NPC Natural Product Communications

2010
Vol. 5
No. 0
1 - 3

Enantioselective Synthesis of Alkaloids from Phenylglycinol-Derived Lactams

Mercedes Amat,* Núria Llor, Rosa Griera, Maria Pérez, Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, Av. Joan XXIII s/n, 08028 Barcelona (Spain)

amat@ub.edu; joanbosch@ub.edu

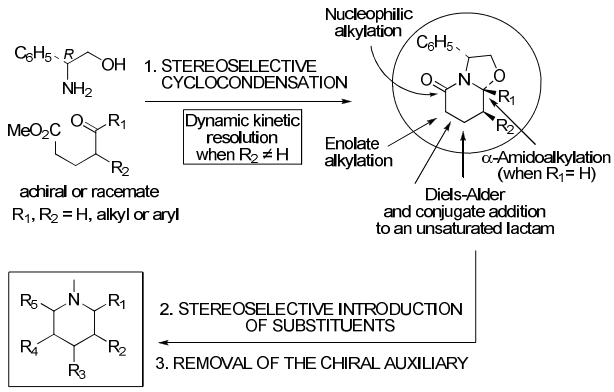
Received: January XX, 2010; Accepted: XX, 2010

This review is focused on recent synthetic achievements and ongoing work from our laboratory on the use of phenylglycinol-derived oxazolopiperidone lactams as starting materials for the enantioselective synthesis of piperidine-containing alkaloids: madangamines, 2,5-disubstituted decahydroquinoline and 1-substituted tetrahydroisoquinoline alkaloids, the indole alkaloids 20*S*- and 20*R*-dihydrocleavamine and quebrachamine, and indole alkaloids of the uleine and silicine groups.

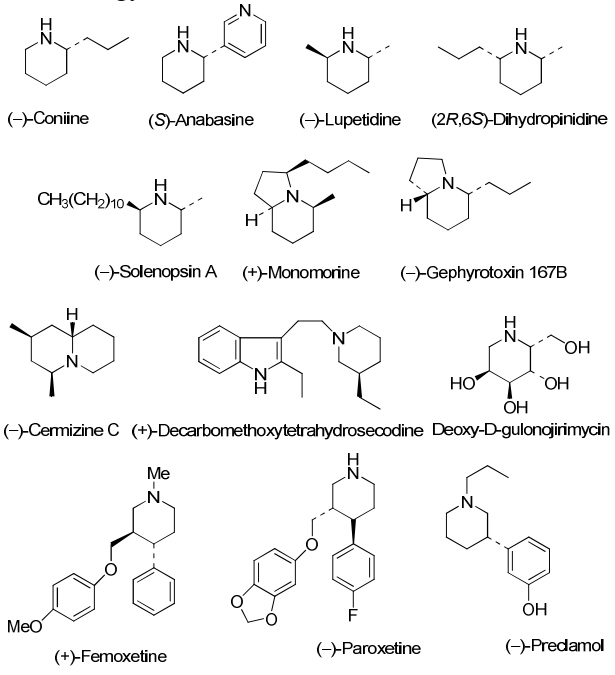
Keywords: alkaloids, piperidine, indole, lactams, total synthesis, phenylglycinol, asymmetric.

1. Introduction

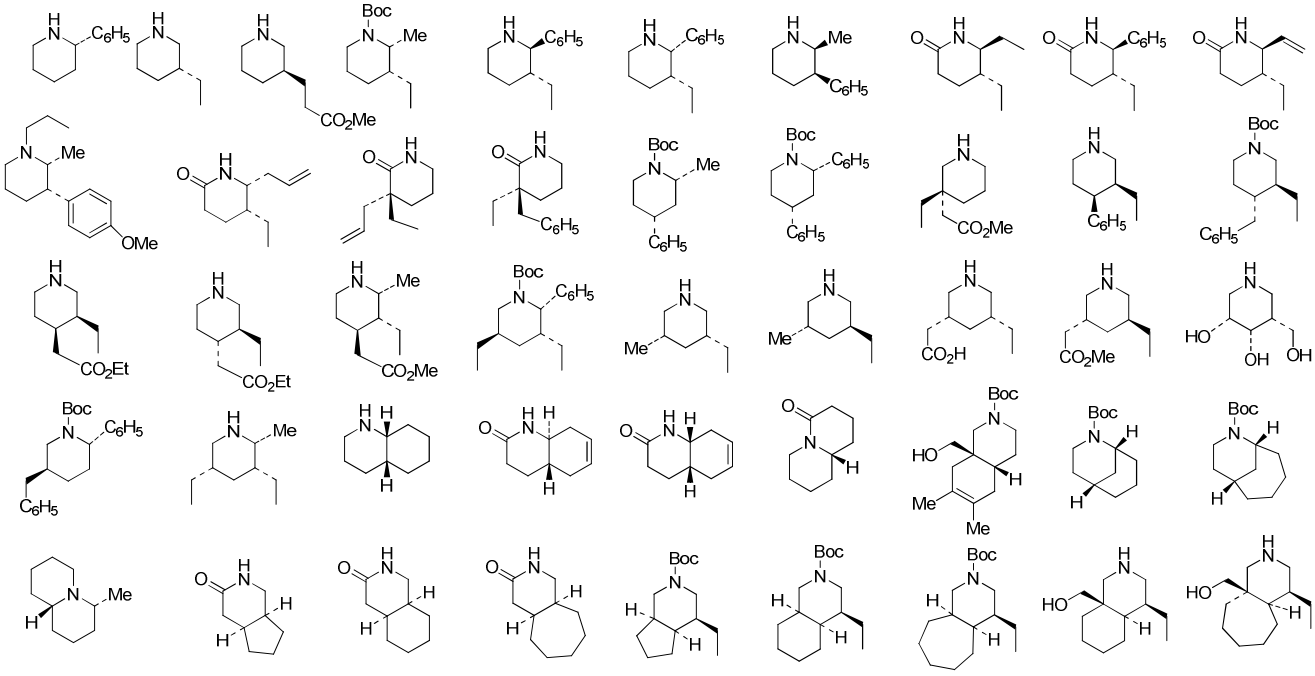
Phenylglycinol-derived oxazolopiperidone lactams have proven to be exceptionally useful building blocks for the enantioselective construction of structurally diverse piperidine-containing natural products and bioactive compounds. These conceptually simple enantiopure molecules are easily accessible by a cyclocondensation reaction between a δ-ceto acid derivative and phenylglycinol,[1] and due to their tactically versatile functionality and conformational rigidity allow the regio- and stereocontrolled introduction of substituents at the different positions of the piperidine ring. A subsequent reductive removal of the chiral auxiliary taking advantage of the benzylic character of the exocyclic C-N bond provides access to enantiopure piperidines bearing virtually any type of substitution pattern (Scheme 1). In fact, in this process phenylglycinol acts as a chiral latent form of ammonia. As both enantiomers of phenylglycinol are commercially available, both enantiomers of a target compound are accessible through the above methodology.



Scheme 1. Synthetic strategy.



Scheme 2. Alkaloids and bioactive compounds prepared from phenylglycinol-derived oxazolopiperidone lactams.



Scheme 3. Enantiopure piperidine-containing derivatives prepared from phenylglycinol-derived oxazolopiperidone lactams.

Chiral bicyclic lactams were originally developed by Meyers, who extensively employed these templates for the synthesis of enantiopure natural and unnatural carbocycles containing quaternary carbon centers[2] and also nitrogen heterocycles (pyrrolidines, piperidines, and tetrahydroisoquino-lines).[3]

Some enantiopure piperidine, indolizidine, and quinolizidine alkaloids, as well as bioactive piperidine derivatives synthesized in our laboratory following the general synthetic strategy outlined in Scheme 1 are depicted in Scheme 2.

In fact, phenylglycinol-derived oxazolopiperidone lactams are versatile scaffolds that allow the construction of enantiopure piperidine libraries. Scheme 3 provides representative examples of diversely substituted enantiopure piperidine-containing derivatives we have prepared from these lactams.

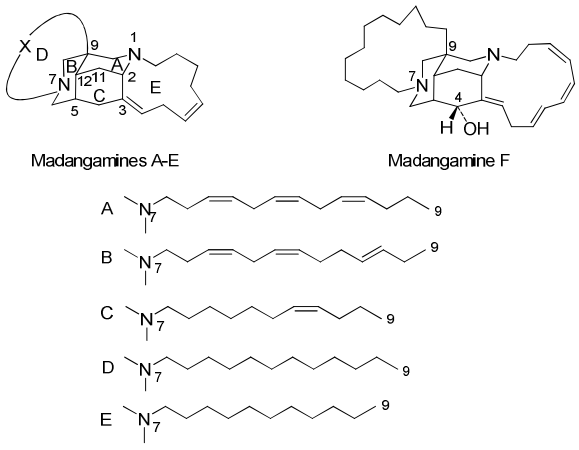
This previous work, surveyed in a previous review published in 2006,[4] has allowed (us?) to (fully?, systematically?) develop the methodologic aspects and sentar las bases for the comprehension (understanding) of the factors governing the facial stereoselectivity in the introduction of substituents on oxazolopiperidone lactams, thus allowing the prediction and the control of the stereochemical outcome of the reactions.

