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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00983 • Publication Date (Web): 27 Jun 2018

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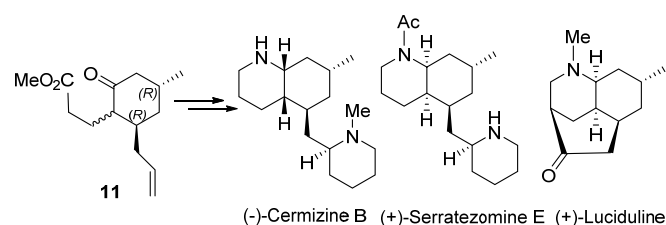
Studies on the Synthesis of Phlegmarine-type *Lycopodium* Alkaloids.
Enantioselective Synthesis of (–)-Cermizine B, (+)-Serratezomine E,
and (+)-Luciduline

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Abstract

The synthesis of the *Lycopodium* alkaloids (–)-cermizine B, (+)-serratezomine E, and (+)-luciduline using phenylglycinol-derived tricyclic lactams as chiral scaffolds, is reported. The requisite lactams are prepared by a cyclocondensation reaction between (*R*)- or (*S*)-phenylglycinol and the substituted δ -keto ester **11**, easily accessible from (*R*)-pulegone. The factors governing the stereoselectivity of these cyclocondensation reactions are discussed. Key steps of the synthesis from the stereochemical standpoint are the stereoselective elaboration of the allyl substituent to an (*S*)-2-(piperidyl)methyl moiety and the stereoselective removal of the chiral inductor to give a *cis*-decahydroquinoline.

Introduction

The decahydroquinoline (DHQ) ring system is a common structural feature present in a large number of biologically active natural products. Unlike most alkaloid types, DHQ-containing alkaloids occur not only in plant species (e.g., phlegmarine in *Lycopodium* and myrioxazine A in *Myrioneuron*)¹ but also in other terrestrial (e.g., pumiliotoxin C and gephyrotoxin 287C in amphibians and arthropods)² and marine (e.g., cylindricines, lepadiformines, and lepadins in tunicates and flatworms)³ organisms (Figure 1).

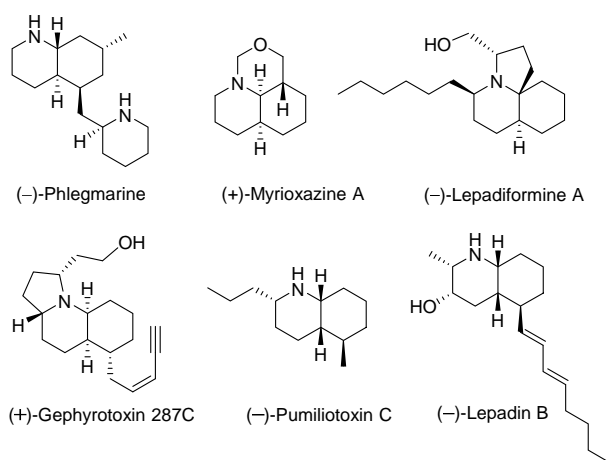


Figure 1. Representative plant, amphibian and marine decahydroquinoline alkaloids.

In particular, *Lycopodium* alkaloids can be grouped in four main structural classes, namely, lycopodine, lycodine, fawcettimine, and phlegmarine (also called the miscellaneous class), each one named after their most representative member. The phlegmarine-type alkaloids are characterized by a *cis*- or *trans*-decahydroquinoline ring system with a 7(*R*)-methyl substituent and a (2-piperidyl)methyl-derived appendage at C-5 with both possible relative stereochemistries (Figure 2). In some members, the piperidine ring is oxidized to a nitron or a pyridine, and in a few cases the DHQ 3- and 5-positions are connected by an oxidized two-carbon unit. Phlegmarine is believed to be the key intermediate in the biosynthesis of all *Lycopodium* alkaloids.

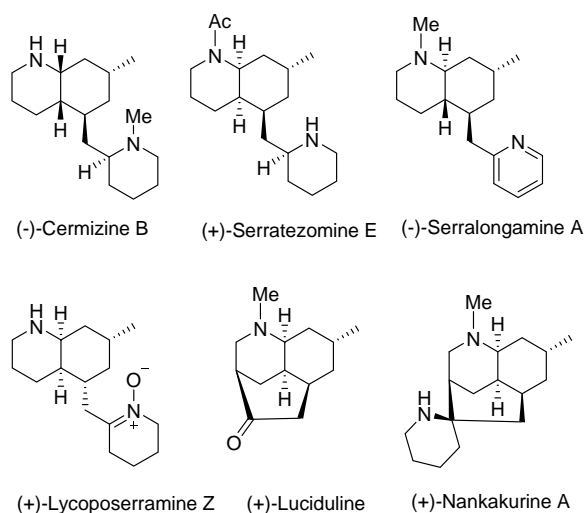
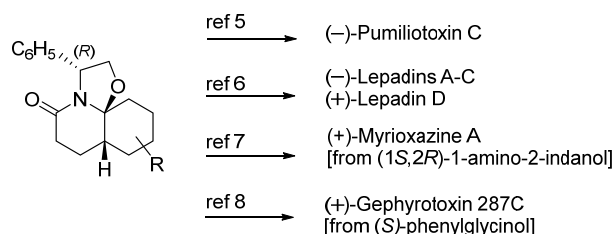


Figure 2. Representative phlegmarine-type *Lycopodium* alkaloids.

As a consequence of their widespread distribution and different biogenetic origins, DHQ-containing alkaloids are structurally diverse in their substitution pattern and stereochemistry, which has stimulated the development of general methodologies and unified synthetic strategies for the stereoselective synthesis of substituted DHQ derivatives.⁴ In this context, in previous work we have used tricyclic aminoalcohol-derived oxazoloquinolone lactams as multipurpose enantiopure scaffolds for diastereoselective transformations into a variety of diversely substituted *cis*-decahydroquinolines, including the DHQ alkaloids (–)-pumiliotoxin, C,⁵ (–)-lepadins A-C,⁶ (+)-lepadin D,^{6b} (+)-myrioxacin A,⁷ and (+)-gephyrotoxin 287C⁸ (Scheme 1).

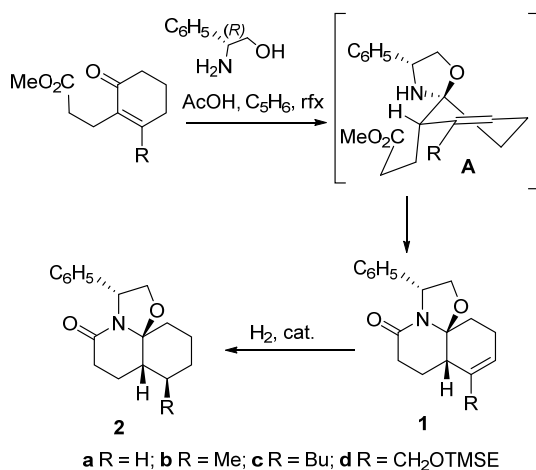
Scheme 1. Access to Decahydroquinoline Alkaloids from Chiral Aminoalcohol-Derived Tricyclic Lactams



From the stereochemical standpoint, crucial steps in our syntheses of pumiliotoxin C and lepadins were a stereoselective cyclocondensation reaction of (*R*)-phenylglycinol with a cyclohexenone-derived

δ -keto ester and the subsequent stereoselective hydrogenation of the resulting rigid *cis*-fused tricyclic lactams **1**^{6,9} (Scheme 2). The configuration of the bridgehead carbons in **1** results from the irreversible lactamization of the intermediate oxazolidine **A** (in equilibrium with other three diastereoisomeric oxazolidines via the corresponding dienamine), through a chair-like transition state in which the ester chain avoids repulsive interactions with the R ($A^{1,2}$ strain) and C_6H_5 substituents. *Trans*-fused lactams cannot be formed due to steric constraints. In turn, the hydrogenation of the C–C double bond of unsaturated lactams **1** takes place stereoselectively from the most accessible face to give lactams **2**, with a 4a-H/5-H *trans* relative configuration (when R \neq H; DHQ numbering).

Scheme 2. Stereoselective Access to Phenylglycinol-Derived Oxazoloquinolone Tricyclic Lactams

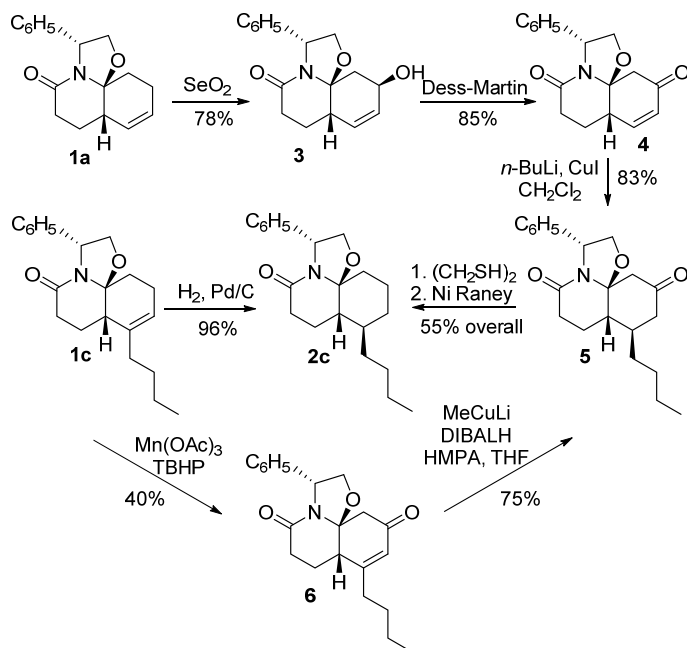


Results and Discussion

We report herein our studies on the enantioselective synthesis of phlegmarine-type *Lycopodium* alkaloids using phenylglycinol-derived tricyclic lactams as chiral scaffolds. Only a limited number of enantioselective synthesis of these alkaloids have been reported to date.¹⁰⁻¹² In a first approach, we envisaged unsaturated lactam **1a** as a suitable starting material, because its allylic oxidation should afford an enone, from which the substituents at the DHQ C-5 and C-7 positions could be incorporated in a stereocontrolled manner. In the event, treatment of **1a** with SeO_2 ¹³ afforded allylic alcohol **3** as a single stereoisomer,¹⁴ which was further oxidized under Dess–Martin conditions to give enone **4** in high

overall yield. To test the feasibility of conjugate addition reactions for the introduction of the DHQ C-5 substituent and easily analyze their stereochemical outcome, in a model experiment enone **4** was allowed to react with *n*-BuLi in the presence of CuI. When the reaction was carried out in the usual THF or Et₂O solvents, a nearly equimolecular mixture (determined by NMR) of **5** and its C-5 epimer was obtained (70-75% yield).¹⁵ However, surprisingly, the conjugate addition proceeded smoothly in CH₂Cl₂ to afford ketone **5** in 83% yield as a single diastereoisomer with a 4a-H/5-H *trans* relationship (Scheme 3). The configuration of **5** was unambiguously established after reduction of the ketone carbonyl. The resulting tricyclic lactam **2c** was identical to that previously obtained⁹ by catalytic hydrogenation of unsaturated lactam **1c**. The observed diastereoselectivity in the above conjugate addition reaction, involving a nucleophilic attack from the most hindered face of the enone, can be rationalized by considering that, in the absence of ethereal solvents, the oxazolidine oxygen coordinates with the nucleophilic species, thus directing the delivery of the nucleophile *syn* with respect to this oxygen.

