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Diastereocontrolled formal syntheses of (±)-lepadiformine A, B, and C and the divergent synthesis of 2-epi-lepadiformine C through unexpected double consecutive epimerizations

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Title: Diastereocontrolled formal syntheses of (±)-lepadiformine A, B, and C and the divergent synthesis of 2-*epi*-lepadiformine C through unexpected double consecutive epimerizations

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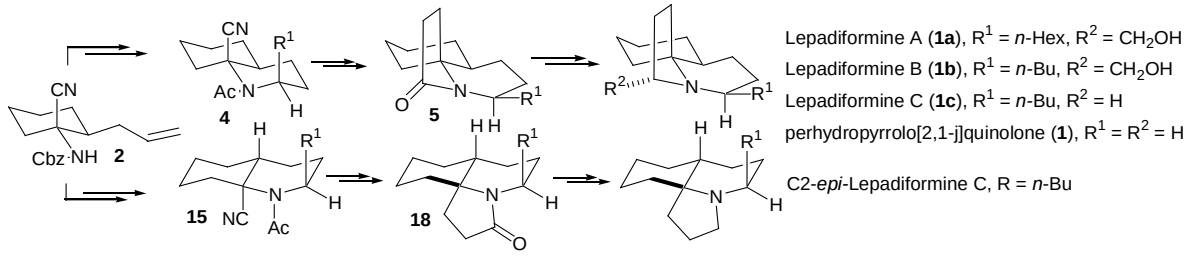
Abstract: We describe here the diastereocontrolled formal racemic syntheses of tricyclic marine alkaloids lepadiformine A, B and C and their C2 epimers, featuring divergent and stereoselective syntheses of the N-acetyl-8a-cyanodecahydroquinoline frameworks and the base-mediated intramolecular cyclization to establish the spiral quaternary center of the tricyclic framework from sterically well-defined α-aminonitrile **2**. The approach allows us to accomplish the tricyclic core structure efficiently from readily available starting materials through simple operations. An unexpected pair of consecutive epimerizations at two contiguous stereocenters is observed on the basis of single-crystal X-ray analyses of the intermediates and derivatives. The findings have been successfully applied to the total synthesis of 2-*epi*-lepadiformine C. The epimerization mechanism has been elucidated through a series of deuterium-labelling controlled experiments.



Introduction:

In 1994, Biard and Clardy reported the isolation of a tricyclic alkaloid Lepadiformine A (**1a**), from the marine ascidian *Clavelina lepadiformis* Müller in Tunisia. [1] The correct stereochemistry of lepadiformine A (**1a**) was established through total synthesis by Kibayashi and coworkers in 2000.[2] The absolute configuration was determined by Weinreb's enantioselective total synthesis in 2002,[3] confirmed shortly afterwards by the Kibayashi group[4,5] in the same year. In 2006, the analogues lepadiformine B (**1b**) and C (**1c**) were isolated from *C. moluccensis* by Sauviet and coworkers in Djibouti waters (Figure 1).[6]

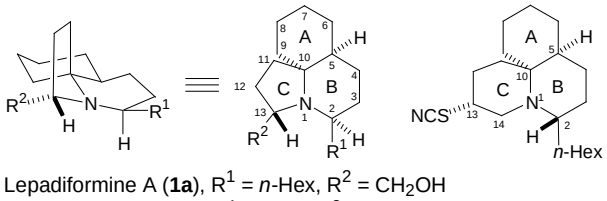
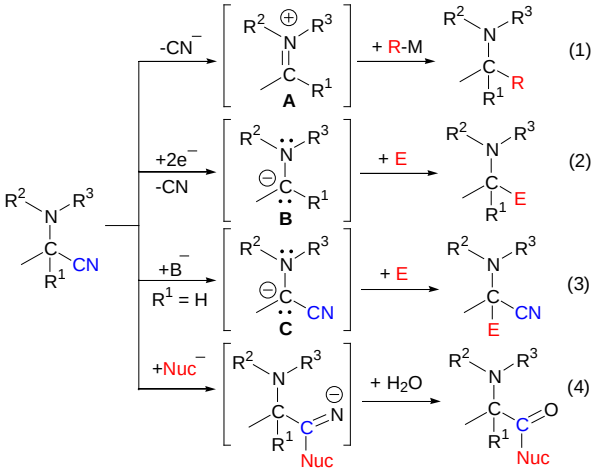


Figure 1. The structures of lepadiformine A, B, C and fasicularin.

Sauviat and coworkers reported lepadiformines A ~ C show strong cardiovascular effects in vitro and in vivo. Lepadiformine A blocks the inward rectifier K current (I_{K1}) with the K_D of 1.4 μM. The research results reveal that the length of the aliphatic chain at the C2 position is involved with the blockage degree. Compared to lepadiformine A, lepadiformine B ihibits I_{K1} by 54%.[6] In addition, these alkaloids exhibit cytotoxicity against several tumor cell lines as well as antiarrhythmic and antihypertensive properties. [1,7] The unique perhydropyrrolo[2,1-*j*]quinolone structure (**1**) and the promising biological activities have prompted chemists to develop various intellectual and elegant strategies toward their synthesis. [8, 9]

As one of the special and interesting bifunctional compounds, the α-aminonitrile is a versatile intermediate for a wide range of synthetic applications and receives an enormous amount of attention since the first discovery by Strecker in 1850.[9] The reactivity modes of α-aminonitriles can be classified in to four types, briefly described as follows (Scheme 1):

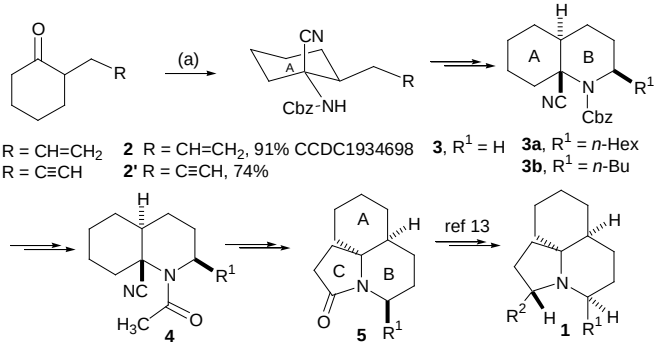
Scheme 1. Reactivity modes of α-aminonitriles



(1) Dissociation of the nucleofugal cyanide group under suitable conditions produces iminium intermediate **A** for further transformations. The process is also known as the Bruylants reaction. Weinreb and coworkers demonstrated the elegant manipulation of α-aminonitriles in the synthesis of enantiopure lepadiformine A (–)-(**1**). [3] (2) Treatment with a strong reducing agent like LiDBB (lithium 4,4'-di-tert-butylbiphenylide) generates a stabilized carbanion **B**. (3). The base-mediated α deprotonation allows for the formation of a nitrile-stablized anion **C**. Both carbanion **B** and carbanion **C** can be transformed to various adducts. Rychnovsky and coworkers adroitly employed type 2 and type 3 reactions, to achieve a variety of spirocyclic ring systems, including lepadiformine B.[10] (4) The electrophilic nature of the nitrile group permits nucleophilic reactions, and constitutes many synthetic transformations to valuable chemicals.

