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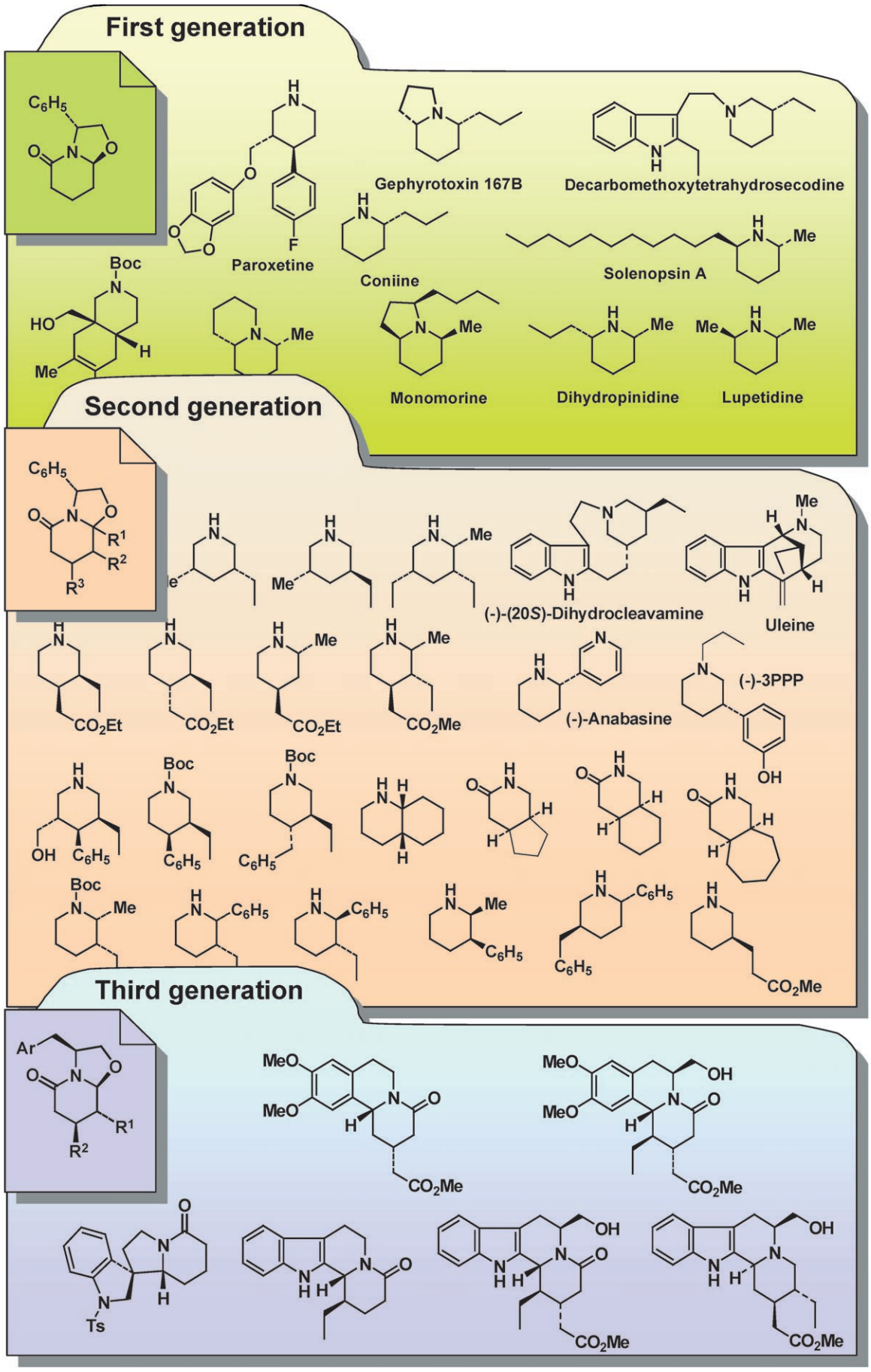
THE EVOLUTION OF A STRATEGY



Chiral Oxazolopiperidone Lactams: Versatile Intermediates for the Enantioselective Synthesis of Piperidine-Containing Natural Products

Carmen Escolano, Mercedes Amat, and Joan Bosch*[a]

Abstract: Phenylglycinol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds. These lactams are readily available in both enantiomeric series by cyclocondensation of the chiral amino alcohol with a δ-oxo acid derivative and allow the substituents to be introduced at the different ring positions in a regio- and stereocontrolled manner, providing access to enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern, and also quinolizidines, indolizidines, perhydroquinolines, hydroisoquinolines, as well as complex indole alkaloids. Of particular interest are cyclocondensation reactions with racemic or prochiral δ-oxo (di)acid derivatives in processes involving dynamic kinetic resolution and/or differentiation of enantiotopic or diastereotopic ester groups, as they directly lead to lactams that already incorporate the carbon substituents on the heterocyclic ring. The use of (*S*)-3,4-dimethoxyphenylalaninol or (*S*)-tryptophanol in the above cyclocondensation reactions expands the potential and the scope of the methodology, providing a straightforward route to enantiopure benzo[*a*]- and indolo[2,3-*a*]quinolizidines.