The aim of this review is to highlight the potential of phenylglycinol-derived oxazolopiperidone lactams in the total synthesis of complex alkaloids belonging to a variety of structural types, as well as to update recent synthetic advancements (achievements, developments) and (to disclose?) ongoing work from our laboratory.

2. Towards the First Synthesis of Madangamine Alkaloids

Madangamines are a small group of complex pentacyclic alkaloids isolated from marine sponges of the order Haplosclerida,[5] biogenetically derived from partially reduced bis-3-alkylpyridine macrocycles, some of them showing cytotoxic activity (Scheme 4). Structurally, these compounds possess a diazatricyclic core (ABC rings), unprecedented among natural products, and two carbon bridges connecting N-7 to C-9 (D ring) and N-1 to C-3 (E ring). The absolute configuration of madangamines remains unknown and no total syntheses of madandamine alkaloids has been reported so far.

Our approach to madangamines involves the enantioselective construction of the bridged diazatricyclic ABC ring system, containing the appropriate substitution and functionality to allow the building of the macrocyclic D and E rings of these



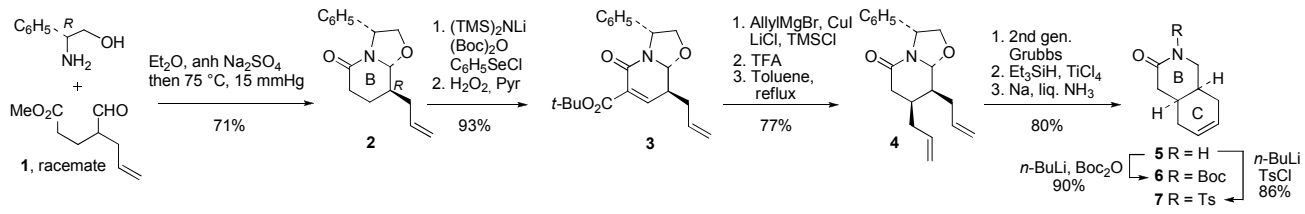
Scheme 4. Madangamine alkaloids.

alkaloids. Scheme 5 outlines the enantioselective synthesis of the pivotal *cis*-hexahydroisoquinolone intermediate **5**. The key steps are (i) a cyclocondensation reaction between (*R*)-phenylglycinol and racemic δ-oxoester **1** to stereoselectively give enantiopure lactam **2** (ring B of the targed alkaloids) with the required R configuration at C-5 (madangamine numbering), in a process that involves a dynamic kinetic resolution; (ii) the stereoselective conjugate addition of an allyl substituent to the activated unsaturated lactam **3** (bond formed C_{11}-C_{12}; madangamine numbering); and (iii) the closure of the carbocyclic C ring (bond formed C_2-C_3) by a ring-closing olefin metathesis reaction leading, after reductive removal of the chiral inductor, to *cis*-hexahydroisoquinolone **5** in 57% overall yield from the starting lactam **2**, and then to the *N*-protected derivatives **6** and **7** (Scheme 5).[6]

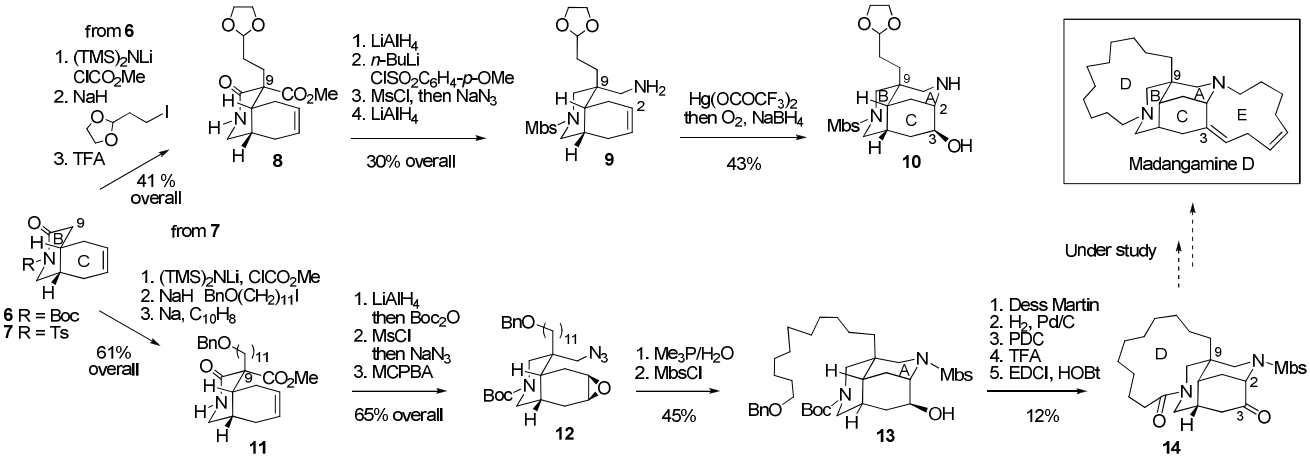
The crucial quaternary stereocenter at C-9 was stereoselectively installed by sequential enolate acylation and alkylation of *N*-protected hexahydro-isoquinolones **6** or **7** with methyl chloroformate and an appropriately functionalized alkyl iodide. The methoxycarbonyl group not only acts as an element of stereocontrol, allowing the subsequent alkylation to occur at the most accessible *exo* face (see **8** and **11**), but is also the precursor of the aminomethyl chain required for the closure of the A ring (Scheme 6). From acetal **8**, after functional group manipulation leading to **9**, this key step was performed[6b] following the Weinreb procedure,[7] by an intramolecular aminomercuriation reaction by using mercuric trifluoroacetate followed by treatment of the organomercury intermediate with oxygen and $NaBH_4$ (bond formed N_1-C_2). The resulting enantiopure diazatrycyclic alcohol **10** possesses suitable functionality both at C-3 and the C-9 chain to allow the building of the macrocyclic D and E rings of madangamines.

With minor modifications, starting from the azabicyclic derivative **11**, which has an 11-carbon chain at C-9 functionalized at the terminal position as required for the closure of the 14-membered D ring of mandangamine D, the strategy was adapted (for the preparation of) to prepare? enantiopure ABCD tetracyclic substructures en route to this alkaloid. The intramolecular aminohydroxylation step was substantially improved by using a different methodology, involving the *meta*-chloroperbenzoic acid oxidation of the cyclohexene double bond of an intermediate azide and the reduction of the resulting azido epoxide **12** with Me_3P/H_2O. Under these conditions the initially formed amino epoxide undergoes smooth cyclization, leading directly to a tricyclic amino alcohol, which was converted to the orthogonally protected sulfonamide **13**.[6b] After oxidation of the C-3 hydroxy group, deprotection and oxidation of the primary alcohol to a carboxylic acid, and removal of the *N*-Boc protecting group, the closure of D ring was accomplished by macrolactamization to give tetracyclic keto lactam **14**.[8]

Four ring positions of the piperidone ring in the starting oxazolopiperidone lactam **2** have been successively involved in the stereoselective assembling of this tetracycle: (i) C-5: generation of the first stereocenter, bearing an allyl substituent, by a dynamic kinetic resolution process; (ii) C-4: introduction of an allyl group by a conjugate addition reaction; (iii) C-3: generation of the C-9 (madangamine numbering) quaternary stereocenter by sequential methoxycarbonylation and enolate alkylation; and (iv) N-1: closure of the 14-membered D ring by a macrolactonization reaction.



Scheme 5. Enantioselective construction of the *cis*-hexahydroisoquinolone moiety.



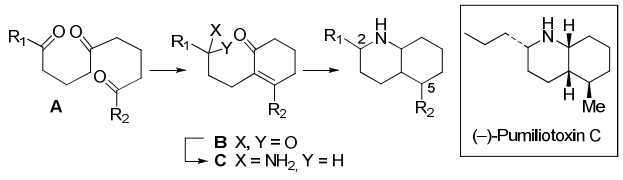
Scheme 6. Towards the enantioselective synthesis of madangamine alkaloids.

Further elaboration of the advanced enantiopure intermediate **14** into madangamine D is currently in progress in our laboratory. By appropriate selection of the alkyl halide in the alkylation step, the strategy we have developed could (might, may) be of application to the synthesis of other alkaloids of this group.