Recently, we serendipitously found a convenient access to quaternary α-aminonitrile **2** with good stereoselectivity on a decagram scale, with the configurations of which are related to those of the quaternary center and the AB junction of the lepadiformine family (Scheme 2).

Scheme 2. Our synthetic plan for lepadiformines using α-aminonitrile **2**[a]



[a]Reagents and conditions: (a) (i) $NH_{3(l)}$, MeOH, -50 °C to 0 °C, (ii) KCN, NH_4Cl, NH_3(aq), rt, (iii) CbzCl, K_2CO_3, THF, H_2O, 0 °C to rt.

The B ring was established by intramolecular condensation with an aldehyde derived from the allyl group of **2**, and completed the 8a-cyanodecahydroquinoline (8a-CDHQ) framework **3**. At this stage, an alkyl side chain was introduced by Lewis-acid mediated reductive alkylation with excellent diastereoselectivity to give a *syn* adduct.[11] We envisioned that direct manipulations of the angular nitrile to other carbonyl derivatives may be difficult due to the sterically demanding nature. Therefore, we considered an intramolecular addition on the nitrile, inspired by an amide group assisted hydrolysis of α-amino-adamantane-2-carbonitrle,[12] a very steric hindered nitrile group. With a carbon nucleophile in the framework, the C-ring was established via an intramolecular condensation, thus we turned our attention to the acetamide **4** instead. Assembly of the C ring as a γ-lactam proceeded by base-mediated condensation of the acetamide with the angular nitrile to furnish the tricyclic lactam core as the Renaud's intermediate **5**,[13] which therefore constituted a formal synthesis of lepadiformine alkaloids.

We wish to present here our divergent approach to the syntheses of the lepadiformine alkaloids as well as their C2 epimers from readily available α-aminonitrile **2**, and the clear experimental and theoretical explanations for the unexpected pair of epimerizations. The discovery of these epimerizations allowed a synthetic route to the C2-epimers of the alkaloids, the configurations of which are identical with those in the A and B rings of marine alkaloid fasicularin.

Results and Discussion:

Our synthesis started from readily available quaternary α-aminonitriles **2** and **2'**, which were synthesized by the Strecker reaction of 2-allylcyclohexanone[14] or 2-propargylcyclohexanone with cyanide in ammonia (Scheme 2). The unstable free α-aminonitriles were immediately protected with CbzCl to yield **2** and **2'** in good yields. The reaction proved highly diastereoselective, providing a single stereoisomer whose stereochemistry was established by X-ray crystallographic analysis (CCDC no. 1934698).[15] Both the cyano group and the methine proton are at the axial positions of the chair cyclohexane ring.

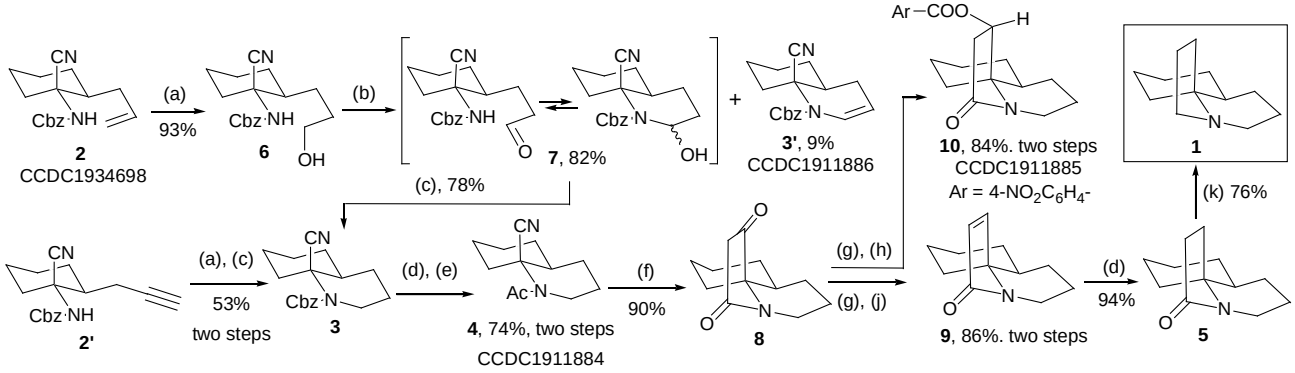
After extensive surveys on hydroboration conditions (e.g., B_2H_6, 9-BBN, Sia_2BH and Cy_2BH) and workup conditions to effect an efficient *anti*-Markovnikov hydration of the terminal alkene to alcohol **6**, we found that the use of Sia_2BH followed by the sodium perborate workup was the best combination giving **6** in 93% yield (Scheme 3). Dess-Martin Periodinane (DMP) oxidation of **6** led to an inseparable isomeric mixture **7** of an acyclic aldehyde and the cyclic hemiaminal (~ 1 : 2) in 82% yield along with enamide **3'** (CCDC no. 1911886),[15] which formed from dehydration of the cyclic hemiaminal. But it did not concern us unduly because subsequent boron trifluoride mediated triethylsilane reduction could produce the 8a-CDHQ

3 in 78% yield. Another short cut was hydration of α-aminonitriles **2'**, through the Sia_2BH protocol followed by the silane reduction of the crude product, to afford **3** in 53% yield over two steps (unoptimised).

Although removal of the Cbz group was easily accomplished by treating **3** with Pd/C in methanol under H_2 atmosphere, the followed acetylation to acetamide **4** proved more difficult than we originally anticipated.[16] The acetylation was successfully performed by treatment with a reactive acetylating agent, generated by mixing acetyl chloride and Et_3N in dichloromethane at -78 °C, to yield **4** (CCDC no. 1911884)[15] in 74 % yield over two steps. To our delight, simple treatment of N-acetyl-8a-CDHQ (**4**) with LiHMDS at -78 °C followed by an acidic workup delivered the tricyclic ketone **8** in 90% yield.[17] Obviously, the enolate moiety could engage the axial nitrile group to construct the C ring. The resulting iminium moiety was hydrolyzed to the ketone **8** during the acidic workup.