Keywords: alkaloids · cyclocondensation · lactams · nitrogen heterocycles · phenylglycinol

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Introduction

The development of general methods for the enantioselective synthesis of natural products has long constituted a challenging goal for synthetic organic chemists. Since the piperidine ring is a common moiety in many biologically active natural products and therapeutic agents, considerable attention has been focused on the development of general methods and strategies for the enantioselective synthesis of piperidine derivatives.[1] The piperidine ring is found in simple diversely substituted piperidine alkaloids, in bicyclic indolizidine, perhydroquinoline, and quinolizidine alkaloids, as well as in many of the most complex polycyclic alkaloids. These nitrogen derivatives occur not only in plants but also in insects and amphibians. The structural diversity of these alkaloids, with a wide variety of substitution patterns, makes them a good vehicle for the testing of synthetic methodology, both in the racemic series and in enantiopure form. On the other hand, piperidine-containing entities constitute important targets for pharmaceutical research, with thousands of them mentioned as drug candidates in clinical and preclinical studies.

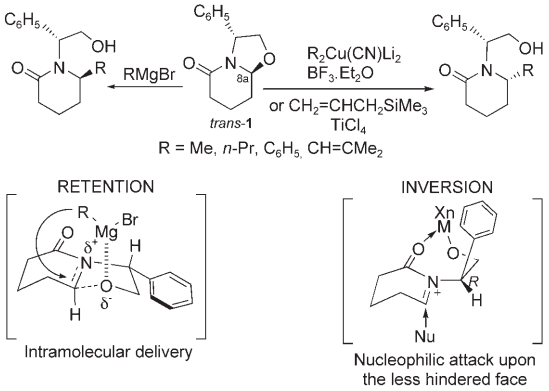
Discussion

First-generation oxazolopiperidone lactams: Chiral, nonracemic amino alcohol-derived bicyclic lactams were initially developed by Meyers, who extensively employed these synthons for the synthesis of enantiopure carbocycles and carboxylic acids bearing a quaternary stereocenter and also nitrogen-containing heterocycles.[2] The aim of this concept article is to highlight the potential of chiral oxazolopiperidone lactams as exceptionally versatile building blocks for the enantioselective synthesis of piperidine-containing derivatives.[3] These lactams are easily accessible by cyclocondensation reaction of δ-oxo acid derivatives with chiral nonracemic amino alcohols. In particular, simple phenylglycinol-derived lactams *cis*-**1** (H_3-H_{8a} *cis*) and *trans*-**1** (H_3-H_{8a} *trans*) allow the stereocontrolled formation of C–C bonds at the

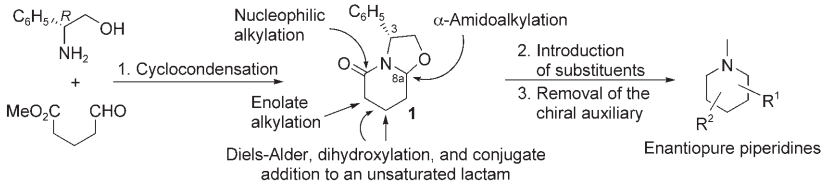
different positions of the nitrogen heterocycle, as outlined in Scheme 1, ultimately leading to diversely substituted enantiopure piperidines.

The introduction of substituents at the piperidine α-position is efficiently accomplished by asymmetric α-amidoalkylation, either with retention of the configuration at the C-8a methine carbon atom when using Grignard reagents[4] or with inversion when using indole,[5] TMSCN, allyltrimethylsilane, or higher order cyanocuprates in the presence of a Lewis acid (Scheme 2).[6,7]

The alkylpiperidones resulting from the above amidoalkylation reactions are synthetic precursors not only of enantiopure 2-substituted piperidines, but also of both *cis*- and *trans*-2,6-dialkylpiperidines.[6] Thus, partial reduction of the lactam carbonyl group, followed by nucleophilic alkylation



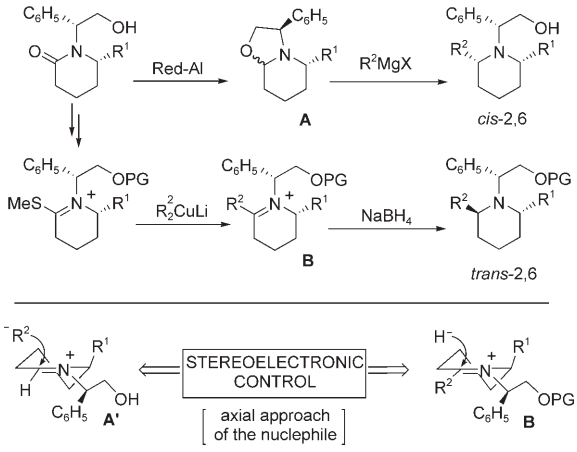
Scheme 2. Stereocontrolled α-amidoalkylation reactions. Synthesis of enantiopure 2-substituted piperidines.



Scheme 1. First-generation oxazolopiperidone lactams.