3. Biomimetic Synthesis of Decahydroquinoline Dendrobatid Alkaloids

2,5-Disubstituted decahydroquinolines represent one of the major classes of amphibian alkaloids,[9] which were first isolated from the skin extracts of dedrobatid frogs. The most representative member of this group is *cis*-**195A** (also called pumiliotoxin C), first isolated in 1969 from a Panamarian population of *Dendrobates pumilio*.[10] Although there are no conclusive studies concerning their biosynthesis, it is thought that these alkaloids might derive from the polyketide pathway, by aminocyclization of 1,5-polycarbonyl derivatives **A**, via cyclohexenone intermediates (**B**, **C**), as outlined in Scheme 7.[11]

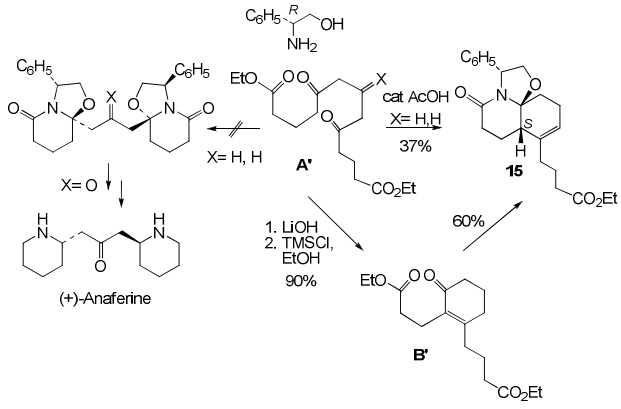
Mimicking these key steps believed to occur in nature, we have developed a straightforward procedure for the enantioselective construction of the hydroisoquinoline ring system from 1,5-polycarbonyl derivatives, using



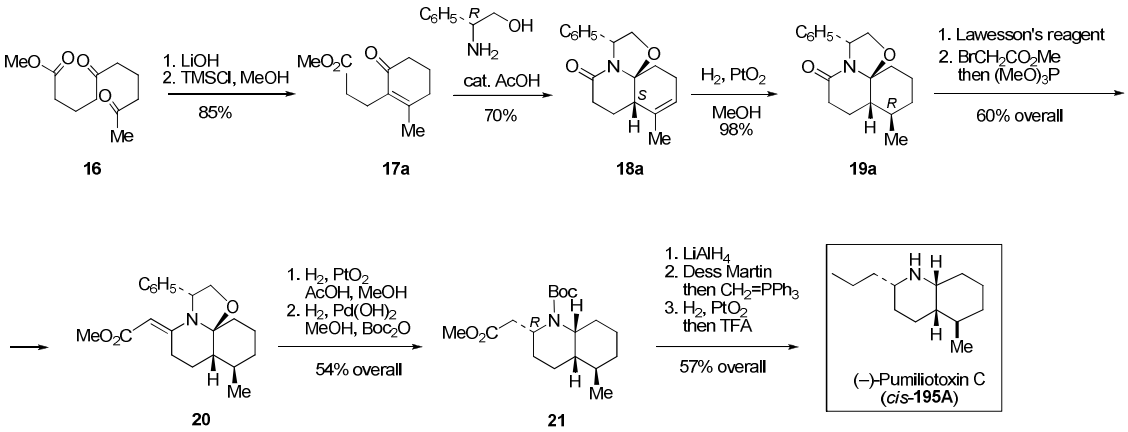
Scheme 7. Hypothetical biosynthetic pathway to amphibian decahydroquinoline alkaloids.

(*R*)-penylglycinol as a chiral latent form of ammonia. Appropriate elaboration of the resulting tricyclic lactams results in diastereodivergent routes to enantiopure 2,5-disubstituted *cis*-decahydroquinolines.[12]

Our biomimetic approach was inspired by a serendipitous observation when attempting a double phenylglycinol-induced cyclocondensation from the polycarbonyl derivative **A'** (X = H, H) in the context of model studies on the synthesis of (+)-anaferine; tricyclic lactam **15** was isolated instead (Scheme 8). Its formation can be rationalized by considering that, after an initial aldol cyclocondensation from the starting diketone **A'**, the resulting cyclohexenone **B'** undergoes a phenylglycinol-promoted cyclocondensation in an overall process that parallels the biogenetic postulate outlined in Scheme 7. In accordance with this interpretation, diketone **A'** was first cyclized to the intermediate cyclohexenone **B'** in excellent yield and then converted into tricyclic lactam **15** by reaction with (*R*)-phenylglycinol.



Scheme 8. Discovery of the biomimetic aminocyclization.

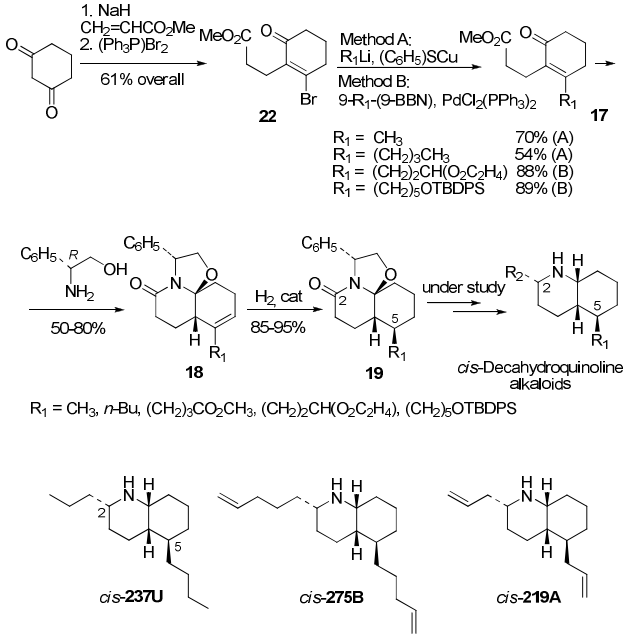


Scheme 9. Biomimetic synthesis of (–)-pumiliotoxin C.

By choosing the appropriate 1,5-polycarbonyl derivative, the above biomimetic double cyclocondensation can be adapted to the enantioselective synthesis of a variety of 2,5-disubstituted *cis*-decahydroquinoline derivatives, as exemplified by the synthesis of (–)-pumiliotoxin C outlined in Scheme 9.

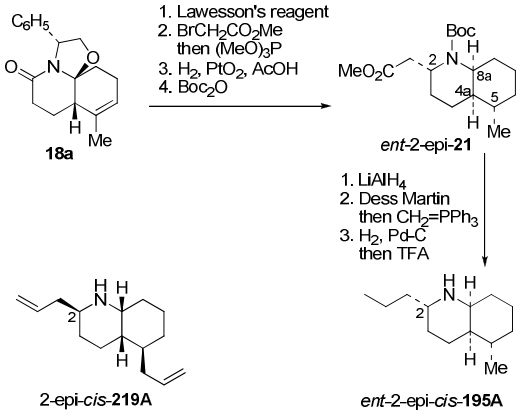
The key steps of the synthesis are: (i) the stereoselective generation of the tricyclic unsaturated lactam **18a** from diketo ester **16**, via cyclohexenone **17a**, by successive aldol and phenylglycinol-promoted cyclocondensations; (ii) the stereoselective hydrogenation of the carbon-carbon double bond to install the appropriate configuration at the quinoline 5-position; (iii) an Eschenmoser sulfide contraction taking advantage of the lactam carbonyl present in the resulting saturated lactam **19a**; and (iv) a PtO_2-catalyzed hydrogenation that brought about both the stereoselective reduction of the vinylogous urethane double bond and the cleavage of the oxazolidine C-O bond of **20**, thus ensuring the complete relative stereochemistry of the alkaloid. A subsequent debenzylation in the presence of Boc_2O led to *cis*-decahydroquinoline **21**. Finally, a one-carbon homologation completed the enantioselective synthesis of (–)-pumiliotoxin C.[12]

We have developed an alternative route for the preparation of the starting cyclohexenone derivatives **17** (Scheme 10) that allow a variety of R_1 substituents, either alkyl (via lithium phenylthio(alkyl)cuprates; method A) or functionalized carbon chains incorporating a protected aldehyde or hydroxy group (via a B-alkyl Suzuki-Miyama coupling; method B), to be introduced at the β-position of the cyclohexenone ring from a common bromoenone intermediate **22**. A phenylglycinol-promoted cyclocondensation reaction from **17**, followed by a stereoselective catalytic hydrogenation leads to a variety C-5 substituted lactams **19**, which can be envisaged as synthetic precursors of *cis*-decahydroquinoline alkaloids (Scheme 10).[13]



Scheme 10. A general approach to the enantioselective synthesis of *cis*-decahydroquinoline alkaloids.

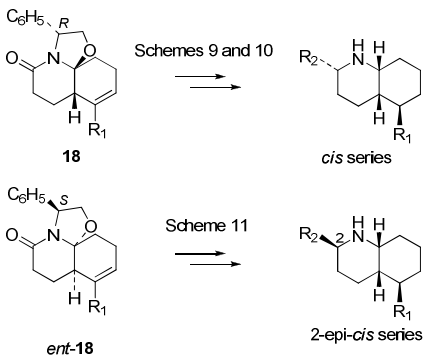
Interestingly, reversing the order of the catalytic hydrogenation of the endocyclic double bond and the Eschenmoser sulfide contraction reactions from **18a** resulted in a dramatic change in the overall stereochemical outcome of the process, leading to the 4a,5,8a diastereoisomer of **21** (*i.e*, *ent*-2-epi-**21**), which was then converted to *ent*-2-epi-*cis*-**195A** following a synthetic sequence similar to that previouly developed in the pumiliotoxin C series[12b] (Scheme11).