After reduction of **8** with $NaBH_4$, the resulting secondary alcohol was converted to a mesylate, which was treated with DBU to afford conjugated lactam **9** in 86% overall yield for the three-step sequence. Meanwhile, direct esterification of the crude alcohol with *para*-nitrobenzoyl chloride yielded benzoate **10** as a single isomer in 84% yield over two steps, the structure of which was established unequivocally by X-ray analysis (CCDC no. 1911885).[15] The X-ray structure confirmed the present tricyclic structure, and disclosed the hydride reduction proceeds to the C11 carbonyl group with excellent diastereoselectivity, through the space of the B ring side. Catalytic hydrogenation of **9** furnished the tricyclic lactam core **5** in 94% yield, a versatile intermediate to other alkaloids. $LiAlH_4$ reduction afforded perhydropyrrolo[2,1-*j*]quinolone (**1**) in 76% yield.

Scheme 3. Synthesis of perhydropyrrolo[2,1-*j*]quinolone (**1**) [a]

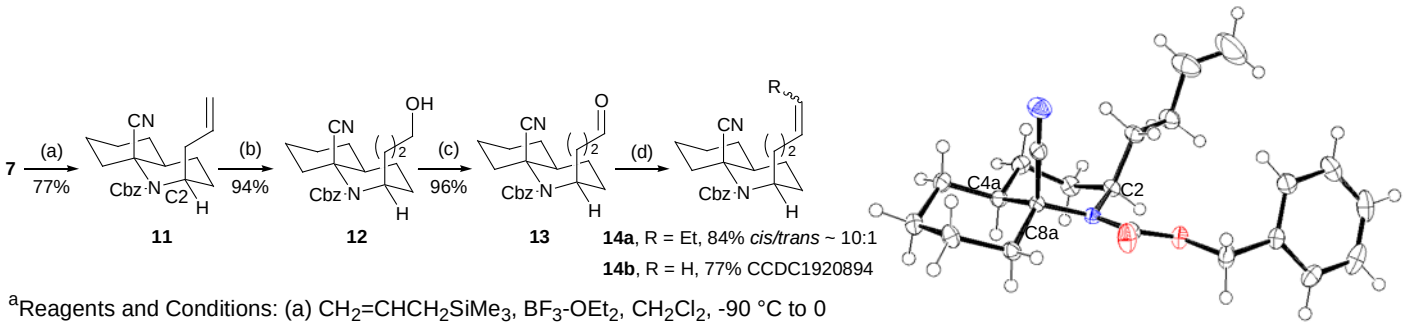


[a]Reagents and Conditions: (a) (i) Sia_2BH, THF, rt, (ii) $NaBO_3$, H_2O, 0 °C to rt; (b) DMP, CH_2Cl_2, 0 °C to rt; (c) Et_3SiH, BF_3-OEt_2, CH_2Cl_2, -78 °C to 0 °C; (d) Pd/C, H_2, MeOH, rt; (e) AcCl, Et_3N, CH_2Cl_2 -78 °C to 0 °C; (f) (i) LiHMDS , THF, -78 °C to 0 °C, (ii) $HCl_{(aq)}$ EtOAc, reflux; (g) $NaBH_4$, MeOH, 0 °C; (h) p-$NO_2C_6H_4COCl$, pyridine, reflux; (j) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, (ii) DBU, CH_2Cl_2, reflux; (k). $LiAlH_4$. THF, reflux.

Having demonstrated that perhydropyrrolo[2,1-*j*]quinolone (**1**) could be readily achieved based on the developed transformation sequence, we sought to apply the strategy to our goal (Scheme 4). Since the lepadiformine targets differ in a linear side chain, our approach is to introduce an allyl group at the C2 position as a common intermediate, and then extend to either a four or six carbon appendage afterwards, according to appropriate functional group transformations.[18] Thus, direct treatment of **7** with trimethylallylsilane and $BF_3{\cdot}OEt_2$ yielded **11** in 77% yield as a single isomer. Subsequent hydration to alcohol **12** was achieved in 94% yield according to the hydroboration–oxidation conditions. DMP oxidation of **12** generated aldehyde **13** in 96% yield. The aldehyde **13** was allowed to react with the Wittig phosphoranes, either $Ph_3P{=}CHCH_2CH_3$ or $Ph_3P{=}CH_2$, to produce **14a** in 84% yield (*cis/trans* ~ 10:1) and

14b in 77% yield, respectively. The structure of **14b** is confirmed unequivocally by X-ray analysis (CCDC no. 1920894, Scheme 4), which discloses the *syn* relationship between the nitrile group and the C2 substituent, and suggests that the silyl addition proceeds in a *syn* manner.[19]

Scheme 4. Syntheses of 2-substituted 8a-CDHQ **14a** and **14b**,[a] and the X-ray structure of **14b**