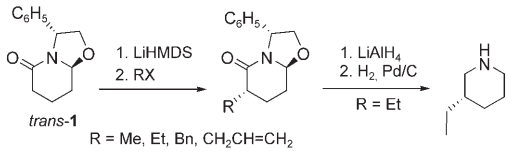
of the resulting masked iminium cation **A** with a Grignard reagent leads to enantiopure *cis*-2,6-dialkylpiperidines (Scheme 3). Reversal of this sequence, that is, nucleophilic alkylation with an organometallic reagent and then hydride reduction of the resulting iminium species **B** affords enantiopure *trans*-2,6-dialkylpiperidines. In this case, the iminium cation **B** is generated via a thioimidate salt. The stereochemical outcome of these processes is a consequence of the stereoelectronically preferred axial approach of the nucleophile to the iminium intermediates **A′** or **B**. By using a Grignard reagent bearing a protected aldehyde or ketone group, this methodology can be extended to the synthesis of diversely substituted enantiopure indolizidines and quinolizidines, the closure of the second ring occurring by reductive amination during the removal of the phenylethanol moiety by catalytic hydrogenation.

Abstract in Spanish: *Las lactamas con estructura de oxazolopiperidona derivadas del fenilglicinol constituyen intermedios excepcionalmente versátiles para la construcción enantioselectiva de productos naturales y compuestos bioactivos estructuralmente diversos que contienen una unidad de piperidina. Estas lactamas son fácilmente accesibles en ambas series enantioméricas mediante ciclocondensación del amino alcohol quiral con un derivado de δ-oxo ácido y permiten la introducción regio y estereocontrolada de sustituyentes en las diversas posiciones del anillo para conducir a piperidinas polisustituidas enantiopuras con prácticamente cualquier tipo de sustitución, así como a quinolizidinas, indolizidinas, perhidroquinolinas, hidroisoquinolinas y alcaloides indólicos complejos. Las reacciones de ciclocondensación con derivados de δ-oxo (di)ácido racémicos o proquirales, en procesos que implican una resolución cinética dinámica y/o la diferenciación de grupos ester enantiotópicos o diastereotópicos, son de particular interés ya que proporcionan directamente lactamas que ya incorporan los sustituyentes carbonados en el anillo heterocíclico. La utilización de (S)-3,4-dimetoxifenilalaninol o (S)-triptofanol en las anteriores reacciones de ciclocondensación amplía el potencial y el alcance de la metodología, y establece una ruta directa hacia benzo[a]- e indolo[2,3-a]quinolizidinas enantiopuras.*



Scheme 3. Stereocontrolled access to enantiopure *cis*- and *trans*-2,6-dialkylpiperidines.

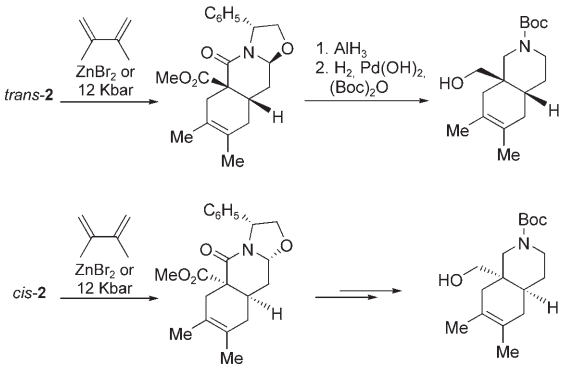
The versatility of bicyclic lactam *trans*-**1** is further illustrated by the stereoselective alkylations shown in Scheme 4, which open the way for the preparation of enantiopure 3-alkylpiperidines.[8,9]



Scheme 4. Stereoselective enolate alkylations. Enantiopure 3-alkylpiperidines.

The stereoselective introduction of substituents at the piperidine 4-position involves a conjugate addition reaction from unsaturated lactams derived from **1**. In particular, the addition of lower order alkyl- or arylcyanocuprates requires the presence of an additional activating substituent. Interestingly, unsaturated lactams *trans*-**2** and *cis*-**2** undergo conjugate addition with opposite facial selectivity, providing diastereoisomeric-substituted oxazolopiperidones, which can be converted to the corresponding enantiomeric *trans*-3,4-disubstituted piperidines.[10] Taking into account that the starting lactams are easily accessible from the same enantiomer of phenylglycinol, the example outlined in Scheme 5 represents an enantiodivergent synthesis of the two enantiomers of the antidepressant drug paroxetine. The observed stereoselectivities of the above conjugate additions can be rationalized by considering a stereocontrolled kinetic axial attack of the nucleophile.