Scheme 11. Access to the 2-epi-*cis* series.

The resulting configuration at C-5 is the result of an hydrogen uptake from the less hindered β-face of the endocyclic double bond, whereas the C-4a configuration, opposite to that in the starting lactam **18a**, can be accounted for by considering that the iminium intermediate formed by AcOH-promoted opening of the oxazolidine ring is in equilibrium, via the corresponding enamine, with the most stable 4a-Hα epimer, which undergoes a stereoselective hydrogenation of the C=N bond. A subsequent debenzylation followed by protection with Boc_2O leads to *cis*-decahydroquinoline *ent*-2-epi-*cis*-**195A**.

The above diastereodivergent syntheses of enantiopure 2,5-disubstituted *cis*-decahydroquinolines open general enantioselective routes to both the *cis*- and the 2-epi-*cis* (for instance, 2-epi-*cis*-**219A**; see Scheme 11) series of these alkaloids. Starting from an appropriate (*R*)-phenylglycinol-derived tricyclic lactam **18**, the route outlined in Schemes 9 and 10 provides access to the normal *cis* series, whereas when using the enantiomeric (*S*)-phenylglycinol-derived lactam *ent*-**18**, the route depicted in Scheme 11 would lead to decahydroquinoline alkaloids of the 2-epi-*cis* series (Scheme 12).

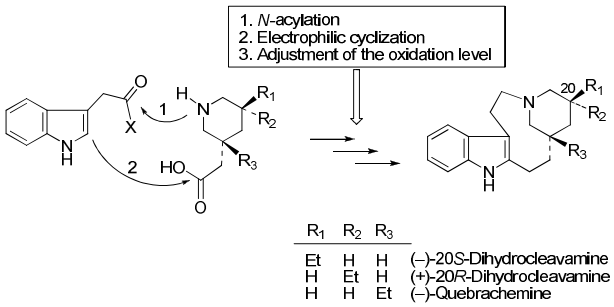


Scheme 12. A synthetic approach to *cis*-decahydroquinoline alkaloids epimeric at C-2.

4. Synthesis of Dihydrocleavamines and Quebrachamine

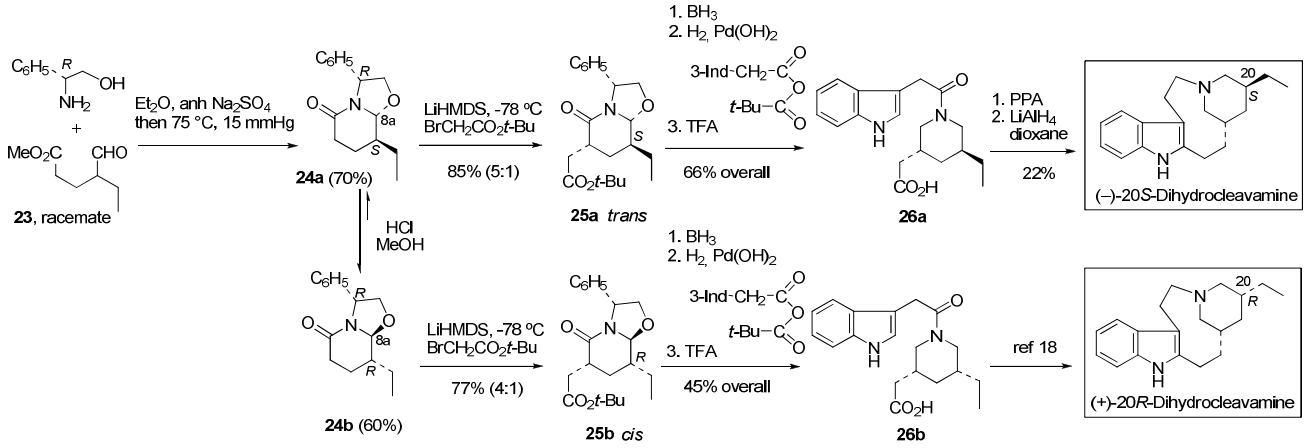
The indole alkaloids 20*S*- and 20*R*-dihydrocleavamine[14] and quebrachamine[15] incorporate a common tetracyclic framework, characterized by the presence of a central nine-membered ring fused to the 1- and 3-positions of an ethyl-substituted piperidine, but differ in the substitution pattern of the piperidine moiety. Whereas both dihydrocleavamines embody a 3,5-disubstituted piperidine (*trans* in 20*S*-dihydrocleavamine but *cis* in the 20*R* isomer) differing in the configuration of the carbon bearing the ethyl substituent, quebrachamine incorporates a 3,3-disubstituted piperidine fragment.

The structural similarities of (between) these alkaloids suggested a common strategy for their synthesis, starting from an appropriate enantiopure 3- or 5-ethylpiperidine-3-acetic acid, in which the key steps would be (i) the acylation of the piperidine nitrogen with a indole-3-acetic acid derivative, (ii) closure of the nine-membered ring by electrophilic cyclization on the indole-2-position, and (iii) the reduction of the acylindole and lactam carbonyl groups (Scheme 13).

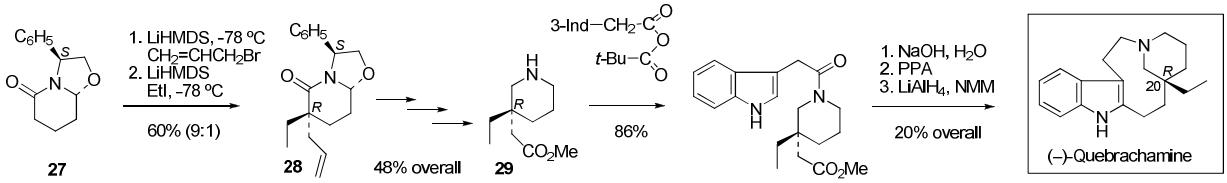


Scheme 13. Synthetic strategy.

The required *trans*-3,5-, *cis*-3,5-, and 3,3-disubstitued piperidine derivatives were prepared taking advantage of the capacity (ability) of phenylglycinol-derived oxazolopiperidone lactams to undergo stereoselective enolate alkylation reactions. Thus, lactam **24a**, already incorporating the ethyl substituent at the piperidine β-position with the absolute configuration required for the synthesis of 20*S*-dihydrocleavamine, was prepared by a ciclocondensation reaction of racemic δ-oxo ester **23** with (*R*)-phenylglycinol in a process that involves a dynamic kinetic resolution of the racemic substrate. Alkylation of the lactam enolate of **24a** with *tert*-butyl bromoacetate to install the acetate chain took place with high *endo* facial selectivity leading to *trans*-lactam **25a**. A subsequent borane reduction, followed by hydrogenolysis in the presence of indole-3-acetic pivalic anydride led to *trans*-piperidine **26a**, which was



Scheme 14. Enantioselective synthesis of (−)-20*S*- and (+)-20*R*-dihydrocleavamine.



Scheme 15. Enantioselective synthesis of (–)-quebrachamine.

converted to the target alkaloid as outlined in Scheme 14.[16]

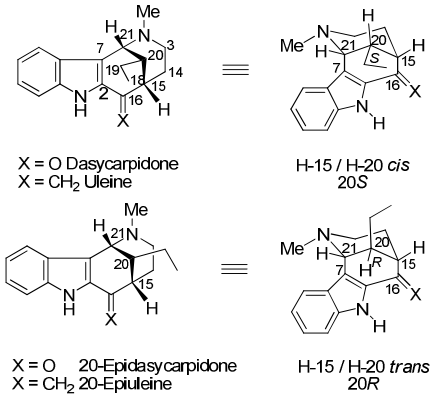
A similar reaction sequence from lactam **24b**, easily accessible by acid-promoted isomerization of **24a**,[17] led to *cis*-3,5-disubstituted piperidine derivative **26b**,[16] which had been previously converted[18] to 20*R*-dihydrocleavamine. Key from the stereochemical standoint, the alkylation of lactam **24b** occurred with *exo* facial selectivity, thus pointing out that the stereochemical outcome of the enolate alkylation of bicyclic oxazolopiperidone lactams **24** depends on the relative configuration of the methine 8a-carbon.

Following a route that parallels the ones used in the above syntheses of dihydrocleavamines, (*R*)-3,3-disubstituted piperidine **29** was converted to (–)-quebrachamine[19] (Scheme 15). Amino ester **29** had previously been used in the racemic series as a platform for the synthesis of several indole alkaloids such as (±)-eburnamonine, (±)-aspidospermidine, and (±)-quebrachamine.[20] The synthesis of enantiopure **29** was satisfactorily accomplished from the simple (*S*)-phenylglycinol-derived lactam **27**, by a sequential enolate dialkylation, with allyl bromide and then with ethyl iodide, followed by conventional oxidation-reduction steps from the resulting *gem*-disubstituted lactam **28**, which possesses the absolute configuration required for the synthesis of (–)-quebrachamine.