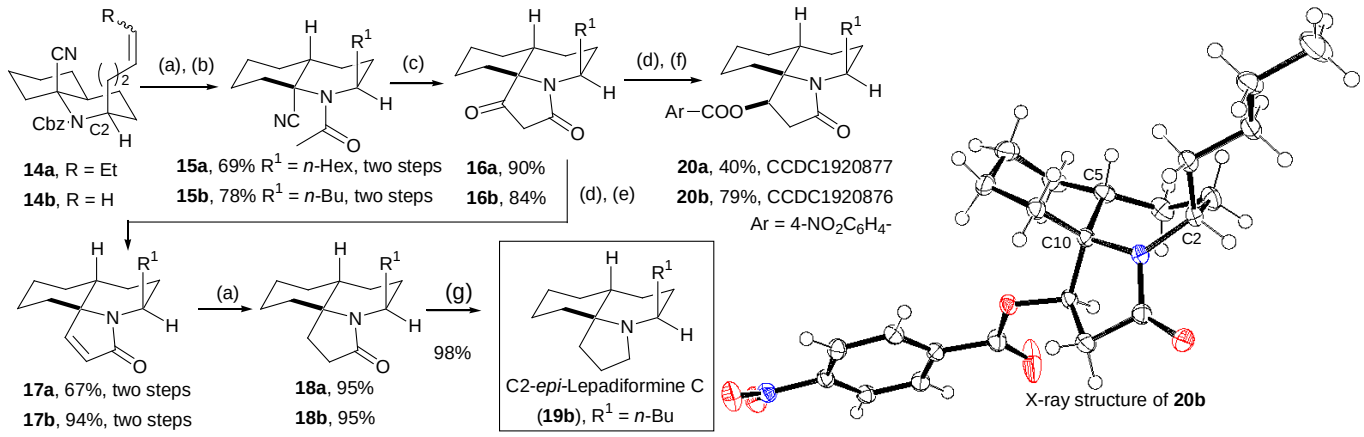


X-ray structure of **14b**

[a]Reagents and Conditions: (a) CH_2=$CHCH_2SiMe_3$, BF_3-OEt_2, CH_2Cl_2, -90 °C to 0 °C; (b) (i) Sia_2BH, THF, rt, (ii) $NaBO_3$, H_2O, 0 °C to rt; (c) DMP, CH_2Cl_2, 0 °C to rt; (d) Ph_3PCH_2R-Br, LiHMDS, 0 °C, THF, 0 °C then **13** -78 °C to rt.

Exposure of alkene **14a** under the catalytic hydrogenation conditions reduced the double bond and remove the Cbz group in one pot, acetylation then afforded acetamide **15a** in 69% yield for the two-step sequence, while the identical transformation for *n*-butyl analogue **14b** afforded **15b** in 78% yield (Scheme 5). The acetamide **15b** was treated with LiHMDS at low temperature, and then hydrolyzed under acidic conditions, affording the ketone **16b** in 84% yield. This tactic was employed for the formation of **16a** in 90% yield. The ketone **16a** and **16b** were subjected to the reduction–mesylation–elimination sequence to yielded **17a** in 67% overall yield and **17b** in 94% overall yield, respectively. Catalytic hydrogenation of **17a** and **17b** yielded the tricycle **18a** and **18b** in good yield, respectively. However, there are non-negligible differences in the ^{13}C-NMR spectrum of **18b** from the reported data[20] (See the spectrum comparison in the Figure S2 in the Supporting Information). In addition, subsequent $LiAlH_4$ reduction of **18b** afforded 98% yield of the tricyclic amine **19b**, which was expected to be lepadiformine C. But the ^{13}C NMR spectrum was not consistent with that reported in literature[21] (see the comparison in the Figure S3). Therefore, impeccable evidence for the structure determination is necessary to account for the inconsistency.

Scheme 5. Syntheses of C2-*epi* tricyclic lactam **18a**, **18b**, and C2-*epi*-lepadiformine C (**19b**)[a] and the X-ray structure of **20b**



X-ray structure of **20b**

[a]Reagents and Conditions: (a) Pd/C, H_2, MeOH, rt; (b) AcCl, Et_3N, CH_2Cl_2 -78 °C to 0 °C; (c) (i) LiHMDS, THF, -78 °C to 0 °C, (ii) HCl(aq) EtOAc, reflux; (d) $NaBH_4$, MeOH, 0 °C; (e) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C , (ii) DBU, CH_2Cl_2, reflux; (f) p-$NO_2C_6H_4COCl$, pyridine reflux; (g) $LiAlH_4$, THF, reflux.

Gratifyingly, the X-ray crystal structures of the benzoate derivatives **20a** (CCDC no. 1920877)[15] and **20b** (CCDC no. 1920876, Scheme 5), obtained through the aforementioned reduction-esterification protocol, unambiguously established the *trans* relationship between the C2 methine and the bridged methine (C5), and the *trans* disposed alkyl chain with respect to the C-ring. It is surprising to learn that unexpected configuration changes occurred during transformations from **14a** to **20a** and those from **14b** to **20b**. Among three relative configurations between the C2, C4a and C8a stereocenters in the 2-substituted 8a-CDHQ framework, except one configuration between C4a and C8a retains the original *trans* configuration, the other two configurations, i.e. that between C2 and C4a and that between C2 and C8a, have been switched to the opposite ones (See the relative stereochemistry among C2, C5 and C10 in the X-ray structure of **20b**). In light of the results, there are two possible causes for the observation: One is the epimerization proceeds only at the C2 position, and the relationships to C2 changes accordingly. The other is that the epimerizations take place at both the C4a and the C8a positions. Therefore, their mutual relationship retains while their relationships to C2 is inverted. Thus, a series of isotope experiments are carried out to find the cause.

