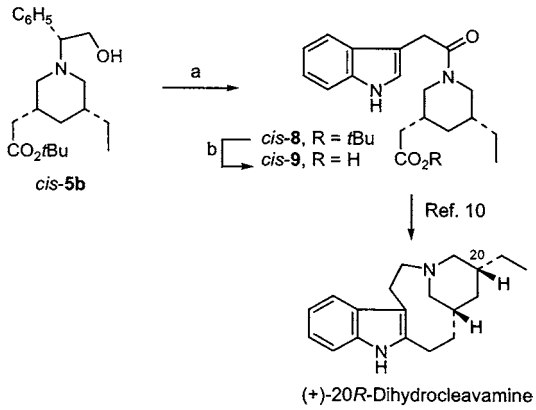
moiety upon the indole 2-position took place in 64% yield by heating *trans*-**9** in the presence of PPA.[6] The resulting tetracyclic keto lactam **10** was then reduced with $LiAlH_4$ to give (−)-20*S*-dihydrocleavamine (34% yield), $[\alpha]^{22}_D$ −97 (*c* 0.9, $CHCl_3$) {$[\alpha]_D$ −87 ($CHCl_3$)[4a]}, thus completing the first enantioselective synthesis[7] of this natural product. The ^{13}C NMR data of our synthetic (−)-20*S*-dihydrocleavamine were in complete agreement with those previously reported.[4b,8] Interestingly, indoloindolizidine **11** was also isolated as a byproduct (∼15% yield) from the above reduction. Its formation can be accounted for by considering a transannular cyclization followed by a ring opening of the resulting quaternary ammonium salt by a Hofmann-type elimination, as depicted in Scheme 4.[9]

Scheme 4



The synthesis of (+)-20*R*-dihydrocleavamine was accomplished simply by following a similar reaction sequence starting from a *cis*-5-ethyl-3-piperidineacetate derivative. Thus, exchange of the chiral inductor on the piperidine nitrogen of *cis*-**5b** for an indolylacetyl substituent as in the above trans series followed by treatment of the resulting amido ester *cis*-**8** with TFA gave acid *cis*-**9** (Scheme 5).

Scheme 5. Enantioselective Formal Synthesis of the Alkaloid (+)-20*R*-Dihydrocleavamine[a]



[a] Reagents and conditions: (a) H_2, $Pd(OH)_2$, then mixed anhydride of indole-3-acetic acid and pivalic acid, 80%; (b) TFA, rt, 5 min., 95%.

Taking into account that *cis*-**9** has previously been converted to (+)-20*R*-dihydrocleavamine,[10] the above synthesis constitutes an enantioselective formal total synthesis of this natural product.[11]

The above results expand the potential of chiral nonracemic phenylglycinol-derived bicyclic lactams as building blocks for the enantioselective construction of piperidine-

(5) Szántay, C.; Bölcskei, H.; Gács-Baitz, E.; Keve, T. *Tetrahedron* **1990**, *46*, 1687−1710.

(6) For a discussion of the mechanism and the yield of related cyclizations, see: (a) Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342−2346. (b) See also: Imanishi, T.; Nakai, A.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1981**, *29*, 901−903.

(7) For syntheses of dihydrocleavamines in the racemic series, see: (a) Kutney, J. P.; Cretney, W. J.; Le Quesne, P.; McKague, B.; Piers, E. *J. Am. Chem. Soc.* **1970**, *92*, 1712−1726. (b) Takano, S.; Hirama, M.; Araki, T.; Ogasawara, K. *J. Am. Chem. Soc.* **1976**, *98*, 7084−7085. (c) Atta-ur-Rahman; Beisler, J. A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063−1070. (d) Takano, S.; Yonaga, M.; Yamada, S.; Hatake-Yama, S.; Ogasawara, K. *Heterocycles* **1981**, *15*, 309−316. See also: (e) Kutney, J. P.; Brown, R. T.; Piers, E. *Can. J. Chem.* **1965**, *43*, 1545−1552.

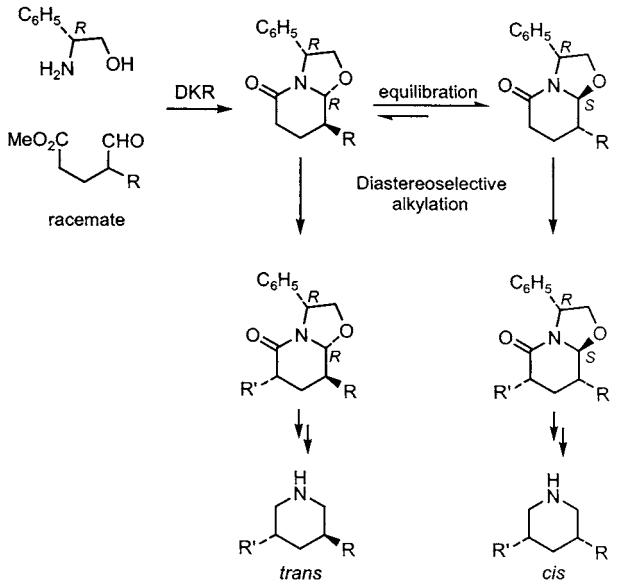
(8) Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.; Zsadon, B. *Helv. Chim. Acta* **1976**, *59*, 2711−2723.

(9) For the formation of similar allylindoloindolizidines in the $LiAlH_4$ reduction of related tetracyclic nine-membered 16-oxolactams, see: (a) Narisada, M.; Watanabe, F.; Nagata, W. *Tetrahedron Lett.* **1971**, *39*, 3681−3684. (b) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.* **1973**, *95*, 7458−7463. (c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1979**, *101*, 6414−6420.

(10) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron Lett.* **2000**, *41*, 3489−3492.

(11) For another enantioselective synthesis, see: Kanada, R. M.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7311−7313.

Scheme 6. Stereodivergent Route to Enantiopure *cis*- and *trans*-3,5-Disubstituted Piperidines



containing natural and nonnatural products.[1] Most of these syntheses are based on the successive stereocontrolled formation of C−C bonds at the carbon atom positions of the nitrogen heterocycle. Advantageously, in the procedure described herein, the first stereocenter is generated, with control of its absolute configuration, during the cyclocondensation step. The subsequent diastereoselective alkylation of the resulting γ-substituted δ-lactams provides a simple and practical route for the generation of either cis or trans enantiopure 3,5-disubstituted piperidines (Scheme 6). Taking into account that (*S*)-phenylglycinol is also commercially available, the procedure can provide access to *cis*- and *trans*-3,5-disubstituted piperidines in both enantiomeric series.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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