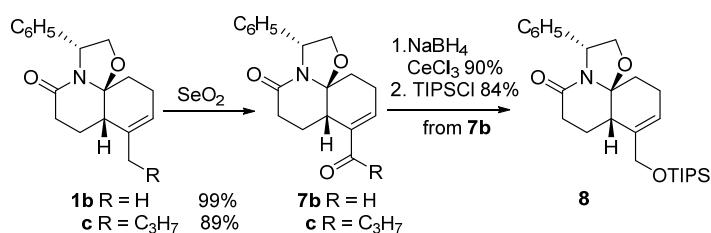
Scheme 3. The Decahydroquinoline C-5 Stereocenter. Model Studies



These results prompted us to investigate an alternative way of generating the DHQ C-5 stereocenter, by conjugate reduction of enone **6**. However, SeO₂-promoted allylic oxidation of unsaturated lactam **1c**

took place at the exocyclic methylene carbon instead of the endocyclic DHQ C-7 position to give ketone **7c** in excellent yield (Scheme 4). A similar oxidation from **1b** gave aldehyde **7b** in nearly quantitative yield. Steric factors probably account for the regioselectivity of the oxidation. Aldehyde **7b** was efficiently converted in two steps to the silyl derivative **8**, the TIPS analog of the intermediate **1d** in our synthesis of lepadins.⁶

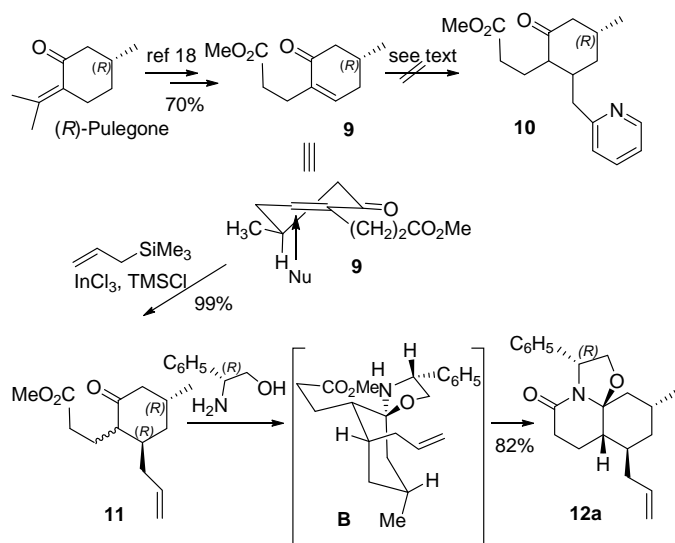
Scheme 4. Regioselective Exocyclic Allylic Oxidation



The desired regioselective endocyclic allylic oxidation of unsaturated lactam **1c** was accomplished, although in moderate yield, by manganese(III) acetate-catalyzed oxidation using TBHP as the cooxidant.¹⁶ A subsequent methylcopper(I)-catalyzed conjugate reduction of the resulting enone **6** by DIBALH in the presence of HMPA¹⁷ afforded in good yield and complete facial selectivity the same tricyclic ketone **5** previously obtained by conjugate addition of a butyl residue. This result makes evident that the conjugate additions of hydride and butyl occur with opposite facial selectivity, both leading to the same *trans* 4a-H/5-H (DHQ numbering) relative stereochemistry, which had also been obtained by hydrogenation of the unsaturated lactams **1** resulting from the cyclocondensation reaction (Scheme 2).

Although the above approach would allow the stepwise preparation of tricyclic lactams bearing substituents at the DHQ C-5 and C-7 positions, en route to phlegmarine-type alkaloids, at this point we turned our attention to an alternative, more efficient approach based on the direct generation of such disubstituted lactams using appropriately substituted cyclohexanone-derived δ -keto esters in the reaction with (*R*)- or (*S*)-phenylglycinol. These keto esters would be accessible by a conjugate addition to enone **9**, which already incorporates the methyl substituent with the (*R*) absolute stereochemistry characteristic of the target alkaloids (Scheme 5).

Scheme 5. Preparation of the Starting Enantiomeric Scaffold for the Synthesis of (–)-Cermizine B

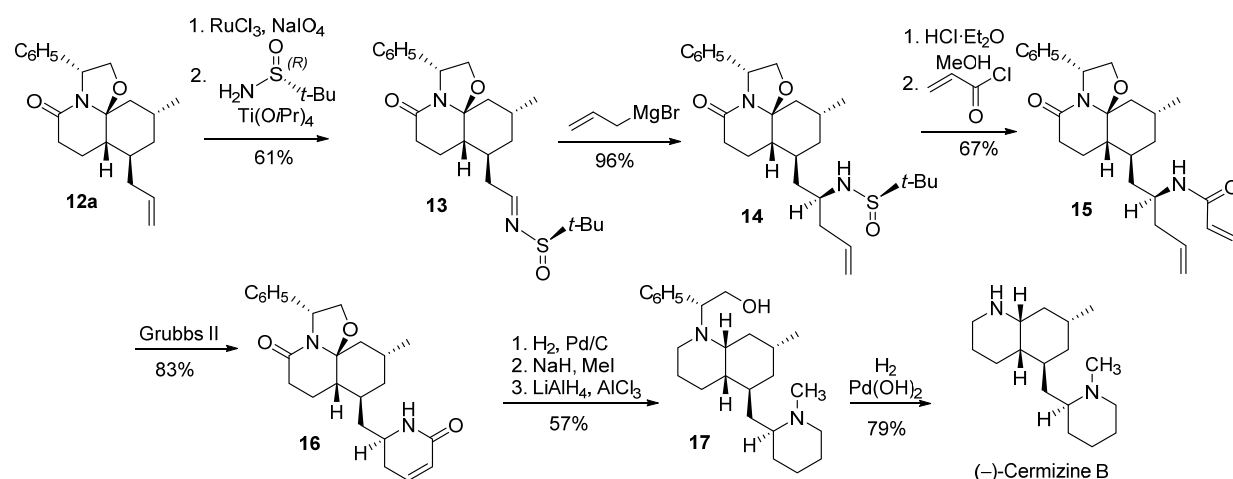


Enone **9** was prepared in four steps on a multigram scale (~70% overall yield) following literature procedures¹⁸ from (R)-pulegone, a commercially available compound of the chiral pool.¹⁹ Unfortunately, attempts to directly introduce a (2-pyridyl)methyl substituent by conjugate addition of a metalated 2-picoline to enone **9** under a variety of experimental conditions²⁰ were unsuccessful and the desired adduct **10** was not detected. To circumvent this problem, we decided to perform the conjugate addition of an allyl group, which would be subsequently elaborated to the (2-piperidyl)methyl moiety present in most phlegmarine-type alkaloids. The 1,4-addition was satisfactorily accomplished in nearly quantitative yield by an InCl_3 -catalyzed Sakurai reaction²¹ of enone **9** with allyltrimethylsilane in the presence of TMSCl . The reaction was completely stereoselective due to the stereoelectronic control,²² affording 3,5-*trans* cyclohexanone **11** as an inconsequential 1:1 mixture of C-2 epimers. The subsequent acid-catalyzed cyclocondensation of **11** with (R)-phenylglycinol also took place with complete stereoselectivity, via oxazolidine **B**, leading to the anticipated tricyclic lactam **12a**¹⁴ in 82% yield, in a process that involves the epimerization of the configurationally labile stereocenter α to the ketone group.²³ The DHQ 4a-, 5-, and 7-carbons in lactam **12a** had the required configuration for the synthesis of (–)-cermizine B, an alkaloid isolated from the club moss of *Lycopodium cernuum*.²⁴ To

complete the synthesis, it was only necessary to stereoselectively install the (*S*)-(2-piperidyl)methyl moiety by manipulating the allyl substituent and generate the *cis* fusion for the DHQ system by stereoselective cleavage of the oxazolidine ring.

The *S* stereogenic center α to the amino group of the DHQ C-5 substituent was installed by reaction of *N*-sulfinyl imine **13** with allylmagnesium bromide,²⁵ which led to sulfinamide **14** as a single stereoisomer in 96% yield. Compound **13** was prepared from lactam **12a** by RuCl₃/NaIO₄-promoted²⁶ oxidative cleavage of the allyl group, followed by Ti(O-*i*-Pr)₄-mediated condensation of the resulting aldehyde with (*R*)-(+)-*tert*-butanesulfinamide²⁷ (Scheme 6).

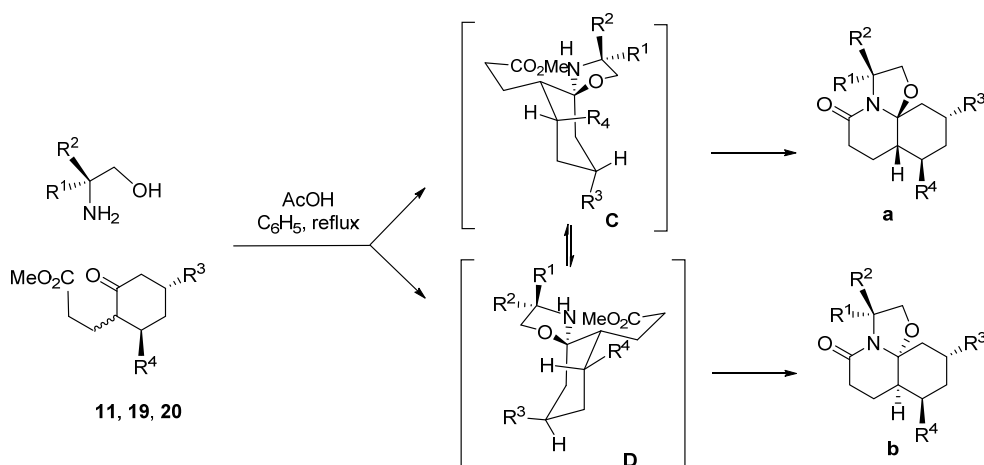
Scheme 6. Enantioselective Synthesis of (–)-Cermizine B



The six-membered heterocyclic ring of the DHQ C-5 side chain was assembled from sulfinamide **14** in the three steps: cleavage of the sulfinyl group by acidic methanolysis, acylation of the resulting primary homoallylic amine with acryloyl chloride to give diene **15** (67% overall yield), and a final ring-closing metathesis reaction (83% yield). After catalytic hydrogenation of the C–C double bond of dihydropyridone **16** and methylation of the resulting piperidone, treatment with LiAlH₄-AlCl₃ caused both the reduction of the piperidone and perhydroquinolone lactam carbonyls and the stereoselective reductive cleavage of the oxazolidine C–O bond to give *cis*-DHQ **17** in 57% overall yield. A final

debenzylation by catalytic hydrogenation afforded (–)-cermizine B, whose NMR spectroscopic data matched those reported for the natural product.^{24,28}

The above successful result prompted us to develop a similar sequence for the synthesis of (+)-serratezomine E, a *cis*-DHQ alkaloid isolated from the club moss *Lycopodium serratum* var. *serratum*²⁹ bearing the same C-5 and C-7 absolute configuration as (–)-cermizine B, but with the opposite configuration at the ring fusion carbons. It was expected that using (*S*)-phenylglycinol instead of the *R* enantiomer in the reaction with δ -keto ester **11** would afford tricyclic lactam **18b**, with the required stereochemistry. As observed in related cyclocondensations,⁵⁻⁹ lactamization would preferentially take place from an oxazolidine (**D**; R¹=H, R²=C₆H₅) in which the ester group approaches the nitrogen atom avoiding the repulsive interactions of the methoxy group with the phenyl substituent. Such interactions would occur in the tetrahedral intermediate generated in the alternative cyclization from oxazolidine **C** (R¹=H, R²=C₆H₅). However, unexpectedly, in sharp contrast with the result of the cyclocondensation with (*R*)-phenylglycinol (Scheme 5 and Table 1, entry 1), the reaction of **11** with (*S*)-phenylglycinol was not stereoselective, affording (78% yield) a nearly equimolecular mixture of the expected lactam **18b** and its diastereoisomer **18a** (entry 2).³⁰ To gain insight into the factors governing the stereoselectivity of the above cyclocondensation reactions, we studied the reaction of **11** with 2-aminoethanol, which lacks the phenyl substituent of the amino alcohol moiety, as well as other cyclocondensations using δ -keto esters **19** and **20** (mixtures of C-2 diastereoisomers), related to **11** but lacking one of the substituents at the cyclohexanone ring. The results are summarized in Table 1.²³

Table 1. Cyclocondensation Reactions

entry	amino alcohol	R ¹	R ²	δ-keto ester	R ³	R ⁴	products	a/b ratio	yield (%)
1	(<i>R</i>)-Phenylglycinol	C ₆ H ₅	H	11	CH ₃	CH ₂ CH=CH ₂	12	1:0	82
2	(<i>S</i>)-Phenylglycinol	H	C ₆ H ₅	11	CH ₃	CH ₂ CH=CH ₂	18	55:45	78
3	2-Aminoethanol	H	H	11	CH ₃	CH ₂ CH=CH ₂	21	85:15	81
4	(<i>R</i>)-Phenylglycinol	C ₆ H ₅	H	19	CH ₃	H	22	1:0	76
5	(<i>S</i>)-Phenylglycinol	H	C ₆ H ₅	19	CH ₃	H	23	85:15	83
6	(<i>R</i>)-Phenylglycinol	C ₆ H ₅	H	20	H	CH ₃	24	1:1	68
7	(<i>S</i>)-Phenylglycinol	H	C ₆ H ₅	20	H	CH ₃	25	0:1	76