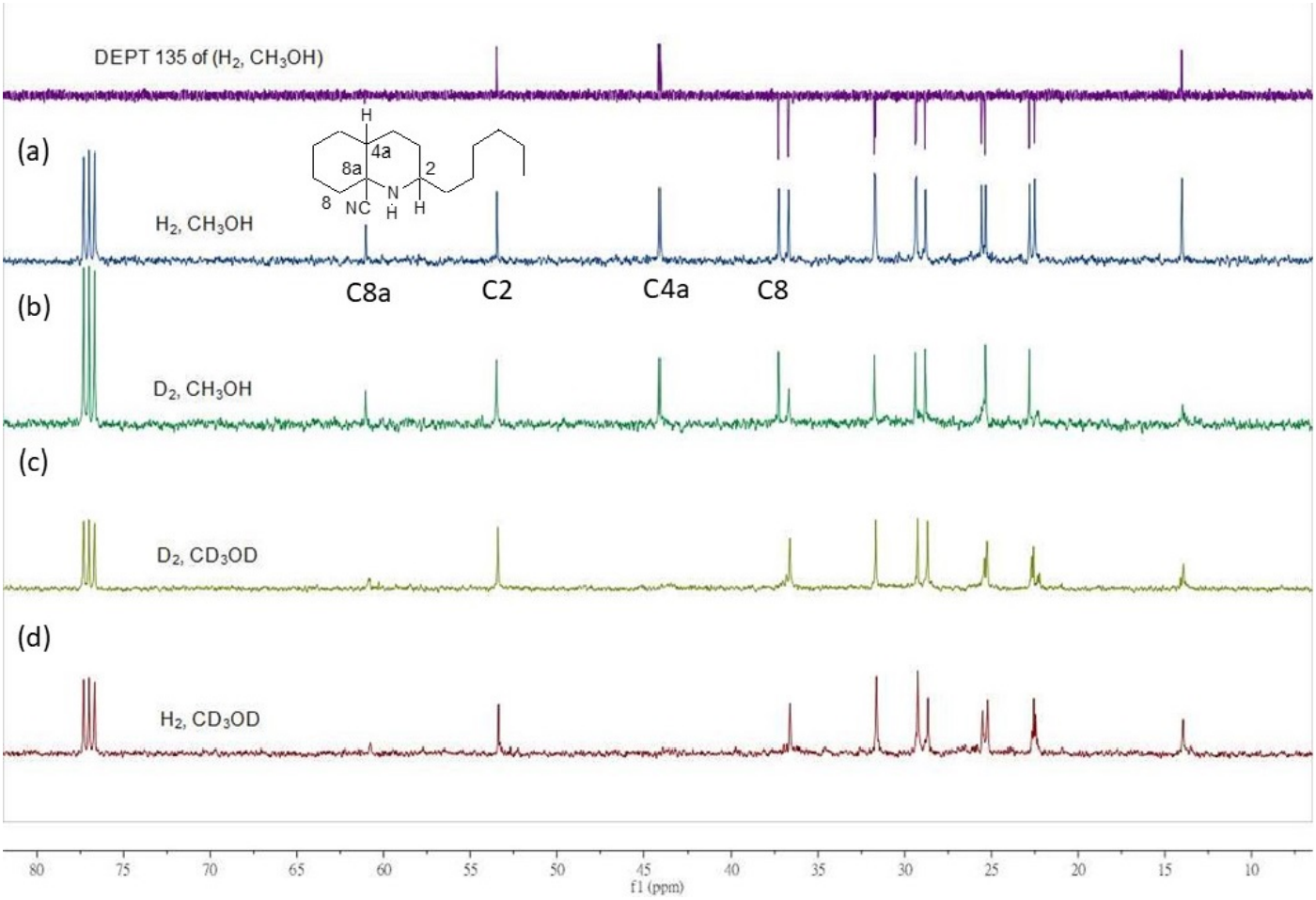


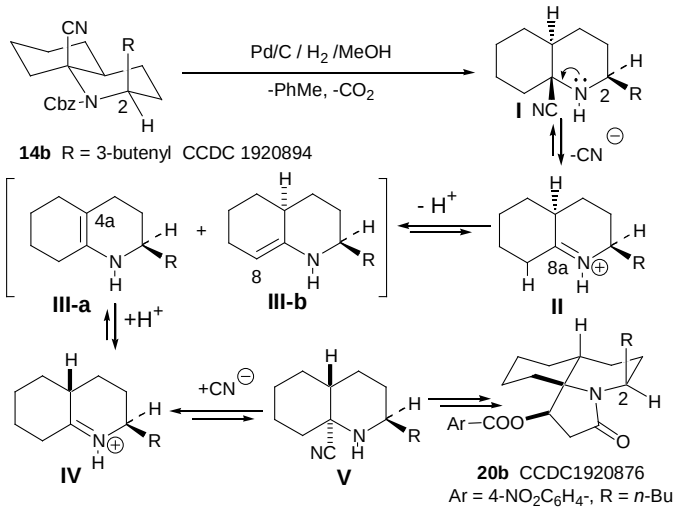
Figure 2. The ^{13}C-NMR spectra of the crude free amine product from isotope labelling experiments in the Pd-catalyzed hydrogenation conditions.

When DCl/D_2O were added in the hydrolysis stage after LiHMDS treatment of **4** and **15a**, there was no deuterium incorporation. The results excluded the possibility of base-mediated epimerization(s) at the labile methine position(s), and suggested the epimerization occurred at an early stage. We therefore considered the last reaction, i.e. H_2 and Pd/C in CH_3OH, in which the olefin hydrogenation and the Cbz deprotection proceeded concurrently. Analyses on the ^{13}C and DEPT spectra of the crude free amine product after

treatment of **14a** under the conditions provided valuable information for peak assignments (a, in Figure 2). As H_2 was replaced by D_2 (b, in Figure 2), two methine peaks remained intact and two peaks in the upper region changed, which showed that only saturation of the olefin with deuterium occurred. When the reaction was carried out in CD_3OD under D_2, it was surprising to find that the resonances of C4a, C8 and two peaks in the upper region disappeared (c, in Figure 2). Moreover, replacement with CD_3OD under H_2 resulted in the absence of both peaks of C4a and C8a, but two peaks at the upper region came out again (d, in Figure 2).

Miyazawa and coworkers reported a Pd/C catalyzed retro reductive amination process via the corresponding imine.[22] The process might allow for the epimerization at the C2 position. However, based on the observation that the C2 methine keeps intact in the four conditions, the C2 configuration needs to be retained in the reaction. Moreover, one can conclude that the presence of methanol triggers the observed epimerization process because the peaks of C4a and C8 disappear only in CD_3OD. The resulting epimerized 8a-CDHQ is then acetylated to the epimerized acetamide **15a**, instead of **4a** as we anticipate. Such an epimerization process is probably driven thermodynamically by product stability. Thus, we propose a mechanism as shown in Scheme 6:

Scheme 6. The proposed mechanism for the consecutive double epimerizations

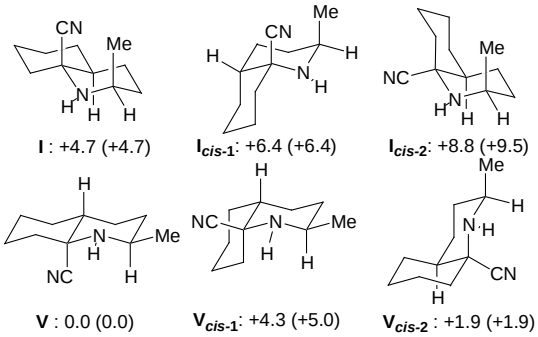


Removal of the Cbz group of **14** in methanol produces free amine **I**. The free α-aminonitrilie **I** can undergo a retro-Strecker reaction to form an iminium intermediate **II** through release of the cyanide in a locally basic environment. Subsequent loss of a β hydrogen at either the C4a or C8 positions of iminium intermediate **II** produces two possible enamine intermediates **III-a** and **III-b**. Protonation of the enamine intermediate **III** with solvent affords other stable iminium **IV**, and then cyanide addition follows to generate another stable amine epimer **V**.