5. Synthesis of Alkaloids of the Uleine Group

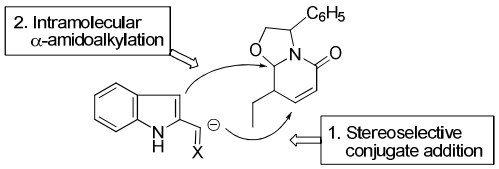
The uleine alkaloids constitute a comparatively small group of tetracyclic indole alkaloids lacking the tryptamine carbon atoms present in the greater part of monoterpenoid indole alkaloids.[21] They can be envisaged as 2,4-bridged, 2,3,4-trisubstituted piperidines bearing an ethyl substituent at the piperidine 3-position. While the absolute configuration of the bridgehead C-15[22] position results from their biogenetic origin from secologamin, there are alkaloids with each of the two possible configurations at C-20: H-15 and H-20 are *cis*, and consequently the ethyl substituent is equatorial with respect to the piperidine ring in most of the alkaloids of this group, but *trans* in the alkaloids of the 20-epi series (Scheme 16).

The synthetic strategy for the synthesis of uleine alkaloids from phenylglycinol-derived oxazolo-piperidone lactams is outlined in Scheme 17. The main problem is the control of the relative and absolute configuration of the C-15 and C-20 stereocenters. This was accomplished by stereocontrolled conjugate addition of an appropriate 2-indolylmethyl anion equivalent to a suitable α,β-unsaturated lactam bearing the ethyl substituent with the required 20*S* (normal series) or 20*R* (epi series) absolute configuration (bond formed C_{15}-C_{16}). A subsequent



Scheme 16. Alkaloids of the uleine group.

intramolecular α-amidoalkylation on the indole 3-position of the masked acyl iminium ion present in the resulting enentiopure *cis*- or *trans*-4,5-disubstituted 2-piperidones (bond formed C_7-C_{21}) assembles the tetracyclic framework of these natural products, either in the natural or epi series, respectively.

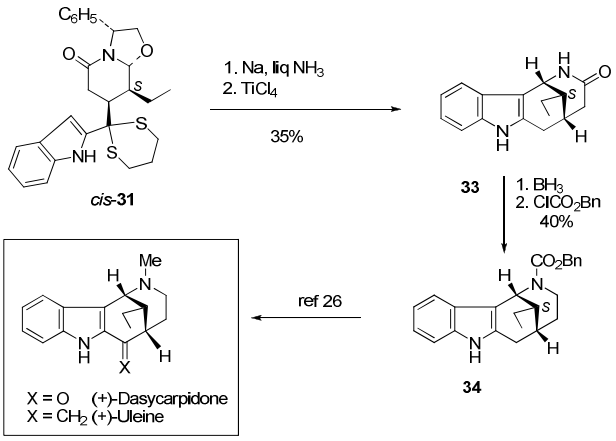


Scheme 17. Synthetic strategy.

As a consequence of the bridgehead character of the C-15 and C-21 stereocenters, the absolute configuration of the stereogenic center generated at the piperidine 4-position (C-15) after the conjugate addition reaction determines that of C-21 in the cyclization step.

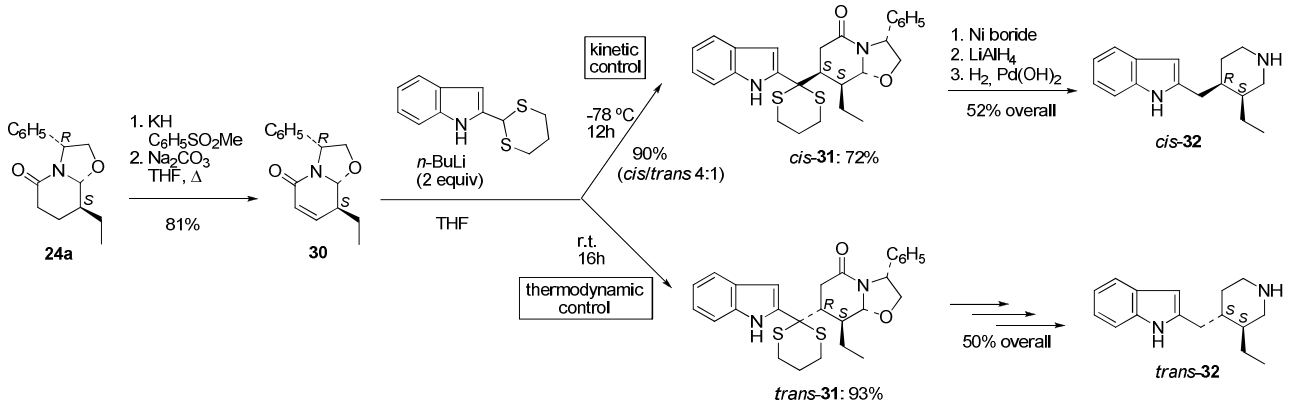
Scheme 18 outlines a diastereodivergent synthesis of *cis*- and *trans*-(piperidylmethyl)indoles **32** from a common lactam **24a**.[23] The key step is a stereocontrolled conjugate addition, either under kinetic (stereoelectronic) or thermodynamic control, of the dilithium salt of 2-(2-indolyl)-1,3-dithiane to unsaturated lactam **30**, which incorporates the ethyl substituent with the required *S* absolute configuration for the synthesis of the normal 20*S* uleine alkaloids. In the racemic series 2-[(3-ethyl-4-piperidyl)methyl]-indoles have been used as key intermediates in the synthesis of tetracyclic alkaloids of the uleine group and pentacyclic *Strychnos* indole alkaloids[24] (tubotaiwine, tubifoline, tubifolidine, and 19,20-dihydroakuamicine).

Reductive removal of both the chiral inductor and the dithiane ring of *cis*-**31**, followed by $TiCl_4$-promoted cyclization of the resulting 6-hydroxy lactam led to tetracycle **33**, which was then converted to **34**,[25] a known[26] synthetic precursor of (+)-dasycarpidone and (+)-uleine (Scheme 19). Taking into account previous correlations,[24b,27] the above synthesis also represent a formal synthesis of nordasycarpidone, (–)-dasycarpidol, and (–)-17-hydroxydihydrouleine.



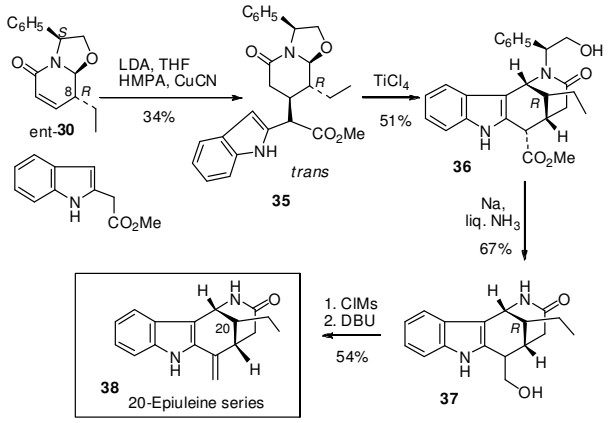
Scheme 19. Formal enantioselective synthesis of (+)-dasycarpidone and (+)-uleine.

The access to tetracyclic derivatives belonging to the 20-epi series requires starting from an unsaturated



Scheme 18. Diastereodivergent synthesis of synthetic precursors of uleine and *Strychnos* alkaloids.

lactam with a 8*R*-ethyl substituent, *i.e. ent*-**30** (derived from *S*-phenylglycinol), and preparing a *trans*-4,5-disubstituted 2-piperidone by a stereocontrolled conjugate addition of an appropriate stabilized nucleophile under equilibrating conditions. This was performed using methyl indole-2-acetate, as outlined in Scheme 20. Intramolecular α-amidoalkylation of the conjugate addition product **35** led to tetracycle **36**, which was then reduced to alcohol **37** and finally converted to the nor-20-epiuleine derivative **38**.[25b]

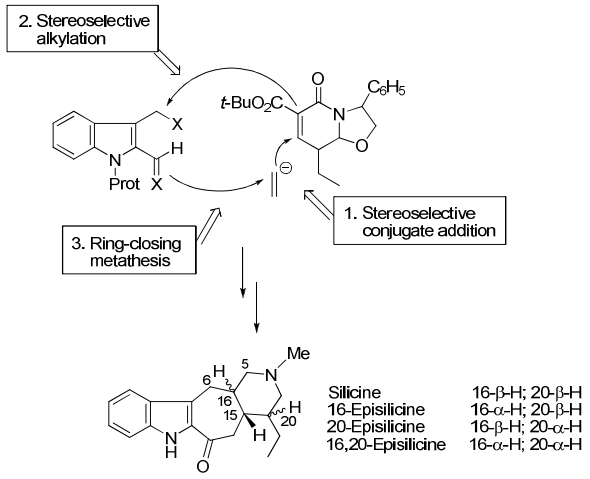


Scheme 20. Enantioselective access to the 20-epi series.