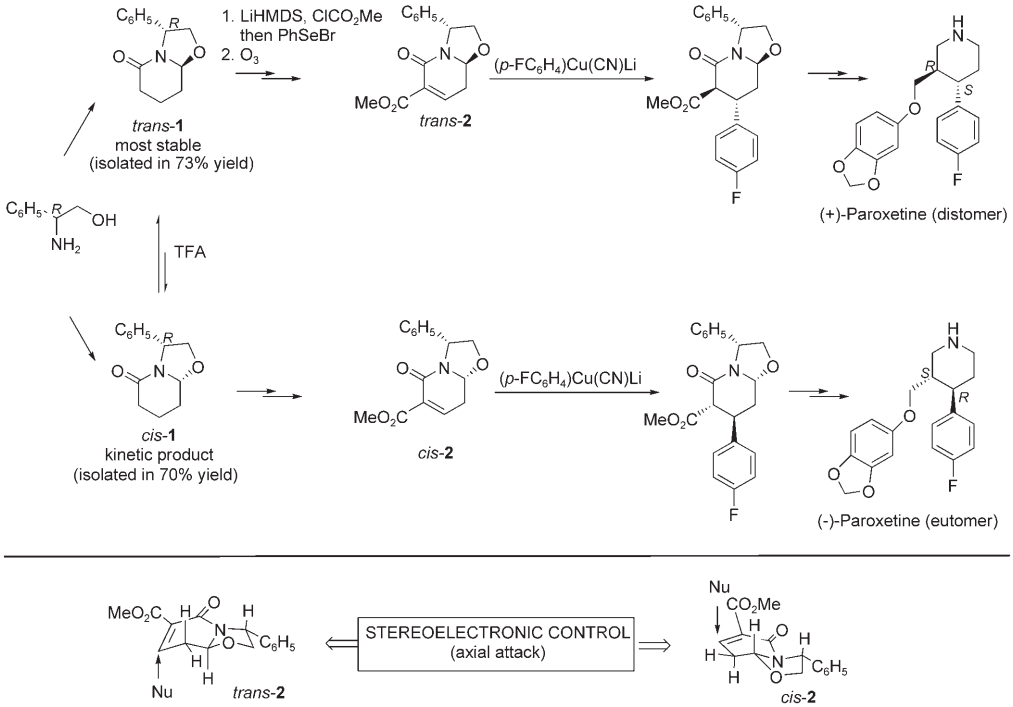
Similarly, unsaturated lactams *trans*-**2** and *cis*-**2** undergo Diels–Alder cycloadditions with opposite facial selectivity as a consequence of the diene approaching the bicyclic lactams by the convex face, leading to enantiopure diastereoisomeric adducts (Scheme 6). This constitutes the key step of an enantiodivergent synthesis of *cis*-hydroisoquinolines.[11]



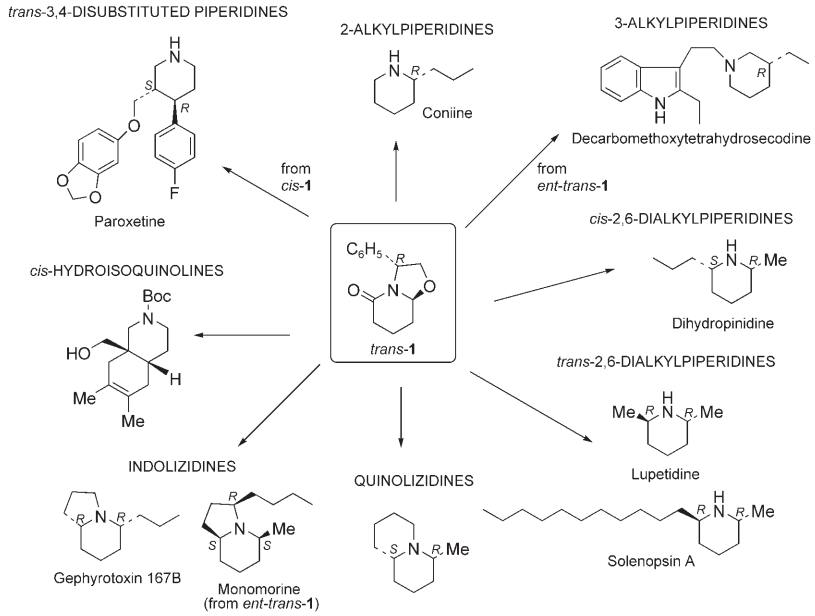
Scheme 6. Stereoselective Diels–Alder reactions from unsaturated lactams.

The most important synthetic goals achieved from phenylglycinol-derived lactams **1** are depicted in Scheme 7. It illustrates the usefulness of these simple lactams in the enantioselective construction of structurally diverse piperidine-containing natural products and therapeutically important drugs. As both enantiomers of phenylglycinol are commercially available, the approach depicted in Scheme 1 provides easy access to enantiopure piperidine derivatives in both enantiomeric series.

Second-generation oxazolopiperidone lactams: Although lactams **1** give excellent results from the stereoselectivity and diversity points of view, providing access to enantiopure piperidines with a wide variety of substitution patterns, a drawback is that the substituents have to be introduced step-by-step.

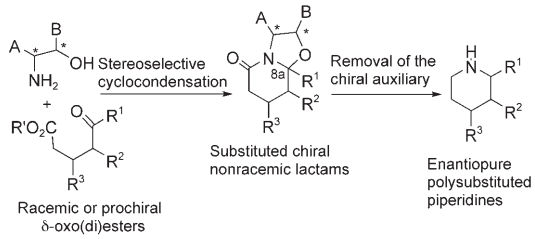


Scheme 5. Enantiodivergent synthesis of *trans*-3,4-disubstituted piperidines.



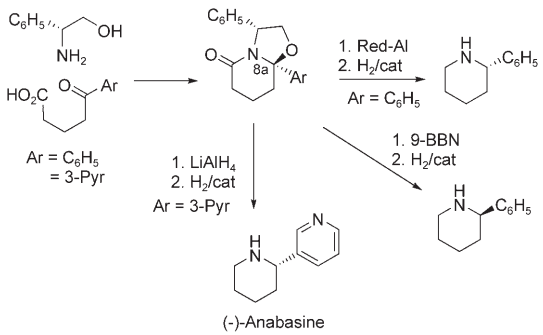
Scheme 7. Enantioselective synthesis of substituted piperidines.