To verify the hypothesis, we performed DFT calculations to find the relative energies of all six possible conformers of both *trans*- and *cis*-8a-CDHQ, with a methyl group at the C2 position (Figure 3). The calculations were carried out at the level of B3LYP/6-311++G (d, p) as well as those in methanol using the CPCM model. To minimize the calculation cost, we substituted a methyl group at the C2 position. The results shows that the epimerized amine **V** bearing with an equatorial methyl group is more stable than the amine **I** bearing with an axial methyl group by 4.7 kcal/mol. The values in gas phase are consistent with those in methanol. Moreover, the compound is also the most stable product among all six possible

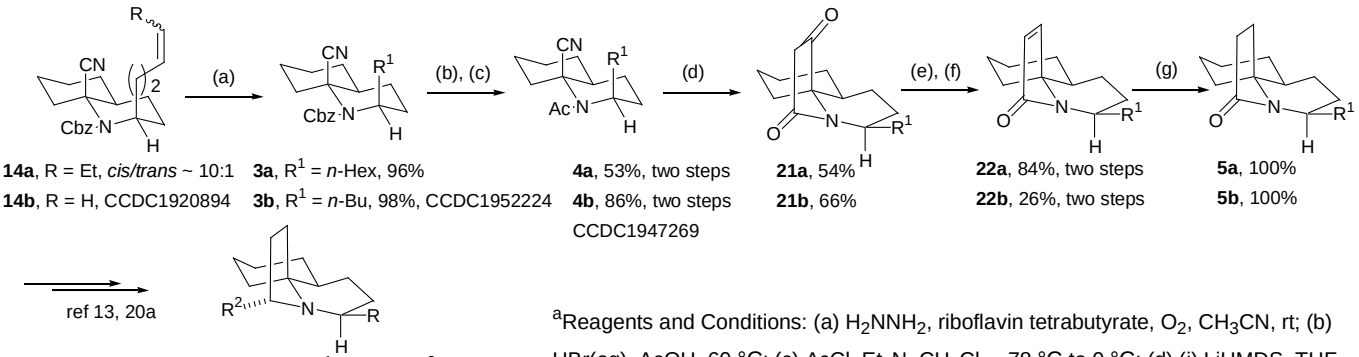
conformers.

Figure 3. Relative energies of the free *trans*- and *cis* 2-methyl-8a-CDHQs. The values (kcal/mol) in the parenthesis are their relative energies in methanol



Having confirmed the unexpected epimerizations were attributed to the conditions of Pd-catalyzed hydrogenation in methanol , we employed an acidic method to remove the protecting group, rather than neutral conditions. Thus, the acid-labile olefin group was supposed to be saturated before removal of the Cbz group (Scheme 7). The saturation of the C=C bond in the side chain of **14b** was successfully achieved by the Naota's aerobic hydrogenation conditions,[23] i.e. in situ generation of diimide by flavin mediated aerobic oxidation of hydrazine, to furnish **3b** in 98% yield. Treatment within a HBr solution containing acetic acid [24] as the co-solvent at 60 ℃ cleaved the Cbz group smoothly,[25] followed by the acetylation to give **4b** in 86% yield. The structures of both **4b** and **3b** were determined by X-ray analyses, which disclosed the *cis* relationship between the cyano group and the *n*-butyl group continued from **14b** to **4b** (CCDC no. 1952224 for **3b**; CCDC no. 1947629 **4b**).[15] Obviously, the acidic conditions prevented the epimerization effectively. Meanwhile, the acetamide **4a** could be achieved using the three-step sequence from **14a**. As the cyclization conditions mentioned above, treatment of **4b** with base and then an acidic workup furnished **21b** in 66% yield, while that of **21a** in 54% yield (Scheme 7).

Scheme 7. Syntheses of lepadiformine A (**1a**), B (**1b**), and C (**1c**) [a]



Lepadiformine A (**1a**), R^1 = *n*-Hex, R^2 = CH_2OH
Lepadiformine B (**1b**), R^1 = *n*-Bu, R^2 = CH_2OH
Lepadiformine C (**1c**), R^1 = *n*-Bu, R^2 = H

[a]Reagents and Conditions: (a) H_2NNH_2, riboflavin tetrabutyrate, O_2, CH_3CN, rt; (b) HBr(aq), AcOH, 60 °C; (c) AcCl, Et_3N, CH_2Cl_2, -78 °C to 0 °C; (d) (i) LiHMDS, THF, -78 °C to 0 °C, (ii) HCl(aq), EtOAc, reflux; (e) $NaBH_4$, MeOH, 0 °C. (f) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, (ii) DBU, CH_2Cl_2, reflux; (g) Pd/C, H_2, MeOH, rt.

The ketone **21a** was subjected to the reduction–mesylation–elimination protocol as stated above to produce **22a** in 84% overall yield, which was hydrogenated to **5a** in quantitative yield. The synthesis of other analogue, **5b** was achieved from **21b** by using the same protocol. The spectral data of **5a** and **5b** were in good agreement with those reported in the literature (See the Figure S1 in the Supporting Information for **5b**).[13, 20] As the intermediate to the syntheses of the lepadiformine family, the lactam **5a** can be further

converted into lepadiformine A (**1a**) according to the Renaud's protocol,[13] which can be applied to transformation of lactam **5b** to lepadiformine B (**1b**). Moreover, while the synthesis of *epi*-lepadiformine C (**19b**) was accomplished in 98% yield by $LiAlH_4$ reduction of lactam **18b** (Scheme 4), lepadiformine C (**1c**) could be obtained by the same reduction of the lactam **5b**, as demonstrated by Aubé and coworkers. [20a]

Conclusion:

In conclusion, concise, divergent and parallel formal racemic syntheses of marine alkaloids lepadiformine A, B and C have been developed, as well as their C2 epimers from the facile preparation of α-aminonitrile **2**. The approach highlights the fully diastereoselective syntheses of the α-aminonitriles and the 2-substituted 8a-cyanodecahydroquinoline frameworks, and the base-mediated intramolecular cyclization, crafting the tricyclic core structure with the spiral quaternary carbon. Subsequent functional group transformations afford the tricyclic lactam **5**; this constitutes a formal synthesis of lepadiformine A, B and C. Perhydropyrrolo[2,1-*j*]quinolone core (**1**) can be accomplished in nine steps with 22% overall yield from α-aminonitrile **2'**. These reactions are ligand-free, readily scalable, and operationally simple, not requring expensive chemicals.

An unexpected epimerizations at two contiguous stereocenters observed by single-crystal X-ray analyses, has been elucidated to occur at two bridged stereocenters of the 8a-CDHQ framework. Controlled experiments with deuterated reagents clearly demonstrate that the epimerizations originate in the thermodynamically driven isomerism through the retro-Strecker/ imine-enamine interchange /Strecker sequence when the free amine has been formed. Such a finding provides a supplementary route to syntheses of the C2-epimers of lepadiformine alkaloids, demonstrated by the synthesis 2-*epi*-lepadiformine C. The application of this methodology in the synthesis of other azatricyclic ring systems and the computational details are currently under investigation within our laboratory.