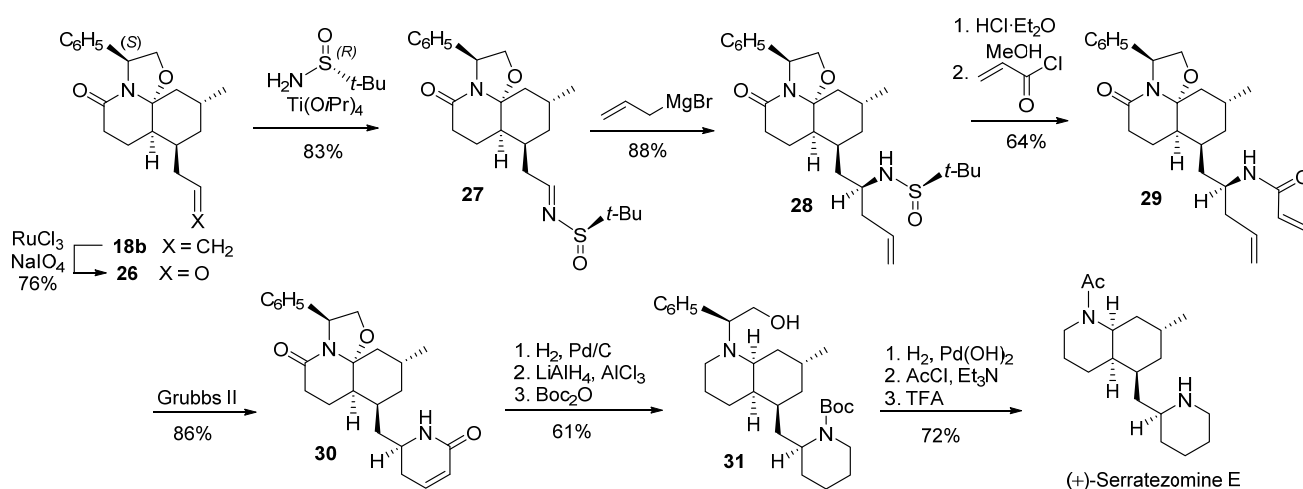
The reaction of **11** with 2-aminoethanol afforded an 85:15 mixture of lactams **21a** and **21b** (entry 3). Taking into account that lactamization of both possible oxazolidine precursors **C** and **D** (R¹ = R² = H) involves a chair-like transition state with one axial substituent (R⁴ or R³) on the cyclohexane ring, the preferential lactamization from oxazolidine **C** (R¹ = R² = H) in the absence of the phenyl substituent can be rationalized by considering that **D** suffers from additional repulsive *gauche* interactions between the equatorial allyl group and the propionate chain. Similar *gauche* interactions would explain the stereochemical outcome of the above cyclocondensation leading to lactams **18a** and **18b**.

In the same way, the stereochemical outcome of the cyclocondensations of keto esters **19** and **20** with (*R*)- and (*S*)-phenylglycinol (table 1, entries 4-7) can be accounted for by analyzing in each case the

repulsive interactions during the irreversible lactamization of the intermediate equilibrating oxazolidines **C** and **D**: i) 1,3-diaxial interactions between the phenyl ring and the methoxy group; ii) axial substituents on the cyclohexane ring; and iii) *gauche* interactions between the equatorial R⁴ substituent and the propionate chain. The existence or not of these interactions determines the stereoconvergent generation of tricyclic lactams **22a** and **25b** in the reactions of keto ester **19** with (*R*)-phenylglycinol (entry 4) and keto ester **20** with (*S*)-phenylglycinol (entry 7), respectively; it also explains why the alternative cyclizations of **19** with (*S*)-phenylglycinol and **20** with (*R*)-phenylglycinol, leading to lactams **23** and **24**, respectively, were less (**a/b** ratio 85:15; entry 5) or even not stereoselective (1:1 ratio; entry 6).

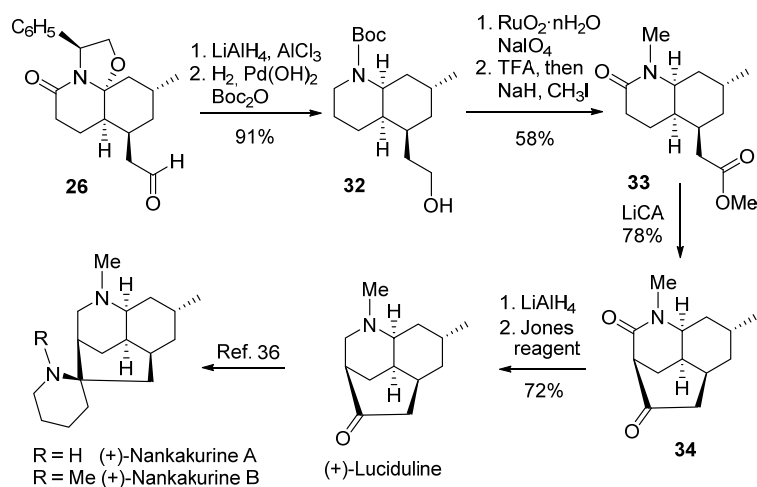
Following our synthetic plan, lactam **18b** was converted to (+)-serratezomine E as outlined in Scheme 7. The synthetic sequence parallels the one previously developed for the synthesis of (–)-cermizine B, and proceeds via aldehyde **26**, *N*-sulfinyl imine **27**, sulfinamide **28**, diene **29**, dihydropyridone **30**, and *cis*-DHQ **31**. The piperidine nitrogen was protected as an *N*-Boc derivative to allow the selective acetylation of the DHQ nitrogen after the reductive removal of the phenylethanol moiety by hydrogenolysis. A final deprotection with TFA gave (+)-serratezomine E. The NMR data of our synthetic (+)-serratezomine E were coincident with those reported in the literature,^{10f} while the specific rotation $\{[\alpha]_{\text{D}} = +6.1$ (*c* 0.62, CHCl₃) $\}$ was in good agreement with the value reported $\{[\alpha]_{\text{D}} = +9.0$ (*c* 1, CHCl₃) $\}$ ^{10f} for this natural product in its basic form.³¹

Scheme 7. Enantioselective Synthesis of (+)-Serratezomine E



Taking into account that luciduline³² and nankakurines A and B³³ (Figure 2) possess the same configuration at the C-4a, C-5, C-7, and C-8a DHQ stereocenters as serratezomine E, tricyclic lactam **18b** was also envisaged as a synthetic precursor of these more complex *Lycopodium* alkaloids. The additional bridged six-membered ring would be assembled taking advantage of the allyl substituent, which would be converted to an acetate chain, able to undergo a base-catalyzed cyclization with the α position of the lactam carbonyl. The stereoselective removal of the chiral inductor, with simultaneous *N*-Boc protection, was accomplished from aldehyde **26** by the usual alane reduction / hydrogenolysis procedure to give the *cis*-DHQ-5-ethanol derivative **32** in 91% yield. A subsequent treatment with ruthenium tetroxide brought about both the reoxidation of the *N*-Boc-DHQ to the corresponding *N*-acyl lactam³⁴ and the oxidation of the alcohol functionality to an acid, which was then converted to ester **33** as shown in Scheme 8. The synthesis of (+)-luciduline was completed by cyclization of lactam ester **33** with lithium isopropylcyclohexylamide, followed by LiAlH₄ reduction of the resulting luciduline lactam **34**³⁵ to give dihydroluciduline and a final Jones oxidation.^{11a} Our synthetic luciduline showed NMR data and a specific rotation coincident with those reported¹¹ for the natural product. Given that luciduline had previously been converted into nankakurines in the racemic series,³⁶ the above synthesis also constitutes a formal total synthesis of (+)-nankakurines A and B.

Scheme 8. Enantioselective Synthesis of (+)-Luciduline



Conclusion

Phenylglycinol-derived tricyclic oxazoloquinolone lactams have proven to be multipurpose scaffolds for the enantioselective synthesis of structurally diverse DHQ-containing alkaloids. The results reported in this paper demonstrate that these lactams can be successfully used to assemble phlegmarine-type *Lycopodium* alkaloids, such as (–)-cermizine B, (+)-serratezomine E, and (+)-luciduline. Key stereoselective steps of the synthesis are the elaboration of the (*S*)-(2-piperidyl)methyl moiety from the allyl substituent and the generation of the *cis*-DHQ ring fusion by reductive opening of the oxazolidine ring.

The chiral lactam scaffolds bearing the required DHQ C-5 and C-7 substituents and stereochemistry are more efficiently prepared by a straightforward cyclocondensation reaction between (*R*)- or (*S*)-phenylglycinol and an appropriately substituted δ -keto ester **11**, easily accessible from the chiral pool, than by a stepwise stereoselective introduction of the DHQ substituents on unsubstituted unsaturated tricyclic lactams. The factors governing the stereoselectivity of these and related cyclocondensation reactions have been rationalized, which will allow the design of related stereocontrolled cyclocondensations leading to enantiopure *cis*-DHQs with different substitution and stereochemical patterns.

Experimental Section

(3*R*,7*aS*,10*R*,11*aS*)-10-Hydroxy-5-oxo-3-phenyl-2,3,5,6,7,7*a*,10,11-octahydrooxazolo[2,3-*j*]

quinoline (3): SeO₂ (1.08 g, 9.76 mmol) was added to a stirring solution of lactam **1a** (610 mg, 2.27 mmol) in anhydrous dioxane (76 mL) at room temperature. The resulting suspension was heated at reflux for 24 h. The solvent was evaporated, and the residue was taken up in EtOAc. The organic solution was washed with water, dried, and concentrated. Flash chromatography (2:8 hexane–EtOAc) afforded alcohol **3** (505 mg, 78 %) as a white solid: $[\alpha]^{23}_{\text{D}} - 26.8$ (*c* 1.2, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 1.58-1.68 (m, 2H, H-7, OH), 1.99 (dd, *J* = 4.8, 14.8 Hz, 1H, H-11), 2.02-2.06 (m, 1H, H-7), 2.26 (dd, *J* = 1.6, 14.8 Hz, 1H, H-11), 2.33-2.36 (m, 1H, H-7*a*), 2.46-2.53 (m, 1H, H-6), 2.68 (dd, *J* = 4.0, 6.0 Hz, 1H, H-6), 4.07-4.12 (m, 2H, H-2, H-10), 4.56 (t, *J* = 8.8 Hz, 1H, H-2), 5.54 (t, *J* = 8.4 Hz, 1H, H-3), 5.83 (dd, *J* = 4.8, 9.6 Hz, 1H, H-9), 5.97 (dd, *J* = 4.8, 10 Hz, 1H, H-8), 7.19 (d, *J* = 8.0 Hz, 2H, H-Ar), 7.24-7.28 (m, 1H, H-Ar), 7.32-7.36 (m, 2H, H-Ar); ¹³C-NMR (75.4 MHz, CDCl₃) δ (ppm): 24.7 (C-7), 31.1 (C-6), 34.2 (C-11), 40.5 (C-7*a*), 58.5 (C-3), 64.9 (C-10), 69.3 (C-2), 94.2 (C-11*a*), 125.3 (2CH-Ar), 127.3 (CH-Ar), 128.3 (C-9), 128.6 (2CH-Ar), 129.1 (C-8), 139.8 (C-Ar), 169.3 (NCO); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₉NO₃H 286.1438; Found 286.1438.