A more straightforward procedure for the synthesis of enantiopure polysubstituted piperidines, involving the direct generation of chiral nonracemic oxazolopiperidone lactams that already incorporate carbon substituents on the heterocyclic ring, is outlined in Scheme 8.



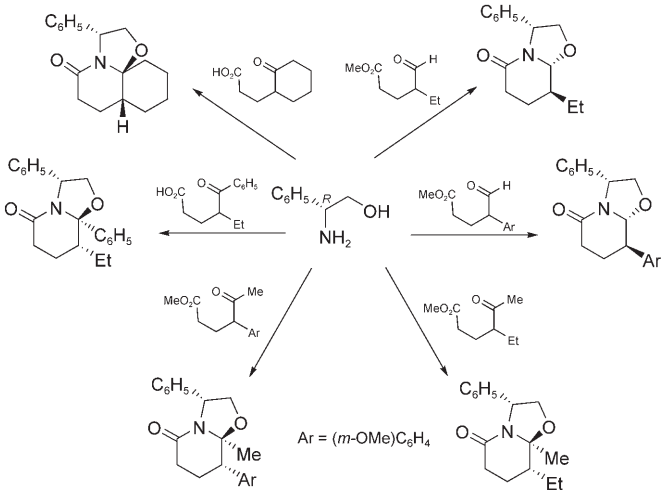
Scheme 8. Second-generation oxazolopiperidone lactams.

Scheme 9 illustrates the use of this approach for the enantiodivergent synthesis of 2-arylpiperidines, including the tobacco alkaloid anabasine. A crucial step is the stereocontrolled reductive opening of the oxazolidine ring, which can be made to occur either with retention or inversion of the configuration at C-8a by choosing the appropriate reductant.[12]



Scheme 9. Enantiodivergent synthesis of 2-arylpiperidines.

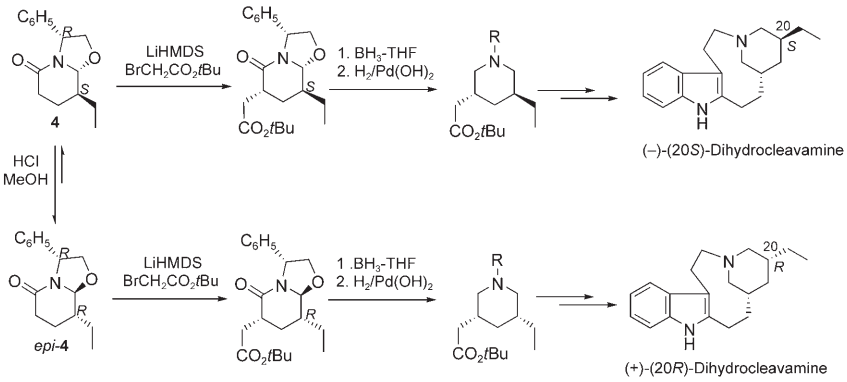
Even more interesting are the cyclocondensation reactions of *R*-phenylglycinol with racemic γ-alkyl (or aryl)-δ-oxo acid derivatives, which incorporate a chirally labile stereocenter capable of undergoing in situ racemization or epimerization during the reaction. These cyclocondensations take place in good chemical yield (60–80%) and stereoselectivity, leading to one of the four possible enantiopure stereoisomeric lactams as the major product (d.r., 4:1), in a process involving a dynamic kinetic resolution (DKR) of the racemic substrate (Scheme 10).[13–15] Although such DKR processes represent a useful tool for preparing enantiopure chiral compounds, they have rarely been used in synthetic sequences due to their reliance on substrates with particular structural requirements.[16]



Scheme 10. Cyclocondensation reactions involving dynamic kinetic resolution.

A subsequent reductive removal of the chiral auxiliary ($LiAlH_4$, AlH_3, Red-Al, BH_3, or 9-BBN, then catalytic hydrogenation)[17] provides an efficient route for the synthesis of enantiopure 3-alkyl-, 3-aryl-, *cis*-2,3-dialkyl-, *cis*-2-alkyl-3-aryl-, and *cis*- and *trans*-2-aryl-3-alkylpiperidines.[13,14] It is worth noting that this methodology allows the preparation of 3-aryl piperidines, for instance the antipsychotic drug pre-

clamol [(−)-3PPP], which are otherwise difficult to access. Alternatively, the above substituted lactams can be further elaborated before the removal of the chiral auxiliary to stereoselectively introduce additional substitutents. Thus, alkylation of the lactam enolate allows the stereoselective introduction of alkyl, allyl, and benzyl substituents at the β-position of the piperidine ring, leading to polysubstituted lactams with a variety of substitution patterns, which can be converted to enantiopure 2,5-, 3,5-, and 2,3,5-substituted piperidines.[18] To illustrate the utility of this approach, Scheme 11 outlines the synthesis of the indole alkaloids (20*S*)- and (20*R*)-dihydrocleavamine by alkylation of lactam **4** or, after equilibration, the more stable epimer *epi*-**4**, respectively.[8]

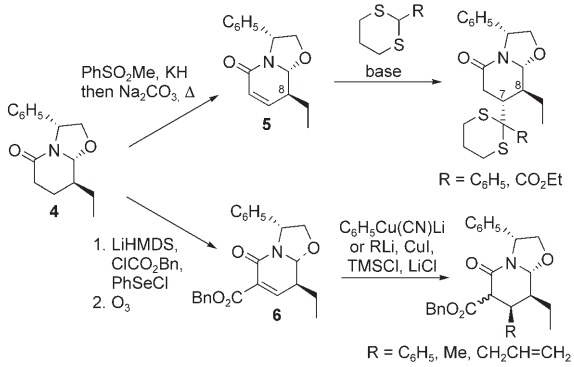


Scheme 11. Enantioselective diastereodivergent synthesis of dihydrocleavamines.