6. A Synthetic Approach to Silicine Alkaloids

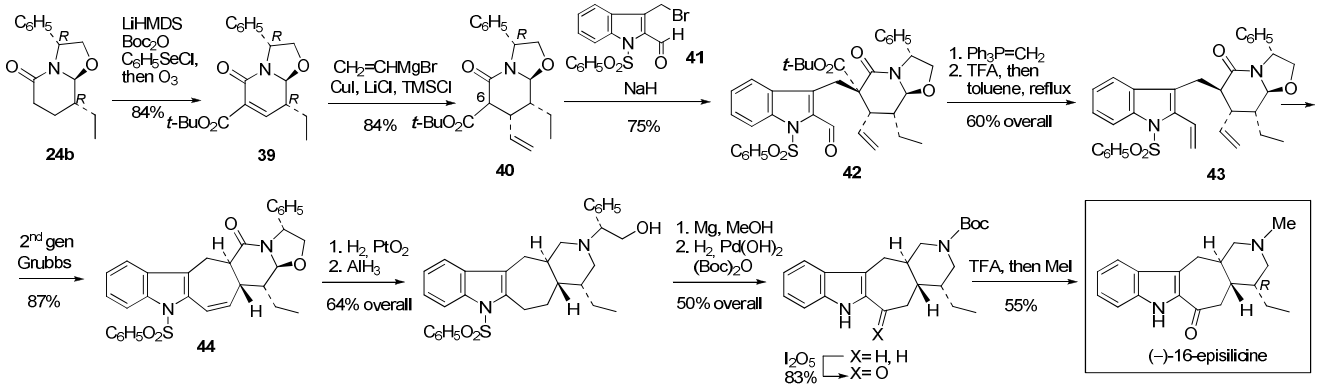
The silicine alkaloids constitute a group of Corynanthean-type 2-acylindole alkaloids with a rearranged skeleton that lacks the characteristic tryptamine moiety present in most indole alkaloids, having an unusual Ind-C_6-C_{16}-C_5-N connectivity instead.[28] They can be envisaged as enantiopure 3,4,5-trisubstituted piperidines that embody an ethyl substituent at the piperidine 3-position and a seven-membered carbocyclic ring fused on the *d* side of the heterocycle.

The assembling of the tetracyclic skeleton of silicine alkaloids from phenylglycinol-derived oxazolopiperione lactams was effected in three steps, as outlined in Scheme 21: (i) stereoselective conjugate addition of a vinyl fragment to an unsaturated lactam already incorporating the ethyl substituent present in the natural targets, (ii) stereoselective alkylation to introduce the 3-indolylmethyl moiety at the α-position of the lactam carbonyl group, and (iii) a ring-closing olefin metathesis reaction to construct the carbocyclic seven-membered ring.



Scheme 21. Synthetic strategy.

Starting from the unsaturated lactam **39**, easily accessible from the known lactam **24b**[17] the above strategy was applied to the enantioselective synthesis of (–)-16-episilicine[29] (Scheme 22). Lactam **39** incorporates an ethyl substituent with the absolute configuration required for the synthesis of this alkaloid and an easily removable electron-withdrawing *tert*-butoxycarbonyl group to provide activation towards the two subsequent conjugate addition and alkylation steps.



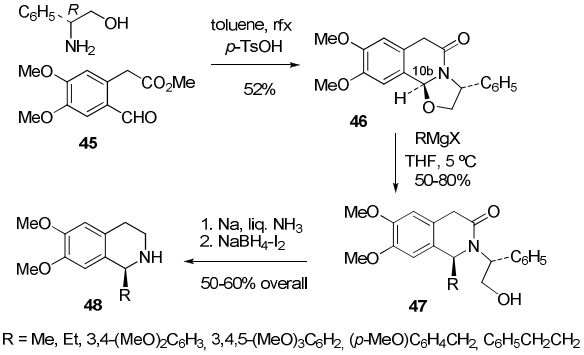
Scheme 22. First enantioselective total synthesis of (–)-16-episilicine.

The introduction of the vinyl substituent was satisfactorily accomplished with complete *exo*-facial selectivity, *cis* with respect to the ethyl substituent as a consequence of the stereoelectronic control, by reaction with vinylmagnesium bromide. Alkylation of the resulting mixture of C-6 epimeric lactams **40** with bromomethylindole **41** took place stereoselectively on the most accessible face of the piperidone ring, providing **42** as a single stereoisomer. After a Wittig methylenation and removal of the activating *tert*-butoxycarbonyl group, diene **43** underwent a ring-closing metathesis reaction to give the *trans*-fused pentacycle **44**, whose absolute configuration was unambiguously established by X-ray crystallographic analysis. Subsequent oxidation-reduction and protecting-deprotecting steps complete the synthesis of (–)-16-episilicine.[30]

7. A General Methodology for the Enantioselective Synthesis of 1-Substituted Tetrahydroisoquinoline Alkaloids

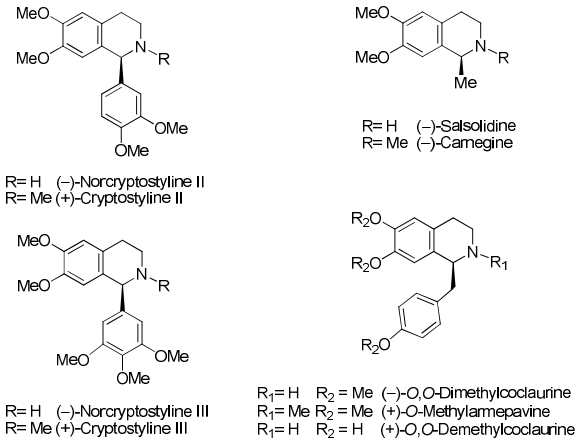
Simple 1-substituted tetrahydroisoquinolines are of great interest not only as alkaloids themselves but also as useful key intermediates in the synthesis of more complex alkaloids.[31]

Phenylglycinol-derived benzo-fused oxazolopiperidone lactams, *e.g.* **46**, are versatile scaffolds that provide general access to enantiopure 1-substituted tetrahydroisoquinoline derivatives **48**, including 1-alkyl, 1-aryl-, and 1-benzyltetrahydroisoquinoline alkaloids. The key step of the synthesis is the stereocontrolled introduction of a substituent at the 1-position of the tetrahydroisoquinoline ring by an asymmetric α-amidoalkylation reaction using an appropriate Grignard reagent (alkyl, aryl, benzyl). Starting from the pivotal tricyclic lactam **46**, which was easily prepared by cyclocondensation of aldehyde ester **45** with (*R*)-phenylglycinol, a variety of 1-substituted tetrahydroisoquinolones **47** were prepared following this methodology. Removal of the phenylethanol moiety and reduction of the lactam carbonyl complete the synthesis (Scheme 23). A related approach involving the direct generation of C-10b substituted lactams starting from acylphenylacetic acid derivatives has been reported by Meyers.[32]



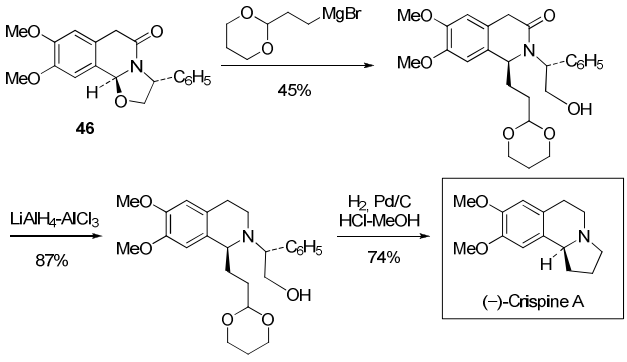
Scheme 23. Enantioselective synthesis of 1-substituted tetrahydroisoquinolines.

The above protocol provides access to (–)-norcryptostyline II, (–)-norcryptostyline III, and the alkaloids (–)-salsolidine and (–)-*O*,*O*-dimethylcoclaurine.[33] Taking into account previous correlations, the above syntheses also constitute a formal synthesis of the alkaloids (–)-carnegine,[34] (+)-cryptostyline II,[35] (+)-cryptostyline III,[35] (+)-*O*-methylarmepavine,[36] and (+)-demethylcoclaurine[37] (Scheme 24).



Scheme 24. Formal and total syntheses of 1-substituted tetrahydroisoquinoline alkaloids from the common phenylglycinol-derived lactam **46**.