(3*R*,7*aS*,11*aS*)-5,10-Dioxo-3-phenyl-2,3,5,6,7,7*a*,10,11-octahydrooxazolo[2,3-*j*]quinoline (4): Dess-Martin periodinane (1.97 g, 4.65 mmol) was added to a stirring solution of alcohol **3** (500 mg) in anhydrous CH₂Cl₂ (186 mL). The resulting suspension was stirred overnight at room temperature. Saturated aqueous NaHCO₃ (60 mL) and saturated aqueous Na₂S₂O₃ (60 mL) were added, and the mixture was stirred for 45 minutes. The layers were separated, and the aqueous solution was extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated. Flash chromatography (3:7 hexane–EtOAc) afforded enone **4** (343 mg, 85%) as a white-yellow residue: $[\alpha]^{23}_{\text{D}} - 119$ (*c* 1.0, CHCl₃); ¹H-NMR (400 MHz, CDCl₃, COSY, g-HSQC) δ (ppm): 1.82-1.97 (m, 1H, H-7), 2.18-2.27 (m, 1H, H-7), 2.52-2.66 (m, 2H, H-7*a*, H-11), 2.72-2.89 (m, 3H, H-6, H-11), 3.98 (t, *J* = 8.2 Hz, 1H, H-2), 4.53 (t, *J* = 8.2 Hz, 1H, H-2), 5.46 (t, *J* = 8.2 Hz, 1H, H-3), 6.09 (d, *J* = 10.2 Hz, 1H, H-9), 6.95 (dd, *J* = 5.6, 10.2 Hz, 1H, H-8), 7.16 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.26 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.34 (t, *J* = 7.4 Hz, 2H, H-Ar); ¹³C-NMR (75.4 MHz, CDCl₃) δ (ppm): 23.7 (C-7), 31.0 (C-6), 41.6 (C-7*a*), 43.9 (C-11), 58.9 (C-3), 69.6 (C-2), 94.9 (C-11*a*), 125.3 (2CH-Ar), 127.6 (CH-Ar), 128.3 (C-9), 128.8 (2CH-Ar), 139.1 (Cq-Ar), 148.0 (C-8), 168.6 (NCO), 194.8 (C=O); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₇H₁₇NO₃H 284.1281; Found 284.1291.

(3R,7aS,8R,11aS)-8-Butyl-5,10-dioxo-3-phenylperhydrooxazolo[2,3-j]quinoline (5): *Method A.* *n*-BuLi (560 μ L, 2.5 M in hexane, 1.41 mmol) was added dropwise under argon to a suspension of CuI (135 mg, 0.71 mmol) in anhydrous Et₂O (3.0 mL) at -20°C . After 30 minutes, the solvent was evaporated under a stream of argon. The resulting residue was dissolved in anhydrous CH₂Cl₂ (5 mL), and the mixture was stirred for 10 min at -20°C . Enone **4** (40 mg, 0.14 mmol) in anhydrous CH₂Cl₂ (1.0 mL) was added dropwise at -78°C . The mixture was stirred at -78°C for 30 minutes and at -30°C for 3 h. Saturated aqueous NH₄Cl was added, the phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated. Flash chromatography (3:7 hexane–EtOAc) afforded compound **5** (40 mg, 83%) as a yellowish oil: $[\alpha]_D^{23} -80.1$ (*c* 0.19, CHCl₃); ¹H-NMR (400 MHz, CDCl₃, COSY, g-HSQC) δ : 0.91 (t, *J* = 6.8 Hz, 3H, CH₃), 1.25-1.37 (m, 4H, H-2', H-3'), 1.39-1.49 (m, 1H, H-1'), 1.57-1.66 (m, 1H, H-1'), 1.77-1.83 (m, 1H, H-8), 1.85-1.92 (m, 1H, H-7a), 1.93-2.01 (m, 1H, H-7), 2.03-2.11 (m, 1H, H-7), 2.42 (dd, *J* = 4.8, 16.0, Hz, 2H, H-9), 2.54 (ddd, *J* = 4.0, 10.8, 18.0 Hz, 1H, H-6), 2.64 (brs, 2H, H-11), 2.73 (dd, *J* = 4.0, 5.6 Hz, 1H, H-6), 3.94 (dd, *J* = 7.6, 8.8 Hz, 1H, H-2), 4.52 (t, *J* = 8.8 Hz, 1H, H-2), 5.41 (t, *J* = 8.2 Hz, 1H, H-3), 7.12 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.24 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.32 (t, *J* = 7.4 Hz, 2H, H-Ar); ¹³C-NMR (100.6 MHz, CDCl₃) δ : 14.0 (CH₃), 22.6 (C-3'), 25.3 (C-7), 29.4 (C-2'), 31.3 (C-6), 34.8 (C-1'), 38.2 (C-8), 41.8 (C-9), 43.7 (C-7a), 45.3 (C-11), 58.0 (C-3), 69.5 (C-2), 96.2 (C-11a), 125.3 (2CH-Ar), 127.4 (CH-Ar), 128.7 (2CH-Ar), 139.4 (Cq-Ar), 169.4 (C-5), 207.1 (C-10); HRMS (ESI-TOF) *m/z*: [*M* + *H*]⁺ Calcd for C₂₁H₂₇NO₃H 342.2064; Found 342.2063.

Method B. MeLi (74 μ L, 1.6 M in Et₂O, 0.12 mmol) was added to a suspension of CuI (23 mg, 0.12 mmol) in anhydrous THF (300 μ L) at 0°C . The resulting yellow/brown suspension was cooled to -50°C , and HMPA (60 μ L, 20 % v/v) and DIBALH (240 μ L, 1 M in hexane, 0.24 mmol) were sequentially added. After 30 minutes, the mixture was cooled to -65°C , and compound **6** (see below; 20 mg, 0.06 mmol) in anhydrous THF (300 μ L) was added dropwise. The mixture was allowed to warm to -50°C , and stirring was continued for 2 h. 1 M aqueous HCl was added, the phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were filtered over Celite®, and the solvent was evaporated. Flash chromatography (4:6 hexane–EtOAc) afforded compound **5** (15 mg, 75%) as a yellowish oil.

(3R,7aS,8R,11aS)-8-Butyl-5-oxo-3-phenylperhydrooxazolo[2,3-j]quinoline (2c): *1st step.* BF₃·Et₂O (5 μ L, 0.04 mmol) was added to a solution of ketone **5** (44 mg, 0.13 mmol) and 1,3-propanedithiol (20 μ L, 0.194 mmol) in anhydrous CH₂Cl₂ (2.0 mL), and the mixture was stirred at room temperature for 16 h. 2 M aqueous NaOH was added, the phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried, and concentrated to afford crude dithiane.

2nd step. Ni-Raney (200 mg) was added to a solution of the above crude in absolute EtOH (2.3 mL), and the slurry suspension was heated to reflux for 23 h. After cooling to room temperature, 5% aqueous HCl was added, and the resulting suspension was filtered over Celite®. The solvent was evaporated, and the residue was re-dissolved in 10% aqueous NaOH and extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated. Flash chromatography (6:4, hexane–EtOAc) afforded lactam **2c** (24 mg, 55% overall yield) as a white residue: $[\alpha]^{23}_{\text{D}} - 77.1$ (*c* 1.1, MeOH); ¹H-NMR (400 MHz, CDCl₃, COSY, g-HSQC) δ (ppm): 0.91 (t, *J* = 6.8 Hz, 3H, H-4'), 1.24-1.84 (m, 15H), 2.11-2.23 (m, 1H), 2.47 (ddd, *J* = 18.5, 11.0, 7.2 Hz, 1H, H-6), 2.64 (dd, *J* = 18.5, 7.2 Hz, 1H, H-6), 3.83 (t, *J* = 8.4 Hz, 1H, H-2), 4.51 (t, *J* = 8.4 Hz, 1H, H-2), 5.30 (t, *J* = 8.4 Hz, 1H, H-3), 7.15-7.33 (m, 5H, H-Ar); ¹³C-NMR (100.6 MHz, CDCl₃) δ (ppm): 14.2 (CH₃), 18.0 (C-10), 22.8 (C-7), 24.2 (C-11), 24.8 (C-7), 30.5 (C-9), 30.6 (CH₂), 31.3 (C-6), 32.9 (CH₂), 39.9 (C-8), 43.7 (C-7a), 58.0 (C-3), 69.6 (C-2), 95.5 (C-11a), 125.4 (2CH-Ar), 127.0 (CH-Ar), 128.5 (2CH-Ar), 140.3 (C-*i*), 169.5 (NCO).

(3R,7aS,11aS)-8-Butyl-5,10-dioxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinolone

(6): Mn(OAc)₃ (8.3 mg, 0.03 mmol) was added under argon to a stirring solution of lactam **1c** (50 mg, 0.15 mmol) and TBHP (140 μ L, 5.5 M in decane, 0.77 mmol) in EtOAc (9 mL) containing 3 Å molecular sieves (180 mg). The mixture was stirred at 50 °C for 40 h and filtered over Celite®. After washing with EtOAc, the solvent was evaporated. Flash chromatography (6:4 hexane–EtOAc) afforded enone **6** (21 mg, 40%) as a colorless oil: $[\alpha]^{23}_{\text{D}} - 97.1$ (*c* 1.05, CHCl₃); ¹H-NMR (400 MHz, CDCl₃, COSY, g-HSQC) δ : 0.95 (t, *J* = 7.4 Hz, 3H, CH₃), 1.34-1.43 (m, 2H, H-3'), 1.45-1.66 (m, 2H, H-2'), 1.79-1.95 (m, 1H, H-1'), 2.21-2.40 (m, 3H, H-7, H-1'), 2.45 (dd, *J* = 3.6, 13.2 Hz, 1H, H-7a), 2.56-2.65 (m, 1H, H-6), 2.72-2.86 (m, 3H, H-6, H-11), 3.94 (t, *J* = 8.4 Hz, 1H, H-2), 4.50 (t, *J* = 8.4 Hz, 1H, H-2), 5.41 (t, *J* = 8.4 Hz, 1H, H-3), 5.95 (s, 1H, H-9), 7.18 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.26 (t, *J* = 7.4 Hz, 1H, H-Ar), 7.34 (t, *J* = 7.4 Hz, 2H, H-Ar); ¹³C-NMR (100.6 MHz, CDCl₃) δ : 13.8 (CH₃), 22.3 (C-3'), 23.7 (C-1'), 29.1 (C-2'), 31.1 (C-6), 35.2 (C-7), 43.1 (C-11), 45.4 (C-7a), 59.1 (C-3), 69.7 (C-2), 95.2 (C-11a), 124.5 (C-9), 125.4 (2CH-Ar), 127.6 (CH-Ar), 128.8 (2CH-Ar), 139.1 (Cq-Ar), 164.3 (C-8), 168.5 (NCO), 194.7 (C=O); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₂₅NO₃H 340.1907; Found 340.1917.

(3R,7aS,11aS)-8-Formyl-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline (7b):

Operating as in the preparation of compound **3**, from lactam **1b** (100 mg, 0.35 mmol) and SeO₂ (169 mg, 1.52 mmol) in anhydrous dioxane (12 mL), aldehyde **7b** (105 mg, 99%) was obtained as a dark orange foam after filtration over a short pad of silica: mp: 175-177 °C; $[\alpha]^{23}_{\text{D}} - 128.7$ (*c* 0.875, CHCl₃); ¹H-NMR (400 MHz CDCl₃, COSY, g-HSQC) δ (ppm): 1.59-1.62 (m, 1H, H-7), 1.80-1.92 (m, 1H, H-11), 1.94-2.04 (m, 1H, H-11), 2.25-2.36 (m, 1H, H-7), 2.39-2.47 (m, 2H, H-10), 2.55-2.59 (m, 2H, H-6), 2.69-2.75 (m, 1H, H-7a), 3.93 (t, *J* = 8.3 Hz, 1H, H-2), 4.56 (t, *J* = 8.3 Hz, 1H, H-2), 5.51 (t, *J* = 8.3 Hz,

1H, H-3), 6.84 (t, $J = 3.6$ Hz, 1H, H-9), 7.18 (dd, $J = 7.2, 3.6$ Hz, 2H, H-Ar), 7.26 (t, $J = 7.2$ Hz, 1H, H-Ar), 7.34 (t, $J = 7.4$ Hz, 2H, H-Ar), 9.48 (s, 1H, CHO); ^{13}C -NMR (100.6 MHz, CDCl_3) δ (ppm): 24.5 (C-10), 25.0 (C-7), 26.4 (C-11), 31.1 (C-6), 37.9 (C-7a), 58.4 (C-3), 69.6 (C-2), 93.2 (C-11a), 125.3 (2CH-Ar.), 127.3 (CH-Ar.), 128.7 (2CH-Ar.), 140.1 (Cq-Ar.), 141.5 (C-8), 149.7 (C-9), 169.5 (C-5), 192.7 (CHO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_3\text{H}$ 298.1438; Found 298.1432.