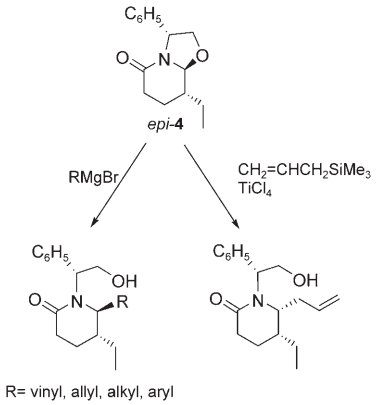
Similarly, α-amidoalkylation reactions from *epi*-**4**, either with inversion or retention of the configuration at C-8a, open stereoselective routes to *cis*- and *trans*-2,3-disubstituted piperidines,[19] respectively (Scheme 12).

On the other hand, the stereocontrolled formation of a C−C bond at the piperidine 4-position can be accomplished either under thermodynamic control from simple unsaturated lactams, such as **5**, to give 7,8-*trans* isomers, or under kinetic control from lactams bearing an additional activating ester substituent, such as **6**, to give 7,8-*cis* isomers[20] (Scheme 13). Factors that govern the stereoselectivity of the process include the nature of the nucleophile, the configuration of the C-8a stereocenter, and the presence or absence of a substituent at C-8. Using appropriate unsaturated organocuprates, a highly stereoselective conjugate addition to lactam **7**, followed by a ring-closing olefin metathesis taking advantage of the C_8 allyl substituent, constitute the key steps of a straightforward synthesis of enantiopure *cis*-perhydroisoquinolin-3-one and its lower and higher homologues bearing a five- and seven-membered carbocyclic ring, respectively[21] (Scheme 14).

The usefulness of unsaturated lactam **5** in the synthesis of natural products is exemplified with the enantioselective synthesis of uleine alkaloids outlined in Scheme 15. The key steps are a stereoselective, kinetically controlled conjugate addition of an indolyldithiane dianion leading to a 7,8-*cis* lactam and an intramolecular α-amidoalkylation on the indole 3-position. Interestingly, starting from the enantiomer of **5**, the stereoselective conjugate addition of an indoleacetate enolate to give the thermodynamically more stable *trans* isomer, followed by an intramolecular α-amidoalkylation, provides a synthetic entry to the 20-epiuleine series[20b] (Scheme 16).

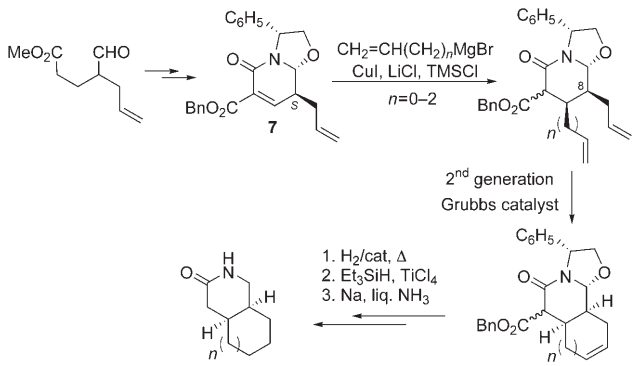


Scheme 13. Stereoselective conjugate additions to C_8-substituted unsaturated lactams.

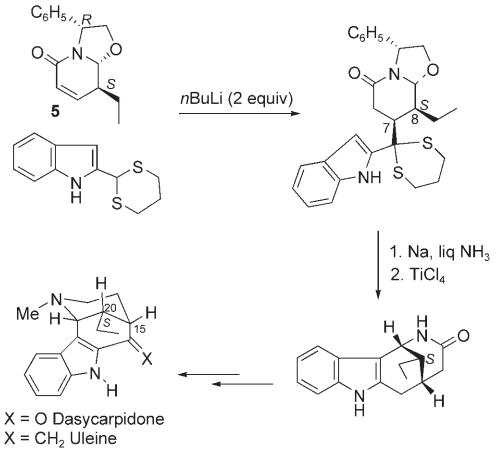


Scheme 12. Synthesis of enantiopure *cis*- and *trans*-2,3-disubstituted piperidines.