Experimental Section:

All reactions were performed under an argon atmosphere and in anhydrous solvent, unless otherwise stated. An oil bath was used for the heat source. The solvents and reagents have been dried or refined according to the literature procedures. The reaction flasks were dried in a 110 °C oven and allowed to cool to room temperature in a desiccator with drying agents and assembled under argon atmosphere. TLC analyses were visualized with UV light, iodine chamber, 10% sulfuric acid or 10% PMA solution. The crude product were purified by flash column chromatography on silica gel to give isolated yield. IR spectra were recorded on an ATR-FTIR apparatus. Melting points were recorded on a melting apparatus. X-ray crystal structure determination have been carried out on an X-ray apparatus and the results have been checked to obtain the corresponding CCDC number. All NMR spectra, i.e., ^{1}H, ^{13}C, DEPT, gCOSY, gHSQC, and gHMBC were recorded on a 400 MHz or 600 MHz NMR spectrometer, which provided all necessary data for the full assignment of each compound. Chemical shifts (δ) are reported in ppm using residual undeuterated solvent as an internal standard. Coupling constants are described in hertz (Hz). Mass spectra were recorded on a mass spectrometer with a magnetic sector, using the electrospray ionization (ESI) or fast atom bombardment (FAB).

Preparation of *E*-2-Alkyl-1-benzyloxycarbonylamino-1-cyanocyclohexane: To a 250 mL three-necked flask equipped with a cold finger condenser at -50 ℃ in a well-ventilated hood, ammonia gas is slowly passed through the system until ca. 40 mL of liquid ammonia has been formed. Under slow flow rate of ammonia atmosphere, the condenser is replaced with an addition funnel containing 2-allylcyclohexanone (10.0 g, 72.4 mmol) dissolved in ca. 30 ml. of methanol. The solution is added to the liquid ammonia, and the funnel is rinsed with a little methanol. The resulting ammonia-methanol solution is warmed up to 0 ℃ and stirred for 1 h. To the solution is added potassium cyanide (6.13 g, 94.1 mmol, 1.3 eq), ammonia chloride (8.90 g, 166 mmol, 2.3 eq) and aqueous ammonia (28%, 64 mL) in sequence. After addition has been complete, the outlets of the reaction flask are equipped with a drying tube, and the solution is stirred at room temperature overnight. Small amount of water is added to dissolve the solid precipitate, and the resulting reaction mixture is extracted with CH_2Cl_2 (30 mL × 4). The combined organic layers are washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a crude α-aminonitrile product. [26] The crude product is used directly without further purification.

To a THF solution (96 mL) of crude α-aminonitrile, K_2CO_3 (28.0 g, 203 mmol, 2.8 eq) in water (48 mL) was added and the solution is stirred for 10 min in an ice bath. CbzCl (15.5 mL, 109 mmol, 1.5 eq) is added slowly via a syringe. After the addition has been finished, the ice bath is removed and the solution is stirred at room temperature overnight. Separated from the reaction mixture, the aqueous layer was subjected to extraction with EtOAc (30 mL × 4). The combined organic layers are washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a crude α-aminonitrile product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant afforded the titled product.

***E*-2-(2-Propenyl)-1-benzyloxycarbonylamino-1-cyanocyclohexane (2):** White solid, (19.8 g, 66.2 mmol, 91%): mp = 68-70 ℃, recrystallized from CH_2Cl_2, CCDC no. 1934698; R_f = 0.29 (EtOAc/Hex = 1 : 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 – 1.29 (m, 1H), 1.29 – 1.43 (m, 1H), 1.46 – 1.78 (m, 5H), 1.86 – 1.96 (m, 1H), 2.00 – 2.13 (m, 1H), 2.46 – 2.59 (m, 1H), 2.73 (d, *J* = 12.5 Hz, 1H), 5.03 – 5.19 (m, 4H), 5.29 (brs, 1H), 5.65 – 5.80 (m, 1H), 7.21 – 7.45 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_2), 24.4 (CH_2), 28.3 (CH_2), 35.5 (CH_2), 36.1 (CH_2), 43.8 (CH), 57.4 (C), 67.2 (CH_2), 117.7 (CH_2), 118.0 (C), 128.2 (CH), 128.3 (CH), 128.5 (CH), 135.3 (CH), 135.7 (C), 154.1 (C); IR (cm^{-1}, film): $\bar{\nu}_{max}$ = 3319, 3068, 3035, 2939, 2863, 1703, 1642, 1524, 1453, 1256, 1025, 915; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{22}N_2O_2^+$ 298.1676, found 298.1685 (Δ = -3.0 ppm).

***E*-2-(2-Propynyl)-1-benzyloxycarbonylamino-1-cycanocyclohexane (2'):** White solid (3.05 g, 10.3 mmol, 74%), mp = 100-102 ℃; R_f = 0.43 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 – 1.33 (m, 1H), 1.35 – 1.66 (m, 3H), 1.66 – 1.80 (m, 2H), 1.80 – 1.94 (m, 1H), 1.97 – 2.11 (m, 2H), 2.15 – 2.31 (m, 1H), 2.56 – 2.79 (m, 2H), 5.01 – 5.18 (m, 2H), 5.80 (s, 1H), 7.17 – 7.49 (m, 5H); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ 154.3 (C), 135.8 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 117.5 (C), 81.9 (C), 71.0 (CH), 67.2 (CH_2), 57.6 (C), 43.8 (CH), 36.2 (CH_2), 29.0 (CH_2), 24.5 (CH_2), 22.5 (CH_2), 21.4 (CH_2); IR (cm^{-1}, film): $\bar{\nu}_{max}$ = 3305, 2941, 2864, 2241, 2120, 1704, 1522, 1256; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{20}N_2O_2^+$ 296.1519, found 296.1517 (Δ = 0.7 ppm).

General Procedure for the Hydroboration-Oxidation: To a BH_3-Me_2S solution (2 M, 12 mL, 24 mmol, 1.8 eq) in an ice bath, was slowly added 2-methyl-2-butene (5.1 mL, 48 mmol, 3.6 eq) via a syringe. The solution was stirred for 2 h in an ice bath. To the freshly prepared Sia_2BH solution, was transferred by cannulation into a THF solution (26 mL) of the olefin substrate (**2**, 4.00 g 13.4 mmol). After the addition has been finished, the ice bath was removed and the reaction mixture was stirred for 1 h. The reaction was quenched with water (40 mL), followed by a sodium perborate tetrahydrate ($NaBO_3$-$4H_2O$, 11.1 g, 72 mmol, 5.4 eq), and the resulting solution was stirred overnight. Separated from the reaction mixture, the aqueous layer was subjected to extraction with EtOAc (30 mL × 4). The combined organic layers are washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a crude product. Purification of the crude product by flash chromatography on silica gel, using EtOAc/n-Hex as the eluant afforded the titled product.