(3R,7aS,11aS)-5-Oxo-8-(4-oxobutyl)-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline

(7c): Operating as in the preparation of compound **3**, from lactam **1c** (50 mg, 0.15 mmol) and SeO_2 (74 mg, 0.66 mmol) in anhydrous dioxane (5 mL), ketone **7c** (47 mg, 89%) was obtained after flash chromatography (7:4 hexane–EtOAc) as a colorless oil: $[\alpha]^{23}_{\text{D}} - 181.8$ (c 1.1, CHCl_3); IR (NaCl): 1663 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3 , COSY, g-HSQC) δ (ppm): 0.93 (t, $J = 7.4$ Hz, 3H, CH_3), 1.47-1.58 (m, 1H, H-7), 1.59-1.74 (m, 2H, H-3'), 1.75-1.88 (m, 1H, H-11), 1.90-1.99 (m, 1H, H-11), 2.19-2.27 (m, 1H, H-7), 2.34 (brs, 2H, H-10), 2.57-2.69 (m, 4H, H-6, H-2'), 2.83 (d, $J = 11.6$ Hz, 1H, H-7a), 3.91 (t, $J = 8.2$ Hz, 1H, H-2), 4.54 (t, $J = 8.2$ Hz, 1H, H-2), 5.49 (t, $J = 8.2$ Hz, 1H, H-3), 6.93 (t, $J = 3.4$ Hz, 1H, H-9), 7.18 (d, $J = 7.4$ Hz, 2H, H-Ar), 7.25 (d, $J = 5.2$ Hz, 1H, Ar), 7.33 (t, $J = 7.4$ Hz, 2H, Ar); ^{13}C -NMR (100.6 MHz, CDCl_3) δ (ppm): 13.8 (CH_3), 18.0 (C-3'), 24.1 (C-10), 25.7 (C-11), 25.8 (C-7), 31.3 (C-6), 38.8 (C-7a), 39.1 (C-2'), 58.5 (C-3), 69.5 (C-2), 93.7 (C-11a), 125.3 (2CH-Ar), 127.2 (CH-Ar), 128.6 (2CH-Ar), 138.6 (C-9), 139.4 (Cq-Ar), 140.2 (C-8), 169.7 (NCO), 199.7 (C=O); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_3\text{H}$ 340.1907; Found 340.1911.

(3R,7aS,11aS)-8-(Hydroxymethyl)-5-oxo-3-phenyl-2,3,5,6,7,7a,10,11-octahydrooxazolo[2,3-*j*]quinoline:

NaBH₄ (13 mg, 0.34 mmol) was added in portions to a stirring solution of aldehyde **7b** (100 mg, 0.34 mmol) in absolute EtOH (3 mL) at 0 °C, and the mixture was stirred at room temperature for 45 minutes. Then, water was added, the ethanol was removed under reduced pressure, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated to afford the title alcohol (90 mg, 90%) as a sticky yellowish solid: $[\alpha]^{23}_{\text{D}} - 101.2$ (c 1.0, CHCl_3); IR (NaCl): 3041, 1655, 1629 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g-HSQC) δ (ppm): 1.61-1.86 (m, 2H, H-11), 1.90 (dd, $J = 14.4, 5.8$ Hz, 1H, H-7), 2.03-2.23 (m, 2H, H-10), 2.25-2.36 (m, 1H, H-7), 2.37 (brs, 1H, H-7a) 2.52 (ddd, $J = 11.4, 7.6, 4.2$ Hz, 1H, H-6), 2.68 (dd, $J = 18.4, 6.4$ Hz, 1H, H-6), 3.91 (t, $J = 8.4$ Hz, 1H, H-2), 4.06-4.18 (m, 2H, CH_2OH) 4.57 (t, $J = 8.4$ Hz, 1H, H-2), 5.47 (t, $J = 8.4$ Hz, 1H, H-3), 5.75 (brs, 1H, H-9), 7.15-7.37 (m, 5H, H-Ar); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 22.9 (C-10), 25.1 (C-7), 26.1 (C-11), 31.3 (C-6), 40.9 (C-11), 58.5 (C-3), 65.3 (CH_2OH), 69.5 (C-2), 94.2 (C-11a), 123.4 (C-9), 125.3 (2CH-Ar), 127.2 (CH-Ar), 128.6 (2CH-Ar), 137.4 (C-8), 140.2 (Cq-Ar), 169.6 (C-5); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{21}\text{NO}_3\text{H}$ 300.1594; Found 300.1591.

(3*R*,7*aS*,11*aS*)-5-Oxo-3-phenyl-8-[(triisopropylsilyloxy)methyl]-2,3,5,6,7,7*a*,10,11-

octahydrooxazolo[2,3-*j*]quinoline (8): TIPSCl (300 μ L, 1.4 mmol) was added to a stirring solution of the above alcohol (280 mg, 0.94 mmol) and imidazole (96 mg, 1.4 mmol) in anhydrous DMF (2 mL), and the mixture was stirred at room temperature for 17 h. Brine was added, and the resulting mixture was stirred for 20 minutes and extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (from hexane to 75:25 hexane–EtOAc) afforded compound **8** (360 mg, 84%) as a sticky white residue: IR (NaCl): 1645 (NCO) cm⁻¹; [α]_D²³ – 37.2 (*c* 0.48 CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 1.05-1.15 [m, 21H, Si(*i*Pr)₃] 1.65-1.92 (m, 3H), 2.05-2.20 (m, 2H), 2.25-2.37 (m, 2H), 2.45-2.54 (m, 1H), 2.68 (dd, *J* = 18.4, 6.4 Hz, 1H), 3.90 (t, *J* = 8.0 Hz, 1H), 4.25 [brs, 2H, CH₂OSi(*i*Pr)₃], 4.56 (t, *J* = 8.0 Hz, 1H), 5.46 (t, *J* = 8.0 Hz, 1H), 5.72 (brs, 1H), 7.18-7.35 (m, 5H, H-Ar); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 12.0 (CH); 18.0 (CH₃); 22.8 (CH₂), 25.4 (CH₂), 26.3 (CH₂), 31.4 (CH₂), 41.2 (CH₂), 58.5 (CH), 65.8 [CH₂OSi(*i*Pr)₃], 69.5 (CH₂) 93.3 (Cq), 120.8 (CH), 125.3 (CH-Ar), 125.4 (CH-Ar), 127.1 (CH-Ar), 128.5 (CH-Ar), 128.6 (CH-Ar), 136.9 (Cq), 140.3 (Cq-Ar), 169.7 (Cq); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₇H₄₁NO₃SiH 456.2928; Found 456.2933.

Methyl (2*R*,4*R*)-2-allyl-4-methyl-6-oxocyclohexanepropionate (11): A solution of compound **9**¹⁸ (4.0 g, 20.4 mmol) in anhydrous CH₂Cl₂ (8.0 mL), TMSCl (13 mL, 102 mmol), and AllylTMS (3.57 mL, 22.44 mmol) were added sequentially to a solution of InCl₃ (451 mg, 2.04 mmol) in anhydrous CH₂Cl₂ (68 mL), and the resulting mixture was stirred at room temperature for 4 h. Saturated aqueous NaHCO₃ was added, and the aqueous phase was separated and extracted with CH₂Cl₂. The combined organic extracts were dried and concentrated. Flash chromatography (96:4 hexane–EtOAc), afforded keto ester **11** (4.8 g, 99%; 1:1 mixture of C-2 epimers) as a colorless oil: ¹H-NMR (400 MHz, CDCl₃, COSY, g-HSQC) δ (ppm): 0.93 and 0.96 (d, *J* = 6.4 Hz, 3H, CH₃), 1.38-1.45 (m, 1H), 1.47-1.54 (m, 1H), 1.59-1.67 (m, 1H), 1.83-1.90 (m, 1H), 1.92-1.98 (m, 1H), 2.00-2.16 (m, 4H), 2.18-2.24 (m, 1H), 2.28 (t, *J* = 7.6 Hz, 1H), 2.32-2.39 (m, 1H), 2.50-2.54 (m, 1H), 3.63 (s, 3H), 4.93-5.03 (m, 2H), 5.58-5.74 (m, 1H); ¹³C-NMR (100.6 MHz, CDCl₃) δ (ppm): 21.0 and 22.2 (CH₃), 21.8 and 24.7 (CH₂), 29.3 and 29.5 (CH), 31.7 and 31.9 (CH₂), 34.3 (CH₂), 36.6 and 39.1 (CH₂), 39.1 and 40.4 (CH), 47.2 and 50.2 (CH₂), 51.4 and 51.5 (OCH₃), 52.7 and 53.6 (CH), 116.4 and 117.0 (CH₂), 135.7 and 136.2 (CH), 173.6 and 173.8 (COO), 211.6 and 213.4 (CO); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₄H₂₂O₃H 239.1642; Found 239.1639.

(3*S*,7*aS*,8*R*,10*R*,11*aS*)-8-Allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (18*a*) and (3*S*,7*aR*,8*R*,10*R*,11*aR*)-8-allyl-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-*j*]quinoline (18*b*): (*S*)-Phenylglycinol (1.7 g, 12.6 mmol) was added to a solution of keto ester **11** (2.0 g, 8.39 mmol) and AcOH (720 μ L, 12.6 mmol) in benzene (67 mL). The mixture was heated at reflux with azeotropic

elimination of water by a Dean-Stark system. After 24 h, the mixture was cooled to room temperature and concentrated, and the resulting oil was taken up in EtOAc. The organic solution was washed with saturated aqueous NaHCO₃, 1 M aqueous HCl and brine, dried, and concentrated. Flash chromatography (from 9:1 to 7:3 hexane–EtOAc) afforded pure lactams **18a** (1.15 mg, 43%) and **18b** (971 mg, 35%) as yellowish residues. **18b** (higher *R_f*): [α]_D²³ + 79.0 (*c* 2.0, CHCl₃); IR (NaCl): 1655, 1398 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 1.13 (d, *J* = 7.6 Hz, 3H, CH₃), 1.32–1.41 (m, 1H, H-9), 1.50 (dt, *J* = 5.2, 13.2 Hz, 1H, H-9), 1.79–1.89 (m, 5H, H-7, H-7a, H-11), 2.11–2.23 (m, 3H, -10, H-1'), 2.30–2.35 (m, 1H, H-8), 2.43–2.53 (m, 1H, H-6), 2.66–2.74 (m, 1H, H-6), 3.92 (t, *J* = 8.6 Hz, 1H, H-2), 4.35 (t, *J* = 8.6 Hz, 1H, H-2), 5.07–5.14 (m, 2H, CH=CH₂), 5.37 (t, *J* = 8.6 Hz, 1H, H-3), 5.78–5.90 (m, 1H, CH=CH₂), 7.23 (d, *J* = 7.4 Hz, 2H, H-Ar), 7.28–7.33 (m, 1H, H-Ar), 7.38 (t, *J* = 7.4 Hz, 2H, H-Ar); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 16.0 (C-11), 19.4 (CH₃), 27.4 (C-10), 30.6 (C-6), 30.7 (C-8), 31.4 (C-9), 34.2 (C-7), 37.7 (C-1'), 43.2 (C-7a), 58.8 (C-3), 69.5 (C-2), 95.9 (C-11a), 116.1 (C=CH₂), 125.3 (2CH-Ar), 127.0 (CH-Ar), 128.5 (2CH-Ar), 136.6 (CH=C), 140.1 (Cq-Ar), 169.2 (C-5); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₂₇NO₂H 326.2115; Found 326.2122. **18a** (lower *R_f*): [α]_D²³ – 44.5 (*c* 2.0, CHCl₃); IR (NaCl): 1656, 1435 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 0.91 (d, *J* = 6.0 Hz, 3H, CH₃), 1.15 (t, *J* = 13.8 Hz, 1H, H-11), 1.33 (dt, *J* = 4.8, 8.4 Hz, 1H, H-9), 1.49–1.53 (m, 1H, H-9), 1.71–1.81 (m, 2H, H-7, H-8), 1.87–1.96 (m, 2H, H-10, H-11), 1.97–2.03 (m, 1H, H-7), 2.05–2.12 (m, 1H, H-7a), 2.22–2.30 (m, 1H, H-1'), 2.32–2.40 (m, 2H, H-6, H-1'), 2.48–2.58 (m, 1H, H-1'), 3.86 (dd, *J* = 1.8, 7.2 Hz, 1H, H-2), 4.35 (dd, *J* = 1.8, 7.2 Hz, 1H, H-2), 4.86 (dd, *J* = 1.8, 7.2 Hz, 1H, H-3), 5.04–5.10 (m, 2H, CH=CH₂), 5.80 (dddd, *J* = 7.2, 10.2, 14.4, 17.2 Hz, 1H, CH=CH₂), 7.15–7.20 (m, 1H, H-Ar), 7.22–7.30 (m, 4H, H-Ar); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 21.9 (CH₃), 24.2 (C-7), 24.6 (C-10), 30.3 (C-1'), 32.8 (C-9), 38.1 (C-11), 38.3 (C-6), 39.4 (C-8), 41.0 (C-7a), 58.6 (C-3), 70.8 (C-2), 95.3 (C-11a), 116.1 (C=CH₂), 126.2 (2CH-Ar), 127.2 (CH-Ar), 128.4 (2CH-Ar), 138.2 (CH=C), 142.1 (Cq-Ar), 167.2 (NCO); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₂₇NO₂H 326.2115; Found 326.2119.