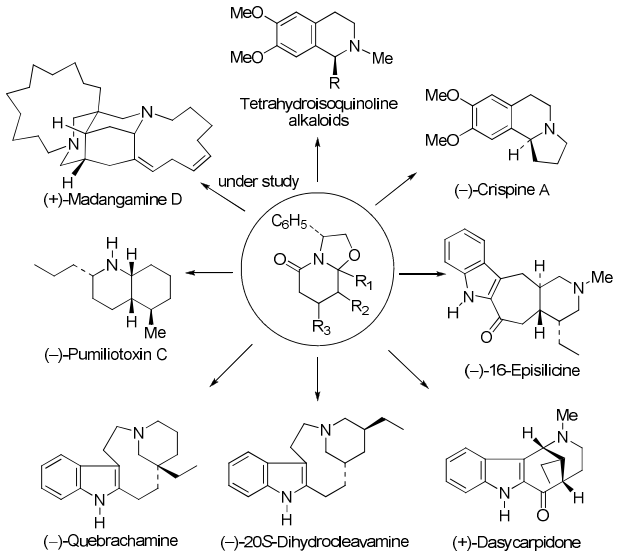
The procedure allows the preparation of the tetrahydroisoquinolines bearing a functionalized C-1 substituent, for instance 2-(1,3-dioxan-2-yl)ethyl, which opens access to more complex tetrahydroisoquinoline alkaloids embodying an additional ring. This was exemplified with the synthesis of the pyrrolo[2,1-*g*]isoquinoline alkaloid (–)-crispine A (Scheme 25).



Scheme 25. Enantioselective synthesis of (–)-crispine A.

8. Conclusion

The examples presented in this review clearly illustrate that bicyclic and tricyclic phenylglycinol-derived oxazolopiperidone lactams are extremely useful building blocks for the enantioselective construction of structurally diverse alkaloids (Scheme 26). All of them have (They) in common the presence of a piperidine moiety, although (but) differ in the piperidine substitution pattern: madangamines (3,3,4,5- tetra-substituted piperidines), pumiliotoxin C (2,5,6-tri-substituted), dihydrocleavamines (*cis*- or *trans*-3,5-disubstituted), quebrachamine (3,3-disubstituted), uleine (2,3,4-trisubstituted), 16-episilicine (3,4,5-trisubstituted).



Scheme 26. Alkaloids synthesized from phenylglycinol-derived oxazolo-piperidone lactams.

Acknowledgments - Financial support from the MICINN, Spain (Projects CTQ2006-02390/BQU and CTQ2009-07021/BQU), and the AGAUR, Generalitat de Catalunya (Grants 2005-SGR-0603 and 2009-SGR-1111) is gratefully acknowledged.

References

[1] For alternative procedures, see: (a) Royer J, Husson HP. (**1993**) A new potential acyl iminium ion for the asymmetric synthesis of piperidine derivatives. *Heterocycles*, 1493–1496, (b) Terán JL, Gnecco D, Galindo A, Juárez J, Bernès S, Enríquez RG (**2001**) New methodology for the synthesis of enantiopure (3*R*,2a*R*)-(–)-3-phenyl-hexahydro-oxazolo[3,2-*a*]-pyridin-5-one: a synthesis of (*S*)-(+)-coniine. *Tetrahedron: Asymmetry*, ***12***, 357–360, (c) Airiau E, Spangenberg T, Girard N, Schoenfelder A, Salvadori J, Taddei M, Mann A. (**2008**) A general approach to aza-heterocycles by means of domino sequences driven by hydroformylation. *Chemistry, A European Journal*, ***14***, 10938–10948, (d) Tojino M, Otsuka N, Fukuyama T, Matsubara H, Ryu I. Selective 6-endo cyclization of the acyl radicals onto the nitrogen of imine and oxazoline C-N bonds (**2006**) *Journal of American Chemistry Society*, ***128***, 7712–7713.

[2] Romo D, Meyers AI. (**1991**) Chiral non-racemic bicyclic lactams. Vehicles for the construction of natural and unnatural products containing quaternary carbon centers. *Tetrahedron*, ***47***, 9503–9569.

[3] (a) Meyers AI, Brengel GP. (**1997**) Chiral bicyclic lactams: useful precursors and templates for asymmetric syntheses. *Chemical Communications*, 1–8, (b) Groaning MD, Meyers AI. (**2000**) Chiral non-racemic bicyclic lactams. Auxiliary-based asymmetric reactions. *Tetrahedron*, ***56***, 9843–9873.

[4] Escolano C, Amat M, Bosch J. (**2006**) Chiral oxazolopiperidone lactams: versatile intermediates for the enantioselective synthesis of piperidine-containing natural products. *Chemistry, A European Journal*, ***12***, 8198–8207.

[5] (a) Kong F, Andersen RJ, Allen TM. (**1994**) Madangamine A, a novel cytotoxic alkaloid from the marine sponge *Xestospongia ingens*. *Journal of American Chemistry Society*, ***116***, 6007–6008, (b) Kong F, Graziani EI, Andersen RJ. (**1998**) Madangamines B-E, pentacyclic alkaloids from the marine sponge *Xestospongia ingens*. *Journal of Natural Products*, ***61***, 267–271, (c) De Oliveira JHHL, Nascimento AM, Kossuga MH, Cavalcanti BC, Pessoa CO, Moraes MO, Macedo ML, Ferreira AG, Hajdu E, Pinheiro US, Berlinck RGS. (**2007**) Cytotoxic alkylpiperidine alkaloids from the brazilian marine sponge *Pachychalina alcaloidifera*. *Journal of Natural Products*, ***70***, 538–543.

[6] (a) Amat M, Pérez M, Minaglia AT, Casamitjana N, Bosch J. (**2005**) An enantioselective entry to *cis*-perhydroisoquinolines. *Organic Letters*, ***7***, 3653–3656, (b) Amat M, Pérez M, Proto S, Gatti T, Bosch J. (**2010**) First enantioselective synthesis of the diazatricyclic core of madangamine alkaloids. *Chemistry, A European Journal*, ***16***, 9438–9441.

[7] Matzanke N, Gregg RJ, Weinreb SM. (**1997**) A concise approach to the tricyclic core of the cytotoxic marine alkaloid Madangamine A. *Journal of Organic Chemistry*, ***62***, 1920–1921.

[8] Amat M, Pérez M, Griera R, Proto S, Fabregat R, Bosch J. (**2010**) An enantiomeric scaffolding strategy for the synthesis of alkaloids: Use of chiral oxazolopiperidone lactams. 3rd EuCheMS Chemistry Congress, Nürnberg, Germany.

[9] Daly JW, Spande TF, Garraffo HM. (**2005**) Alkaloids from amphibian skin: A tabulation of over eight-hundred compounds. *Journal of Natural Products*, ***68***, 1556–1575.

[10] Daly JW, Tokuyama T, Habermehl G, Karle IL, Witkop B. (**1969**) Isolierung und struktur von pumiliotoxin C. *Justus Liebigs Annalen der Chemie*, ***729***, 198–204.

[11] (a) Witkop B, Gössinger E. (**1983**) Amphibian alkaloids. In *The Alkaloids*. Vol. ***21***, Brossi, A. (Ed). Academic Press, New York, 139–253, (b) Daly JW, Spande TF. (**1986**) Amphibian alkaloids: Chemistry, pharmacology, and biology. In *Alkaloids: Chemical and Biological Perspectives*. Vol. ***4***, Pelletier, S. W. (Ed). Wiley, New York, 1–274, (c) Winterfeldt E. (**1979**) Recent progress in alkaloid synthesis. *Heterocycles*, ***12***, 1631–1650. (d) Scholz U, Winterfeldt E. (**2000**) Biomimetic synthesis of alkaloids. *Natural Products Report*, ***17***, 349–366.

[12] (a) Amat M, Griera R, Fabregat R, Molins E, Bosch J. (**2008**) A biomimetic enantioselective approach to the decahydroquinoline class of dendrobatid alkaloids. *Angewandte Chemie International Edition*, ***47***, 3348–3351, (b) Amat M, Fabregat R, Griera R, Florindo P, Molins E, Bosch J. (**2010**) Biomimetic construction of the hydroquinoline ring system. Diastereodivergent enantioselective synthesis of 2,5-disubstituted *cis*-decahydroquinolines. *Journal of Organic Chemistry*, ***75***, 3797–3805.

[13] Amat M, Fabregat R, Griera R, Bosch J. (**2009**) A general synthetic route to enantiopure 5-substituted *cis*-decahydroquinolines. *Journal of Organic Chemistry*, ***74***, 1794–1797.

[14] (a) Cordell, GA. (**1983**) The ibogamine-catharanthine group. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C. (Eds) Wiley, New York, part 4, 467–537. (a) Saxon JE. (**1994**) The ibogamine-catharanthine group. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C. (Eds) Wiley, Chichester, Suppl. to part 4, 487–521.

[15] (a) Saxon JE. (**1983**) The aspidospermne group. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C. (Eds) Wiley, New York, part 4, 331–465, (b) Saxon JE. (**1994**) The aspidospermne group. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C. (Eds) Wiley, Chichester, Suppl. to part 4, 357–436.

[16] (a) Amat M, Escolano C, Lozano O, Llor N, Bosch J. (**2003**) Enantioselective synthesis of *cis*- and *trans*-3,5-disubstituted piperidines. Synthesis of 20*S*- and 20*R*-dihydrocleavamine. *Organic Letters*, ***5***, 3139–3142, (b) Amat M, Escolano C, Lozano O, Gómez-Esqué A, Griera R, Molins E, Bosch J. (**2006**) Alkylation of phenylglycinol-derived oxazolopiperidone lactams. Enantioselective synthesis of β-substituted piperidines. *Journal of Organic Chemistry*, ***71***, 3804–2815.