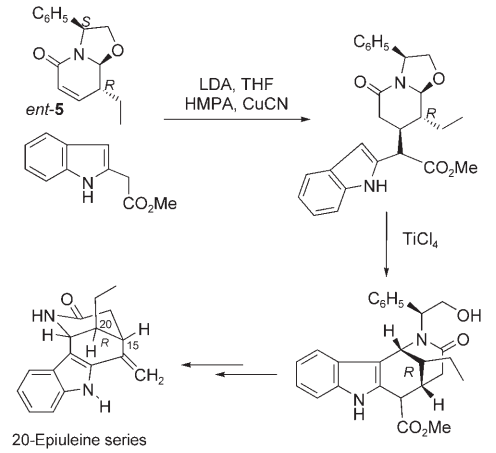
The scope of the methodology for the enantioselective synthesis of piperidine derivatives depicted in Scheme 8 is significantly extended by the use of prochiral or racemic δ-oxo diesters in the cyclocondensation reactions. Starting from prochiral δ-oxo diesters, such reactions involve the desymmetrization[22] of the two enantiotopic ester chains, whereas from racemic derivatives a tandem DKR-diastereotopic differentiation occurs, as shown in Scheme 17.[13] As



Scheme 14. A general synthetic entry to enantiopure *cis*-2-azabicyclo-[4.n.0]alkan-3-ones.

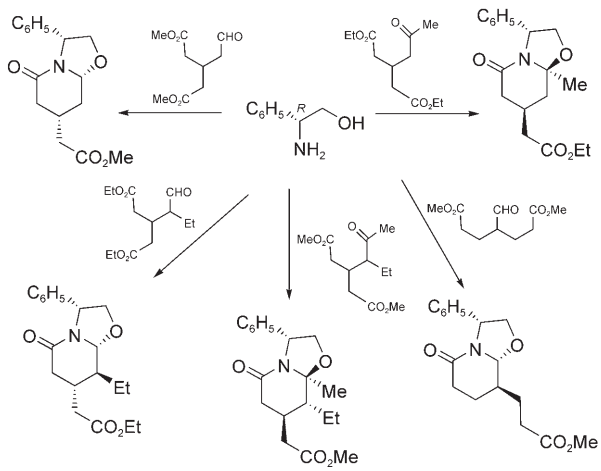


Scheme 15. Enantioselective synthesis of indole alkaloids of the uleine group.



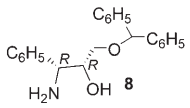
Scheme 16. Enantioselective entry to the 20-epiuleine series.

many as three stereogenic centers can be generated in high chemical yield (70–95%) and excellent stereoselectivity (d.r., 4–9:1) in a single synthetic step. Remarkably, the stereoselectivity of cyclocondensation reactions with racemic

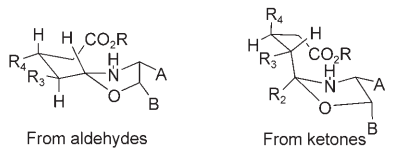


Scheme 17. Cyclocondensation reactions involving desymmetrization of enantiotopic ester chains or tandem DKR differentiation of diastereotopic ester chains.

or prochiral aldehyde(di)esters is even higher (d.r., 9–20:1) when using the more complex amino alcohol **8**.



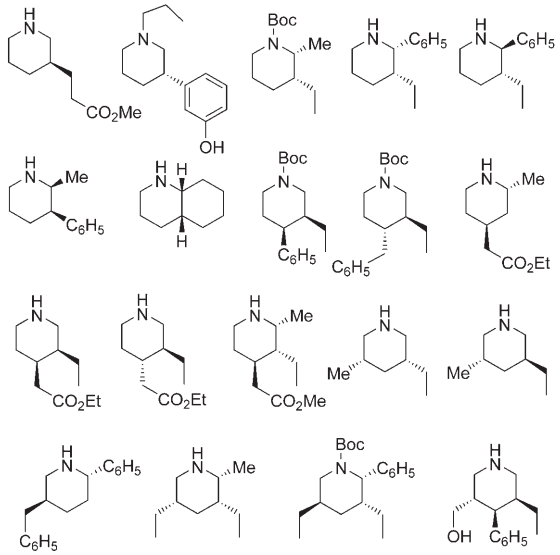
The equilibrium oxazolidine⇄imine⇄enamine and the irreversible lactamization from the diastereoisomer that allows a less hindered approach of the ester group to the nitrogen atom, via a transition state in which all the substituents in the incipient chair-like six-membered lactam are equatorial (Scheme 18), account for the stereoselectivities observed in all the above cyclocondensation reactions.



Scheme 18. Stereochemical outcome of cyclocondensation reactions.

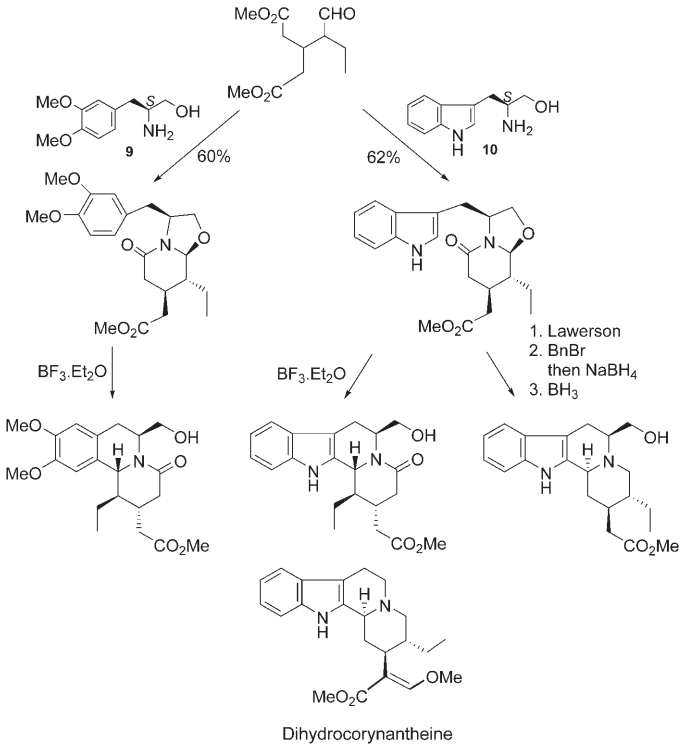
In summary, second-generation oxazolopiperidone lactams are valuable building blocks for the synthesis of enantiopure piperidines bearing virtually any type of substitution pattern. Scheme 19 provides representative examples of diversely substituted enantiopure piperidines prepared from these lactams.