(3*S*,7*aR*,8*S*,10*R*,11*aR*)-10-Methyl-5-oxo-8-(2-oxoethyl)-3-phenylperhydrooxazolo[2,3-*j*]quinoline (26): RuCl₃.*n*H₂O in H₂O (3.9 mL, 0.14 mmol, 0.035 M stock solution) was added to a solution of lactam **18b** (1.27 g, 3.9 mmol) in MeCN (23 mL) under vigorous stirring. NaIO₄ (1.67 g, 7.8 mmol) was then added in portions over 5 min, and the stirring was continued for 1 h 20 min. Saturated aqueous Na₂S₂O₃ was added, the resulting mixture was diluted with EtOAc, the phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded aldehyde **26** (970 mg, 76%) as a white foam: [α]_D²³ + 121.1 (*c* 1.1, CHCl₃); IR (NaCl): 2931, 2707 and 1721, 1611 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 1.11 (d, *J* = 7.6 Hz, 3H, CH₃), 1.28–1.32 (m, 1H, H-9),

1.51 (ddd, $J = 21.2, 6.8, 5.6$ Hz, 1H, H-9), 1.72-1.86 (m, 5H, H-7, H-7a, H-11), 2.03-2.08 (m, 1H, H-10), 2.34-2.47 (m, 3H, H-6, H-1'), 2.66 (dd, $J = 18, 6.4$ Hz, 1H, H-6), 2.86-2.94 (m, 1H, H-8), 3.87 (dd, $J = 8.4, 8.8$ Hz, 1H, H-2), 4.53 (t, $J = 8.8$ Hz, 1H, H-2), 5.31 (t, $J = 8.2$ Hz, 1H, H-3), 7.16-7.18 (m, 2H, H-Ar), 7.22-7.26 (m, 1H, H-Ar), 7.30-7.34 (m, 2H, H-Ar), 9.76 (s, 1H, CHO); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 16.5 (C-7), 19.2 (CH_3), 25.9 (C-8), 27.2 (C-10), 30.4 (C-6), 31.3 (C-9), 33.7 (C-11), 43.5 (C-7a), 47.2 (C-1'), 58.8 (C-3), 69.4 (C-2), 95.4 (C-11a), 125.2 (2CH-Ar), 127.0 (CH-Ar), 128.4 (2CH-Ar), 140.0 (Cq-Ar), 168.8 (NCO), 201.2 (CHO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{25}\text{NO}_3\text{H}$ 328.1907; Found 328.1916.

(3S,7aR,8S,10R,11aR)-8-[(R,E)-2-(tert-Butylsulfinylimino)ethyl]-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-j]quinoline (27): (*R*)-(+)-*tert*-butanesulfinamide (63 mg, 0.55 mmol) was added to a solution of **26** (131 mg, 0.4 mmol) and $\text{Ti}(i\text{OPr})_4$ (270 μL , 0.88 mmol) in anhydrous THF (2 mL) under vigorous stirring. After 7 h at room temperature, brine was added under vigorous stirring, and the mixture was diluted with EtOAc. The suspension was filtered over Celite® and washed with EtOAc. The filtrate was dried and concentrated. Flash chromatography (4:6 hexane–EtOAc) afforded compound **27** (143 mg, 83%) as a white foam: $[\alpha]^{23}_{\text{D}} - 98.35$ (c 0.85, CHCl_3); IR (NaCl): 1654, 1622, 1082 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g -HSQC) δ (ppm): 1.08 (d, $J = 7.2$ Hz, 3H, CH_3), 1.21 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.36-1.40 (m, 1H, H-9), 1.54 (ddd, $J = 21.2, 6.6, 5.4$ Hz, 1H, H-9), 1.78-1.89 (m, 5H, H-7, H-7a, H-11), 2.02-2.11 (m, 1H, H-10), 2.34-2.43 (m, 1H, H-6), 2.51-2.55 (m, 2H, H-1'), 2.64-2.70 (m, 1H, H-6), 2.76-2.85 (m, 1H, H-8), 3.86 (dd, $J = 8.8, 8.0$ Hz, 1H, H-2), 4.51 (t, $J = 8.8$ Hz, 1H, H-2), 5.30 (t, $J = 8.4$ Hz, 1H, H-3), 7.16-7.18 (m, 2H, H-Ar), 7.22-7.26 (m, 1H, H-Ar), 7.32 (t, $J = 7.4$ Hz, 2H, H-Ar), 8.09 (t, $J = 4.8$ Hz, 1H, H-2'); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 16.5 (C-7), 19.5 (CH_3), 22.4 [$\text{C}(\text{CH}_3)_3$], 27.4 (C-10), 28.7 (C-8), 30.5 (C-6), 31.4 (C-9), 34.1 (C-11), 39.9 (C-1'), 43.9 (C-7a), 56.6 [$\text{C}(\text{CH}_3)_3$], 58.9 (C-3), 69.6 (C-2), 95.5 (C-11a), 125.4 (2CH-Ar), 127.2 (CH-Ar), 128.6 (2CH-Ar), 140.0 (Cq-Ar), 168.2 (NCO), 168.9 (HC=NSO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_3\text{SH}$ 431.2363; Found 431.2365.

(3S,7aR,8S,10R,11aR)-8-[(S)-2-[(R)-tert-Butylsulfinylamino]pent-4-enyl]-10-methyl-5-oxo-3-phenylperhydrooxazolo[2,3-j]quinoline (28): Allylmagnesium bromide (4.64 mL, 1 M in Et_2O , 4.64 mmol) was slowly added to a stirring solution of *N*-sulfinyl imine **27** (1.0 g, 2.32 mmol) in anhydrous CH_2Cl_2 (23 mL) at 0 °C. After 2 h, saturated aqueous NH_4Cl was added, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (from CH_2Cl_2 to 9.85:0.15 CH_2Cl_2 –MeOH) afforded sulfinamide **28** (965 mg, 88%) as a yellow foam: $[\alpha]^{23}_{\text{D}} + 46.3$ (c 0.88, CHCl_3); IR (NaCl): 3427, 1645, 1056 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g -HSQC) δ (ppm): 1.04 (d, $J = 7.2$ Hz, 3H, CH_3), 1.22-1.26 [m, 10H, $\text{C}(\text{CH}_3)_3$, H-9], 1.36-1.53 (m, 3H, H-9, H-1'),

1.69-1.84 (m, 5H, H-7, H-7a, H-11), 2.00-2.06 (m, 1H, H-10), 2.35-2.47 (m, 4H, H-6, H-3', H-8), 2.65 (dd, $J=6.2, 18.2$ Hz, 1H, H-6), 3.22 (d, $J=7.6$ Hz, 1H, NH), 3.29-3.38 (m, 1H, H-2'), 3.83 (dd, $J=8.0, 8.8$ Hz, 1H, H-2), 4.43 (t, $J=8.6$ Hz, 1H, H-2), 5.15-5.19 (m, 2H, H-5'), 5.29 (t, $J=8.2$ Hz, 1H, H-3), 5.73-5.84 (m, 1H, H-4'), 7.15-7.17 (m, 2H, H-Ar), 7.21-7.24 (m, 1H, H-Ar), 7.29-7.33 (m, 2H, H-Ar); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 16.2 (C-7), 19.4 (CH_3), 22.7 [$\text{C}(\text{CH}_3)_3$], 26.9 (C-8), 27.4 (C-10), 30.6 (C-6), 32.0 (C-9), 34.2 (C-11), 38.4 (C-1'), 41.0 (C-3'), 42.7 (C-7a), 52.9 (C-2'), 56.0 [$\text{C}(\text{CH}_3)_3$], 58.8 (C-3), 69.4 (C-2), 95.7 (C-11a), 119.4 (C-5'), 125.4 (2CH-Ar), 127.1 (CH-Ar), 128.5 (2CH-Ar), 133.6 (C-4'), 140.0 (Cq-Ar), 169.1 (NCO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{27}\text{H}_{40}\text{N}_2\text{O}_3\text{SH}$ 473.2832; Found 473.2841.

(3S,7aR,8S,10R,11aR)-8-[(S)-2-(Acryloylamino)pent-4-enyl]-10-methyl-5-oxo-3-

phenylperhydrooxazolo[2,3-*j*]quinoline (29): *1st step.* 1 M HCl in Et_2O (4.14 mL, 4.14 mmol) was slowly added to a stirred solution of sulfinamide **28** (738 mg, 1.66 mmol) in anhydrous MeOH (2 mL). After 1 h, the solvent was evaporated, and the resulting amine HCl salt was used without further purification in the next step.

2nd step. Acryloyl chloride (2.0 mL, 26.5 mmol) was slowly added to a biphasic mixture of the above crude amine hydrochloride in H_2O – CH_2Cl_2 (16.5 mL, 1:1) and Et_3N (3.70 mL, 26.5 mmol) at 0 °C. The mixture was stirred for 20 h at room temperature. Then, the mixture was diluted with CHCl_3 , and the layers were separated. The aqueous solution was extracted with CHCl_3 . The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (from 4:6 to 3:7 hexane– EtOAc) afforded acrylamide **29** (445 mg, 64%) as a white foam: $[\alpha]^{23}_{\text{D}} + 83.55$ (c 1.03, CHCl_3); IR (NaCl): 2924, 1655, 1403 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g -HSQC) δ (ppm): 1.04 (d, $J=7.6$ Hz, 3H, CH_3), 1.31-1.33 (m, 1H, H-9), 1.42-1.52 (m, 3H, H-9, H-1'), 1.69-1.80 (m, 5H, H-7, H-7a, H-11), 2.00-2.05 (m, 1H, H-10), 2.16-2.44 (m, 4H, H-6, H-8, H-3'), 2.58-2.64 (m, 1H, H-6), 3.82 (dd, $J=8.0, 8.4$ Hz, 1H, H-2), 4.07-4.16 (m, 1H, H-2'), 4.46 (t, $J=8.8$ Hz, 1H, H-2), 5.06-5.10 (m, 2H, H-5'), 5.25-5.29 (m, 1H, H-3), 5.58 (dd, $J=1.6, 10.0$ Hz, 1H, $\text{CH}_2=\text{CHCO}$), 5.71-5.81 (m, 2H, H-4', NH), 6.06 (dd, $J=10.4, 16.8$ Hz, 1H, $\text{CH}_2=\text{CHCO}$), 6.24 (dd, $J=1.6, 16.8$ Hz, 1H, $\text{CH}_2=\text{CHCO}$), 7.14-7.16 (m, 2H, H-Ar), 7.20-7.23 (m, 1H, H-Ar), 7.28-7.31 (m, 2H, H-Ar); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 16.3 (C-7), 19.4 (CH_3), 27.3 (C-10), 27.6 (C-8), 30.7 (C-6), 31.5 (C-9), 34.2 (C-11), 37.5 (C-1'), 38.7 (C-3'), 43.4 (C-7a), 46.3 (C-2'), 58.8 (C-3), 69.4 (C-2), 95.6 (C-11a), 118.2 (C-5'), 125.3 (2CH-Ar), 126.1 ($\text{CH}_2=\text{CHCO}$), 127.0 (CH-Ar), 128.5 (2CH-Ar), 131.0 ($\text{CH}_2=\text{CHCO}$), 134.0 (C-4'), 140.1 (Cq-Ar), 165.0 (NCO), 169.0 (NCO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_3\text{H}$ 423.2642; Found 423.2640.