[17] Amat M, Escolano C, Gómez-Esqué A, Lozano O, Llor N, Griera R, Molins E, Bosch J. (**2006**) Stereoselective α-amidoalkylation of phenylglycinol-derived lactams. Synthesis of enantiopure 5,6-disubstituted 2-piperidones. *Tetrahedron: Asymmetry*, ***17***, 1581–1588.

[18] Danieli B, Lesma G, Passarella D, Silvani A. (**2000**) Indole alkaloids by a chemoenzymatic approach: two convergent routes for the first enantioselective synthesis of (+)-20*R*-15,20-dihydrocleavamine. *Tetrahedron Letters*, ***41***, 3489–3492.

[19] Amat M, Lozano O, Escolano C, Molins E, Bosch J. (**2007**) Enantioselective synthesis of 3,3-disubstituted piperidine derivatives by enolate dialkylation of phenylglycinol-derived oxazolopiperidone lactams. *Journal of Organic Chemistry*, ***72***, 4431–4439.

[20] (a) Ziegler FE, Kloek JA, Zoretic PA (**1969**) Synthesis of quebrachamine and 3,4-dehydroquebrachamine. *Journal of American Chemistry Society*, ***91***, 2342–2346, (b) Irie K, Ban Y. (**1981**) Total synthesis of (±)-eburnamonine and (±)-epieburnamonine *Heterocycles*, ***15***, 201–206, (c) Imanishi T, Miyashita. K, Nakai A, Inoue M, Hanaoka M. (**1983**) 1,6-Dihydro-3(2H)-pyridinones. V. Total synthesis of (±)-eburnamonine *Chem. Pharm. Bull*, *31*, 1191–1198. (d) Wenkert E, Hudlicky T. (**1988**) Synthesis of eburnamonine and dehydroaspidospermidine. *Journal of Organic Chemistry*, ***53***, 1953–1957.

[21] (a) Joule JA. (**1983**) The uleine-ellipticine-vallesamine group. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In *The Chemistry of Heterocyclic Compounds*, Weissberger, A., Taylor, E. C. (Eds). Wiley, New York, Part 4, Chapter 6, (b) Alvarez M, Joule JA. (**1994**) The akuammidine-quebrachidine-ervatamine-gelsemine-akuammiline group. In *Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C. (Ed). Wiley, Chichester, Suppl. to Part 4, Chapter 6, (c) Alvarez M, Joule JA. (**2001**) Ellipticine, uleine, apparicine and related alkaloids. In *The Alkaloids*. Vol. ***57***, Cordell, G. A. (Ed). Academic Press, New York, Chapter 4.

[22] Le Men J, Taylor WI. (**1965**) A uniform numbering system for indole alkaloids. *Experientia*, ***21***, 508–510.

[23] Amat M, Llor N, Checa B, Pérez M, Bosch J. (**2007**) Enantioselective synthesis of 2-[(3-ethyl-4-piperidyl)methyl]-indoles from a phenylglycinol-derived lactam: formal synthesis of *Strychnos* alkaloids. *Tetrahedron Letters*, ***48***, 6722–6725.

[24] (a) Wu A, Snieckus V. (**1975**) A new synthesis of a stemmadenine model. *Tetrahedron Letters* 2057–2060, (b) Gràcia J, Casamitjana N, Bonjoch J, Bosch J. (**1994**) Total synthesis of uleine-type and *Strychnos* alkaloids through a common intermediate. *Journal of Organic Chemistry,* ***59***, 3939–3951.

[25] (a) Amat M, Pérez M, Llor N, Martinelli M, Molins E, Bosch J. (**2004**) Enantioselective formal synthesis of uleine alkaloids from phenylglycinol-derived bicyclic lactams. *Chemical Communications*, 1602–1603, b) Amat M, Pérez M, Llor N, Escolano C, Luque FJ, Molins E, Bosch J. (**2004**) Conjugate additions to phenylglycinol-derived unsaturated δ-lactams. Enantioselective synthesis of uleine alkaloids. *Journal of Organic Chemistry*, ***69***, 8681–8693.

[26] Saito M, Kawamura M, Hiroya K, Ogasawara K. (**1997**) First enantiocontrolled syntheses of (+)-uleine and (+)-dasycarpidone. *Chemical Communications*, 765–766.

[27] (a) Joule JA, Ohashi M, Gilbert B, Djerasi C. (**1965**) Alkaloid studies–LIII: The structures of nine new alkaloids from *Aspidosperma dasycarpon* A. DC. *Tetrahedron*, ***21***, 1717–1734.

[28] (a) Joule JA. (**1983**) The ervatamine and ervitsine group. Alkaloids with (1) 5,16 and 6,16 bonds but no 5,6 bond and (2) 5,16 5,7, and 6,16 bonds but no 5,6 bond. In *Indoles. The Monoterpenoid Indole Alkaloids*. Vol. ***25***, Saxton, J. E. (Ed). In The Chemistry of Heterocyclic Compounds; Weissberger, A., Taylor, E. C. (Eds) Wiley, New York, part 4, 232–239. (b) Danieli B, Palmisano G. (**1986**) Alkaloids from *Tabernaemontana*. In *The Alkaloids*, Vol. ***27***, Brossi, A. (Ed). Academic Press, Orlando, 1–130.

[29] (a) Zeches M, Debray MM, Ledouble G, Le Men-Olivier L, Le Men J. (**1975**) Alcaloïdes du *Pandaca caducifolia*. *Phytochemistry*, ***14***, 1122–1124, (b) Clivio P, Richard B, Nuzillard JM, Zèches-Hanrot M. (**1995**) 16-*epi*-Silicine, an alkaloid of the ervatamine-type from *Pandaca caducifolia*. *Phytochemistry*, ***40***, 987–990.

[30] (a) Amat M, Checa B, Llor N, Molins E, Bosch J. (**2009**) Enantioselective total synthesis of the indole alkaloid 16-episilicine. *Chemical Communications*, 2935–2937, (b) Amat M, Checa B, Llor N, Molins E, Bosch J. (**2010**) A synthetic approach to ervatamine-silicine alkaloids. Enantioselective total synthesis of (–)-16-episilicine. *Journal of Organic Chemistry*, ***75***, 178–189.

[31] (a) Phillipson JD, Roberts MF, Zenk MH. (Ed) (**1985**) The Chemistry and Biology of Isoquinoline Alkaloids, Springer-Verlag, Berlín, , (b) Atta-ur-Rahman (**1994**) *In Handbook of Natural Products Data*, Vol. ***3***, Elsevier, Amsterdam. (c) Scott JD, Williams RM. (**2002**) Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. *Chemical Review*, ***102***, 1669–1730, (d) Dewick PM. (**2002**) Alkaloids derived from tyrosine phenylethylamines and simple tetrahydroisoquinoline alkaloids. In *Medicinal Natural Products*, Wiley, Chichester, 315–346, (e) Bentley KW. (**2006**) β-Phenylethylamines and the isoquinoline alkaloids. *Natural Product Report, **23***, 444–463.

[32] (a) Munchhof MJ, Meyers AI. (**1995**) A novel route to chiral, nonracemic 1-alkyl- and 1-aryl-substituted tetrahydroisoquinolines. Synthesis of (–)-salsolidine and (+)-cryptostyline II. *Journal of Organic Chemistry*, ***60***, 7086–7087, (b) Munchhof MJ, Meyers AI. (**1996**) A novel asymmetric route to the 1,3-disubstituted tetrahydroisoquinoline, (–)-argemonine. *Journal of Organic Chemistry*, ***61***, 4607–4610.

[33] Amat M, Elias V, Llor N, Subrizi F, Molins E, Bosch J. (**2010**) A general methodology for the enantioselective synthesis of 1-substituted tetrahydroisoquinoline alkaloids. *European Journal of Organic Chemistry*, 4017–4026.

[34] Battersby AR, Edwads TP. (**1960**) Chemical correlation of the absolute configurations of salsolidine, salsoline, and calycotomine with the amino-acids. *Journal of the Chemical Society*, 1214–1221.

[35] Brossi A, Teitel S. (**1971**) Synthesis and absolute configuration of cryptostylines I, II, and III. *Helvetica Chimica Acta*, ***54***, 1564–1571.

[36] Yamazaki N, Suzuki H, Aoyagi S, Kibayashi C. (**1996**) Lewis acid-mediated nucleophilic alkylations on chiral [6,3*a*,4]oxadiazaindano[5,4-*a*]isoquinolines. Asymmetric synthesis of 1-alkyl substituted tetrahydroisoquinolines. *Tetrahedron Letters*, ***37***, 6161–6164.

[37] Leboeuf M, Cavé A, Touché A, Provost J, Forgacs P. (**1981**) Isolement de l'Higénaminea partir de l'*Annona squamosa*; interet des résines adsorbantes macromoléculaires en chimie végétale extractive. *Journal of Natural Products*, ***44***, 53–60.