Third-generation oxazolopiperidone lactams: The synthetic utility of oxazolopiperidone lactams for the enantioselective construction of complex piperidine-containing derivatives is significantly expanded when, in the above cyclocondensation reactions involving prochiral or racemic δ-oxo (di)esters, (*S*)-3,4-dimethoxyphenylalaninol (**9**) or (*S*)-tryptophanol

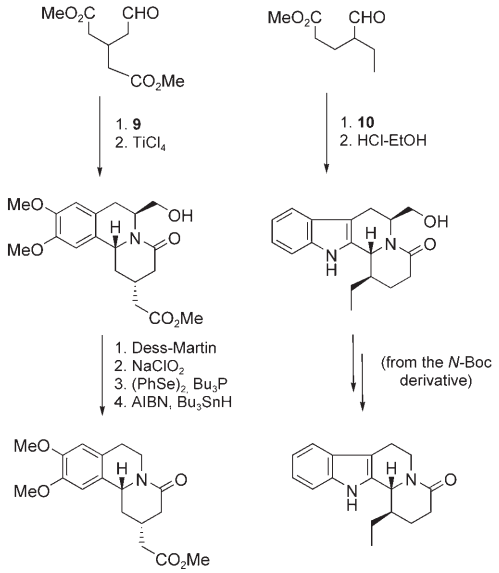


Scheme 19. Diversely substituted enantiopure piperidines.

(**10**) are used as the amino alcohol partners. These amino alcohols not only constitute the source of chirality, acting as chiral inductors, but are also used to assemble the final target polycyclic products by intramolecular α-amidoalkylation upon the aromatic ring. Scheme 20 illustrates the effectiveness of this methodology in the straightforward construction of substituted enantiopure benzo[*a*]- and indolo-[2,3-*a*]quinolizidines.[23,24] Interestingly, cyclization of a thioamide, via a thioimidate salt, provides access to regioisomeric indoloquinolizidines with the connectivity and stereochemistry required for the synthesis of natural products, for instance dihydrocorynantheine. The removal of the hydroxymethyl substitutent can be performed by a radical decarboxylation of the corresponding carboxylic acid,[25] as outlined in Scheme 21.

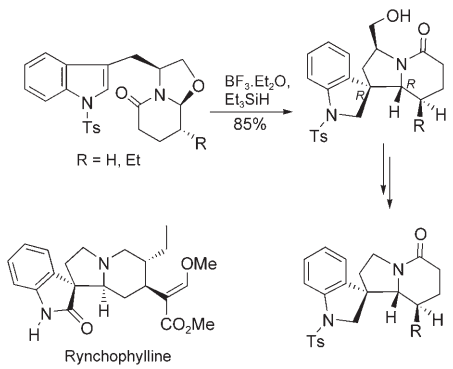


Scheme 20. Third-generation oxazolopiperidone lactams. Enantioselective synthesis of benzo[*a*]- and indolo[2,3-*a*]quinolizidines.



Scheme 21. Removal of the hydroxymethyl substituent.

The promising potential of the above tryptophanol-derived lactams is further illustrated by the spirocyclizations depicted in Scheme 22, which could be applied to the synthesis of oxindole alkaloids.[26] The deactivating tosyl substituent dramatically modifies the regioselectivity of the cyclization, leading to a spiroindoline.



Scheme 22. Towards oxindole alkaloids.

In conclusion, amino alcohol derived oxazolopiperidone lactams have proven to be extremely useful building blocks that allow the preparation of a wide range of enantiopure piperidine derivatives, including simple piperidine alkaloids, more complex piperidine-containing indole and benzo[*a*]qui-

nolizidine alkaloids, as well as synthetic products of biological interest.

Simple phenylglycinol-derived oxazolopiperidone lactams are readily available in both enantiomeric series by a cyclocondensation reaction and allow the substituents to be introduced at the different ring positions in a regio and stereocontrolled manner taking advantage of the functionalization and conformational rigidity of the bicyclic lactam system. A major improvement in the methodology, ultimately leading to polysubstituted piperidines with a wide variety of substitution patterns, consists in the direct preparation of substituted oxazolopiperidone lactams by cyclocondensation reactions involving dynamic kinetic resolution and/or desymmetrization processes. Finally, the use of (*S*)-3,4-dimethoxyphenylalaninol or (*S*)-tryptophanol in these reactions provides straightforward access to enantiopure benzo[*a*]- and indolo-[2,3-*a*]quinolizidine derivatives. These amino alcohols are not only used as chiral inductors but also to construct the final polycyclic targets.

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