(3S,7aR,8S,10R,11aR)-10-Methyl-8-[(S)-6-oxo-2-piperidyl]methyl}-5-oxo-3-phenyl

perhydrooxazolo[2,3-*j*]quinoline (30): Second generation Grubbs' catalyst (33 mg, 0.04 mmol) was

added to a stirring solution of acrylamide **29** (330 mg, 0.78 mmol) in degassed anhydrous CH₂Cl₂ (26 mL). The resulting brown solution was stirred at reflux temperature for 4 h. After cooling to room temperature, the mixture was stirred for an additional hour exposed to air. The solvent was evaporated under reduced pressure. Flash chromatography (from EtOAc to 95:5 EtOAc–MeOH) afforded dihydropyridone **30** (267 mg, 86%) as a brown foam: $[\alpha]^{23}_{\text{D}} + 61.3$ (*c* 0.95, CHCl₃); IR (NaCl): 3229, 1676, 1651 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 1.08 (d, *J* = 7.6 Hz, 3H, CH₃), 1.26-1.29 (m, 1H, H-9), 1.47-1.63 (m, 3H, H-9, H-1'), 1.72-1.87 (m, 5H, H-7, H-7a, H-11), 2.01-2.21 (m, 3H, H-10, H-7'), 2.31-2.46 (m, 2H, H-6, H-8), 2.67 (dd, *J* = 6.8, 18.4 Hz, 1H, H-6), 3.63-3.71 (m, 1H, H-2'), 3.85 (t, *J* = 8.6 Hz, 1H, H-2), 4.51 (t, *J* = 8.6 Hz, 1H, H-2), 5.30 (t, *J* = 8.4 Hz, 1H, H-3), 5.92-6.06 (m, 2H, H-5', NH), 6.59-6.64 (m, 1H, H-6'), 7.16-7.18 (m, 2H, H-Ar), 7.23-7.27 (m, 1H, H-Ar), 7.31-7.35 (m, 2H, H-Ar); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 16.3 (C-7), 19.4 (CH₃), 27.0 (C-8), 27.1 (C-10), 30.1 (C-7'), 30.5 (C-6), 31.6 (C-9), 34.0 (C-11), 38.7 (C-1'), 43.5 (C-7a), 48.2 (C-2'), 58.9 (C-3), 69.5 (C-2), 95.5 (C-11a), 124.5 (C-5'), 125.3 (2CH-Ar), 127.1 (CH-Ar), 128.5 (2CH-Ar), 140.0 (Cq-Ar), 140.3 (C-6'), 166.3 (NCO), 168.8 (NCO); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₄H₃₀N₂O₃H 395.2329; Found 395.2332.

(3*S*,7*aR*,8*S*,10*R*,11*aR*)-10-Methyl-8-([(S)-6-oxo-2-piperidyl]methyl)-5-oxo-3-phenyl

perhydrooxazolo[2,3-*j*]quinoline: A solution of dihydropyridone **30** (262 mg, 0.66 mmol) in MeOH (5.8 mL) containing Pd/C (52 mg, 10% Pd) was stirred under hydrogen at room temperature for 15 h. The catalyst was removed by filtration, and the solvent was evaporated affording the title piperidone (252 mg, 96%) as a colorless oil: $[\alpha]^{23}_{\text{D}} + 87.2$ (*c* 1.11, CHCl₃); IR (NaCl): 2930, 1655 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz, COSY, g-HSQC) δ (ppm): 1.07 (d, *J* = 7.2 Hz, 3H, CH₃), 1.23-1.27 (m, 1H, H-9), 1.34-1.53 (m, 4H, H-9, H-1', H-6'), 1.65-1.84 (m, 5H, H-7, H-9, H-7', H-7a, H-11), 1.89-1.97 (m, 3H, H-10, H-6', H-7'), 2.03-2.08 (m, 1H, H-10), 2.25-2.46 (m, 4H, H-6, H-8, H-5'), 2.66 (dd, *J* = 6.2, 18.6 Hz, 1H, H-6), 3.40-3.48 (m, 1H, H-2'), 3.85 (t, *J* = 8.6 Hz, 1H, H-2), 4.51 (t, *J* = 8.8 Hz, 1H, H-2), 5.30 (t, *J* = 8.2 Hz, 1H, H-3), 6.26 (s, 1H, NH), 7.16-7.18 (m, 2H, H-Ar), 7.22-7.26 (m, 1H, H-Ar), 7.29-7.34 (m, 2H, H-Ar); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 16.3 (C-7), 19.4 (CH₃), 19.6 (C-7'), 26.8 (C-8), 27.1 (C-10), 28.6 (C-6'), 30.5 (C-6), 31.2 (C-5'), 31.6 (C-9), 34.0 (C-11), 40.2 (C-1'), 43.5 (C-7a), 50.1 (C-2'), 58.8 (C-3), 69.4 (C-2), 95.4 (C-11a), 125.2 (2CH-Ar), 127.0 (CH-Ar), 128.4 (2CH-Ar), 140.0 (Cq-Ar), 168.8 (NCO), 172.2 (NCO); HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₄H₃₂N₂O₃H 397.2486; Found 397.2478.

(4*aR*,5*S*,7*R*,8*aS*)-1-[(S)-2-Hydroxy-1-phenylethyl]-7-methyl-5-([(S)-2-piperidyl]

methyl}decahydroquinoline: LiAlH₄ (3.57 mL, 1 M in THF, 3.57 mmol) was added to a stirring solution of AlCl₃ (147 mg, 1.10 mmol) in anhydrous THF (10 mL) at 0 °C. After 10 minutes, the mixture was allowed to warm to room temperature and stirred for an additional 30 minutes. The mixture

was cooled to $-78\text{ }^{\circ}\text{C}$, and after 10 minutes a solution of the above piperidone (218 mg, 0.55 mmol) in anhydrous THF (3.0 mL) was added. The stirring was continued at $-78\text{ }^{\circ}\text{C}$ for 90 min and at room temperature for 2 h. Water was slowly added, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2 –MeOH) afforded the title *cis*-DHQ (157 mg, 77%) as a colorless oil: $[\alpha]^{23}_{\text{D}} - 0.83$ (c 0.68, CHCl_3); IR (NaCl): 3331, 2928 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, *g*-HSQC) δ (ppm): 0.47 (d, $J = 7.2$ Hz, 3H, CH_3), 0.97–1.05 (m, 2H), 1.08–1.14 (m, 1H), 1.18–1.36 (m, 7H), 1.37–1.57 (m, 2H), 1.59–1.71 (m, 4H), 1.75–1.84 (m, 3H), 1.88–1.96 (m, 1H, H-7), 2.47–2.54 (m, 1H), 2.58–2.67 (m, 2H), 2.87–2.94 (m, 2H), 3.09–3.12 (m, 1H), 3.21 (brs, 1H, OH), 3.63 (t, $J = 4.6$, 1H, H-1'), 3.73 (dd, $J = 4.2$, 10.6 Hz, 1H, H-2'), 3.88 (dd, $J = 5.2$, 10.8 Hz, 1H, H-2'), 7.27–7.38 (m, 5H, CH-Ar); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 17.4 (CH_2), 17.8 (CH_3), 23.3 (C-3), 24.4 (CH_2), 25.6 (CH_2), 27.3 (C-7), 29.7 (CH_2), 30.4 (C-5), 32.3 (CH_2), 33.0 (CH_2), 40.1 (CH), 40.2 (CH_2), 43.8 (CH_2), 46.6 (CH_2), 51.8 (CH), 53.7 (CH), 63.1 (C-2'), 67.2 (C-1'), 127.5 (CH-Ar), 128.3 (2CH-Ar), 128.6 (2CH-Ar), 140.1 (Cq-Ar); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{38}\text{N}_2\text{OH}$ 371.3057; Found 371.3045.

(4aR,5S,7R,8aS)-5-[[*(S)*-1-*tert*-(Butoxycarbonyl)-2-piperidyl]methyl]-1-[(*S*)-2-hydroxy-1-phenylethyl]-7-methyldecahydroquinoline (31): Di-*tert*-butyl dicarbonate (86 mg, 0.39 mmol) was added to a stirring solution of the above *cis*-DHQ (132 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (6 mL) at room temperature. After 24 h, the solvent was evaporated under reduced pressure. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2 –MeOH) of the residue afforded carbamate **31** (140 mg, 83%) as a brown oil: $[\alpha]^{23}_{\text{D}} + 2.16$ (c 1.375, CHCl_3); IR (NaCl): 3288, 1686 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm): 0.43 (brs, 3H, CH_3), 1.21–1.30 (m, 7H), 1.31–1.41 (m, 4H), 1.47 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.51–1.57 (m, 3H), 1.63–1.78 (m, 1H), 1.80–1.87 (m, 1H), 1.95 (brs, 1H), 2.05–2.43 (m, 5H), 2.66–2.74 (m, 2H), 3.10 (brs, 1H), 3.64–3.94 (m, 3H), 4.19 (brs, 1H), 7.28–7.34 (m, 3H, CH-Ar), 7.42–7.44 (m, 2H, CH-Ar); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 16.8 (CH_2), 17.5 (CH_3), 18.9 (CH_2), 23.4, 25.6 (CH_2), 27.2 (CH), 28.4 (CH_2), 28.5 [$\text{OC}(\text{CH}_3)_3$], 29.2, 29.6 (CH_2), 30.9 (CH_2), 31.0 (CH), 32.5 (CH_2), 33.0 (CH_2), 38.7 (CH_2), 44.7 (CH_2), 47.8 (CH_2), 63.2 (CH_2), 67.2 (CH), 79.1, [$\text{OC}(\text{CH}_3)_3$], 128.1 (CH-Ar), 128.5 (2CH-Ar), 129.0 (2CH-Ar), 154.9 (NCO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{29}\text{H}_{46}\text{N}_2\text{O}_3\text{H}$ 471.3581; Found 471.3576.

(4aR,5S,7R,8aS)-1-Acetyl-5-[[*(S)*-1-*tert*-(butoxycarbonyl)-2-piperidyl]methyl]-7-methyldecahydroquinoline: *1st step.* A suspension of **31** (120 mg, 0.26 mmol) in MeOH (4.6 mL) containing $\text{Pd}(\text{OH})_2$ (48 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was then removed by filtration over Celite® and washed with MeOH, and the solvent was evaporated to give crude *N*-unsubstituted DHQ.

2nd step. TEA (39 μ L, 0.28 mmol) and acetyl chloride (18 μ L, 0.26 mmol) were added to a stirring solution of the above residue in CH_2Cl_2 (0.5 mL) at 0 $^\circ\text{C}$, and the mixture was stirred for 15 h at room temperature. Then, saturated aqueous NaHCO_3 was added, the phases were separated, and the aqueous solution was extracted with CH_2Cl_2 . The combined organic extracts were dried and concentrated. Flash chromatography (from CH_2Cl_2 to 8:2 CH_2Cl_2 –MeOH) afforded the title *N*-acetyl-DHQ (76 mg, 76%) as a yellow oil: $[\alpha]^{23}_{\text{D}} - 6.22$ (c 0.58, CHCl_3); IR (NaCl): 1686, 1644 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, *g*-HSQC) δ (ppm): 1.08 and 1.04 (d, $J = 7.6, 7.2$ Hz, 3H, CH_3), 1.14–1.20 (m, 2H), 1.28–1.40 (m, 4H), 1.44 and 1.45 [s, 9H, $\text{C}(\text{CH}_3)_3$], 1.47–1.58 (m, 5H), 1.62–1.79 (m, 4H), 1.88–1.94 (m, 1H), 1.95–2.03 (m, 1H), 2.04 and 2.06 (s, 3H, COCH_3), 2.08–2.17 (m, 2H), 2.60 (ddd, $J = 3.2, 13.2, 14.4$ Hz, 0.5H, H-2), 2.74 (t, $J = 12.2$ Hz, 1H, H-4'), 3.11 (ddd, $J = 2.8, 12.6$ Hz, 0.5H, H-2), 3.55 (d, $J = 14.0$ Hz, 0.5H, H-2), 3.87 (ddd, $J = 2.6, 7.6, 8.8$ Hz, 0.5H, H-8a), 3.97 (brs, 1H), 4.18–4.24 (m, 1H, H-4'), 4.47 (dd, $J = 2.8, 13.6$ Hz, 0.5H, H-2), 4.86 (ddd, $J = 4.8, 8.4, 9.2$ Hz, 0.5H, H-8a); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 17.5 and 17.7 (C-4), 18.5 and 18.7 (CH_3), 18.8 and 19.0 (CH_2), 21.2 and 22.1 (COCH_3), 25.1 and 26.1 (C-3), 25.6 (CH_2), 27.3 and 27.7 (C-7), 28.4 (C-8), 28.5 [$\text{C}(\text{CH}_3)_3$], 29.8 (CH_2), 30.7 (C-5), 32.0 and 32.4 (C-6), 32.9 and 33.1 (C-1'), 36.5 and 41.7 (C-2), 38.9 (C-4'), 38.9 and 39.3 (C-4a), 46.3 and 52.1 (C-8a), 47.9 (C-2'), 79.2 [$\text{C}(\text{CH}_3)_3$], 154.9 (NCO), 168.5 and 168.9 (CO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}_3\text{H}$ 393.3112; Found 393.3100.

(+)-Serratezomine E: TFA (41 μ L, 0.535 mmol) was slowly added to a stirring solution of the above DHQ (21 mg, 0.0535 mmol) in anhydrous CH_2Cl_2 (535 μ L) at room temperature. The mixture was stirred for 1 h, and the solvent was evaporated. Flash chromatography (KP-NH Biotage® SNAP cartridges, from CH_2Cl_2 to 8:2 CH_2Cl_2 –MeOH) afforded (+)-serratezomine **E** (14.6 mg, 95%) as a colorless oil: $[\alpha]^{23}_{\text{D}} + 6.10$ (c 0.62, CHCl_3) [$\text{Lit}^{10f} +9$ (c 1, CHCl_3)]; ^1H -NMR (CDCl_3 , 400 MHz) δ (ppm): δ 1.06 and 1.08 (d, $J = 7.2$ Hz, 3H, CH_3), 1.14–1.25 (m, 4H), 1.28–1.46 (m, 6H), 1.51 (m, 1H), 1.60–1.80 (m, 6H), 1.89–1.94 (m, 2H), 2.05 and 2.09 (s, 3H, COCH_3), 2.11–2.15 (m, 1H), 2.39–2.50 (m, 1H), 2.55 (t, $J = 3.2$ Hz, 0.5 H), 2.58–2.65 (m, 1H), 3.03–3.09 (m, 0.5H), 3.12 (td, $J = 4.0, 13.2$ Hz, 1H), 3.55 (m, 0.5H), 3.91 (dt, $J = 4.2, 12.4$ Hz, 0.5H), 4.46 (dd, $J = 4.0, 13.0$ Hz, 0.5 H), 4.88 (dt, $J = 4.4, 13.2$ Hz, 0.5H); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ 17.5 and 17.6 (CH_2), 18.5 and 18.7 (CH_3), 21.3 and 22.1 (COCH_3), 24.7 and 24.8 (CH_2), 25.0 and 26.0 (CH_2), 26.4 and 26.5 (CH_2), 27.3 and 27.7 (CH), 28.5 and 30.0 (CH_2), 29.5 and 29.8 (CH), 32.5 and 32.8 (CH_2), 33.1 and 33.3 (CH_2), 36.4 and 41.8 (CH_2), 38.5 and 39.5 (CH), 40.6 and 40.7 (CH_2), 46.2 and 52.1 (CH), 47.0 and 47.1 (CH_2), 53.4 (CH), 168.6 and 169.1 (CO).

(4a*R*,5*S*,7*R*,8a*S*)-1-(*tert*-Butoxycarbonyl)-5-(2-hydroxyethyl)-7-methyldecahydroquinoline (32):

1st step. LiAlH_4 (5.88 mL, 1 M in THF, 5.88 mmol) was added to a stirring solution of AlCl_3 (2418 mg, 1.84 mmol) in anhydrous THF (18 mL) at 0 $^\circ\text{C}$. After 30 minutes, the mixture was cooled to -78 $^\circ\text{C}$, and

after 10 minutes a solution of **26** (296 mg, 0.9 mmol) in anhydrous THF (3 mL) was added. The stirring was continued at -78°C for 90 min and at room temperature for 3 h. Water was slowly added, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous solution was extracted with EtOAc. The combined organic extracts were dried and concentrated to give crude dialcohol.

2nd step. A solution of the above residue and Boc_2O (237 mg, 1.08 mmol) in MeOH (18 mL) containing $\text{Pd}(\text{OH})_2$ (115 mg) was stirred under hydrogen at room temperature for 24 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (85:15 hexane–EtOAc) afforded *cis*-decahydroquinoline **32** (246 mg, 91%) as a colorless oil: $[\alpha]^{23}_{\text{D}} + 15.7$ (*c* 0.97, CHCl_3); IR (NaCl): 3355, 1732 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g-HSQC) δ (ppm): 1.03 and 1.07 (d, $J = 7.2$ Hz, 3H, CH_3), 1.14–1.24 (m, 2H), 1.28–1.35 (m, 2H), 1.38–1.42 (m, 2H), 1.42–1.47 [m, 10H, $\text{C}(\text{CH}_3)_3$], 1.48–1.57 (m, 1H), 1.60–1.73 (m, 3H), 1.89–1.97 (m, 2H), 2.09–2.10 (m, 1H, H-7), 2.70–2.84 (m, 1H, H-2), 3.60–3.69 (m, 2H, CH_2OH), 3.82–3.86 (m, 0.5H, H-2), 3.90–3.93 (m, 0.5H, H-2), 4.20 (dt, $J = 4.2, 13.2$ Hz, 0.5H, H-8a), 4.37 (m, $J = 4.4, 13.2$ Hz, 0.5H, H-8a); ^{13}C -NMR (CDCl_3 , 100.6 MHz) δ (ppm): 17.3 and 17.4 (CH_2), 18.3 and 18.7 (CH_3), 25.2 and 25.6 (CH_2), 27.5 and 27.7 (C-7), 28.4 and 28.9 (CH_2), 28.4 and 28.5 [$\text{OC}(\text{CH}_3)_3$], 30.3 and 30.4 (CH), 32.3 and 32.5 (CH_2), 36.2 and 36.3 (CH_2), 38.4 and 39.4 (C-2), 39.0 and 39.2 (CH), 48.2 and 49.4 (CH), 60.7 and 60.9 (CH_2OH), 79.0 and 79.1 [$\text{OC}(\text{CH}_3)_3$], 154.7 and 155.1 (NCO); HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{H}$ 298.2377; Found 298.2380.

Methyl (4a*R*,5*S*,7*R*,8*aS*)-1,7-dimethyl-2-oxodecahydroquinolin-5-acetate (33): *1st step.* 10% aqueous solution of NaIO_4 (4.1 mL) and $\text{RuO}_2 \cdot n\text{H}_2\text{O}$ (3 mg, 0.02 mmol) were added to a stirred solution of **32** (246 mg, 0.83 mmol) in EtOAc (1.6 mL). After 17 h, EtOAc (1.5 mL) was added, the organic layer was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were filtered over Celite®, and the filtrate was dried and concentrated to give a crude lactam acid.

2nd step. TFA (630 μL , 8.3 mmol) was slowly added to a stirring solution of the above acid in anhydrous CH_2Cl_2 (8.3 mL) at room temperature. After 1 h of stirring, the solvent was evaporated and the residue was taken up with anhydrous DMF (8.3 mL). NaH (99 mg, 4.13 mmol) was added to the solution, and the resulting suspension was stirred at room temperature for 1 h. Then, MeI (256 μL , 4.13 mmol) was added, and the stirring was continued for 48 h. Saturated aqueous NH_4Cl was added, the mixture was diluted with CH_2Cl_2 , the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (3:1 hexane–acetone) afforded **33** (121 mg, 58%) as a yellowish oil: $[\alpha]^{23}_{\text{D}} + 22.2$ (*c* 1.42, CHCl_3); IR (NaCl): 1736, 1639 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz, COSY, g-HSQC) δ (ppm): 1.04 (d, $J = 7.2$ Hz, 3H, CH_3), 1.23–1.28 (m, 1H), 1.41 (ddd, $J = 5.0, 6.4, 21.6$ Hz, 1H), 1.49–1.58 (m, 2H),

1.72-1.83 (m, 2H), 2.02-2.09 (m, 1H), 2.10-2.15 (m, 1H), 2.18-2.32 (m, 3H), 2.34-2.40 (m, 1H), 2.42-2.48 (m, 1H), 2.89 (s, 3H, NCH₃), 3.41 (dt, $J = 4.6, 12.4$ Hz, 1H, H-8a), 3.66 (s, 3H, COCH₃); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 15.4 (CH₂), 18.4 (CH₃), 27.2 (CH), 30.6 (CH), 31.1 (CH₂), 31.9 (CH₂), 32.0 (CH₂), 33.7 (NCH₃), 37.4 (CH), 38.1 (CH₂), 51.6 (COCH₃), 56.8 (C-8a), 169.6 (NCO), 172.8 (CO₂Me); HRMS (ESI-TOF) m/z : [M + H]⁺ Calcd for C₁₄H₂₃NO₃H 254.1751; Found 254.1753.

(+)-Luciduline lactam (34): A solution of *N*-isopropylcyclohexylamine (190 μ L, 1.15 mmol) in anhydrous THF (3.8 mL) was treated with *n*-BuLi (720 μ L, 1.6 M in THF, 1.15 mmol) at -78 °C, and the mixture was stirred for 30 min at this temperature. The resulting solution was added dropwise under argon at -78 °C over 20 min to a solution of **33** (117 mg, 0.46 mmol) in anhydrous THF (23 mL). After stirring at this temperature for 2 h, the solution was poured into 1 M HCl at 0 °C, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried, and concentrated. Flash chromatography (3:1 hexane–acetone) afforded **34** (80 mg, 78%) as a colourless oil: $[\alpha]_D^{23} + 92.8$ (c 0.79, CHCl₃); ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 0.96 (d, $J = 6.8$ Hz, 3H, CH₃), 1.34-1.40 (m, 1H), 1.55-1.59 (m, 1H), 1.63-1.72 (m, 2H), 2.03-2.10 (m, 2H), 2.23-2.28 (m, 2H), 2.30-2.41 (m, 2H), 2.62 (dd, $J = 12.4, 14.4$ Hz, 1H), 2.99 (s, 3H, NCH₃), 3.32-3.33 (m, 1H), 3.66-3.68 (m, 1H); ¹³C-NMR (CDCl₃, 100.6 MHz) δ (ppm): 20.1 (CH), 21.8 (CH₃), 30.4 (NCH₃), 31.3 (CH₂), 33.0 (CH), 36.4 (CH), 38.1 (CH₂), 38.9 (CH₂), 42.7 (CH₂), 55.8 (CH), 58.2 (CH), 167.7 (NCO), 205.8 (CO).

(+)-Luciduline: 1st step. LiAlH₄ (1.25 mL, 1 M in THF, 5.88 mmol) was added to a stirring solution of **34** (55 mg, 0.248 mmol) in anhydrous Et₂O (15 mL) at 0 °C, and the mixture was stirred at reflux temperature for 1 h. After cooling, water was slowly added at 0 °C, and the resulting mixture was diluted with EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried and concentrated to give crude alcohol.

2nd step. A solution of the above residue in acetone (1.6 mL) was added at room temperature to Jones reagent (2.5 mL) freshly prepared by dissolving CrO₃ (700 mg) in water (5 mL), H₂SO₄ (1.2 mL), and acetone (100 mL). After 30 min, water was slowly added at 0 °C, and the resulting mixture was basified with 3 M aqueous NaOH. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried and concentrated. Flash chromatography (KP-NH Biotage® SNAP cartridges, from hexane to 8:2 hexane–AcOEt) afforded **(+)-luciduline** (37 mg, 72%) as an unstable light yellow oil: $[\alpha]_D^{23} + 86.0$ (c 0.13, MeOH) [Lit.^{11a} + 87 (c 2.05, MeOH); Lit.^{11b} + 85.3 (c 0.15, MeOH); Lit.^{11c} + 87.3 (c 0.495, MeOH)]; ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 0.89 (d, $J = 6.8$ Hz, 3H, CH₃), 0.95-1.02 (m, 1H), 1.21-1.29 (m, 1H), 1.50-1.56 (m, 1H), 1.69 (br s, 1H), 1.81-1.90 (m, 2H), 1.91-2.01 (m, 1H), 2.02-2.08 (m, 1H), 2.12-2.18 (m, 1H), 2.13 (s, 3H, NCH₃), 2.23-2.25 (m, 1H), 2.27-2.37 (m, 2H), 2.39-2.43 (m, 1H), 2.81-2.85 (m, 1H), 3.04 (dd, $J = 11.8, 16.4$ Hz, 1H).

Supporting Information Available

Copies of the ^1H and ^{13}C NMR spectra of all new compounds, and X-ray crystallographic data for compound **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Acknowledgment

Financial support from the MINECO/FEDER (Project CTQ2015-65384-R) and the Generalitat de Catalunya (Grant 2014-SGR-155) is gratefully acknowledged. We also acknowledge the networking contribution from the COST Action CM1407, the MECD (Spain) for a fellowship to A. P., and the Serra Hunter programme (R. G.).

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