***E*-2-(3-Hydroxypropyl)-1-benzyloxycarbonylamino-1-cycanocyclohexane (6)**: Light Colorless oil, (3.96 g, 12.5 mmol, 93%), R_f = 0.21 (EtOAc/Hex = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 – 1.47 (m, 6H), 1.48 – 1.62 (m, 2H), 1.62 – 1.76 (m, 3H), 1.80 – 1.93(m, 2H), 2.73 (d, *J* = 12.3 Hz, 1H), 3.53 – 3.65 (m, 2H), 5.00 – 5.16 (m, 2H), 6.22 (brs, 1H), 7.17 – 7.43 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 22.4 (CH_2), 24.5 (CH_2), 26.8 (CH_2), 28.3 (CH_2), 28.9 (CH_2), 36.1 (CH_2), 43.4 (CH), 57.2 (C), 61.8 (CH_2), 66.9 (CH_2), 118.2 (C), 128.0 (CH), 128.1 (CH), 128.4 (CH), 135.8 (C),154.6 (C),; IR (cm^{-1}, film): $\bar{\nu}_{max}$ = 3479, 3318, 2939, 2865, 2240, 1705, 1528, 1454, 1254, 1027; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{24}N_2O_3^+$ 316.1781, found 316.1788 (Δ = -2.2 ppm).

***rel*-(2*S*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-8a-cyano-2-(3-hydroxypropyl)decahydroquinoline (12):** White solid (2.227 g, 6.20 mmol, 94%) mp = 86-88 °C; R_f = 0.22 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 – 1.42 (m, 5H), 1.42 – 1.55 (m, 3H), 1.55 – 1.83 (m, 9H), 1.83 – 2.03 (m, 3H), 3.42 – 3.54 (m, 3H), 4.21 – 4.29 (m, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 7.45 – 7.28 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 23.3 (CH_2 × 2), 25.0 (CH_2), 26.4 (CH_2), 28.5 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 36.0 (CH_2), 46.5 (CH), 55.8 (CH), 58.6 (C), 62.0 (CH_2), 67.6 (CH_2), 119.9 (C), 128.3 (CH), 128.5 (CH × 2), 135.7 (C), 157.0 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2938, 2865, 1709, 1456, 1383, 1276, 1261, 1152, 1112 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{21}H_{28}N_2O_3$ 356.2094, found 356.2104 (Δ = -2.8 ppm).

General Procedure for the Dess-Martin Periodinane Oxidation: To a CH_2Cl_2 solution (47 mL) of alcohol **6** (3.01 g, 9.5 mmol, 1.0 eq) in an ice bath under argon, was added Dess-Martin reagent (4.44 g, 10.5 mmol, 1.1 eq) in portions. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. Upon completion of the reaction monitored by TLC analysis, the reaction was quenched with saturated $NaHCO_3$ solution (30 mL). After filtration with a short celite pad and separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (20 mL × 4). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a crude product. The crude product was purified by flash chromatography on silica gel, using ethyl acetate/*n*-hexane as the eluant, afforded the products as followed:

***E*-2-(3-Oxopropyl)-1-benzyloxycarbonylamino-1-cycanocyclohexane (7):** Colorless oil, (2.45 g, 7.8 mmol, 82%), aldehyde as major: R_f = 0.23 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 – 1.42 (m, 4H), 1.45 – 1.86 (m, 7H), 1.93 – 2.08 (m, 2H), 2.10 – 2.31 (m, 1H), 2.44 – 2.60 (m, 1H), 2.60 – 2.75 (m,

1H), 2.88 (d, *J* = 12.1 Hz, 1H), 3.09 (d, *J* = 12.9 Hz, 1H), 5.07 – 5.33 (m, 2H), 5.77 (dd, *J* = 15.9, 13.1 Hz, 1H), 7.25 – 7.50 (m, 5H), 9.74 (d, *J* = 12.3 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) [27] δ 18.4, 19.7, 21.0, 22.1, 22.3, 22.9, 23.0, 23.1, 23.3, 24.6, 24.7, 24.8, 25.0, 26.6, 28.9, 29.5, 29.6, 29.9, 30.1, 30.4, 30.8, 36.0, 36.1, 38.4, 41.0, 41.1, 43.5, 46.0, 56.9, 57.3, 58.4, 58.5, 66.8, 68.0, 68.2, 75.7, 76.6, 78.5, 118.0, 118.4, 119.5, 128.1, 128.3, 128.4, 128.6, 135.4, 154.5, 154.8, 156.8, 203.1; IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 3483, 3330, 2940, 2864, 2237, 1711, 1523, 1454,1399, 1309, 1277, 1260, 1116, 1044, 1010; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{22}N_2O_3^+$ 314.1628, found 314.1637 (Δ = -2.9 ppm).

***trans*-*N*-Benzyloxycarbonyl-8a-cyano-2,3-didehydrodecahydroquinoline (3'):** White solid, (261 mg, 0.9 mmol, 9%), mp = 82-84 °C, recrystallized from CH_2Cl_2, CCDC no. 1911886; R_f = 0.44 (EtOAc/Hex = 1 : 5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 – 1.45 (m, 2H), 1.47 – 1.61 (m, 1H), 1.63 – 1.88 (m, 5H), 1.88 – 1.98 (m, 1H), 2.00 – 2.11 (m, 1H), 3.48 (d, *J* = 12.4 Hz, 1H), 5.01 (ddd, *J* = 8.5, 6.5, 2.1 Hz, 1H), 5.14 – 5.30 (m, 2H), 6.67 – 6.81 (m, 1H), 7.22 – 7.51 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 23.1 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 30.0 (CH_2), 34.7 (CH_2), 42.2 (CH), 59.2 (C), 68.2 (CH_2), 106.1 (CH), 117.8 (C), 125.3 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 129.8 (CH), 135.4 (C), 152.9 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2932, 2861, 1720, 1664, 1454, 1384, 1307, 1256, 1159, 1117, 1011, 750; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{20}N_2O_2^+$ 296.1519, found 296.1528 (Δ = -3.0 ppm).

***rel*-(2*S*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-8a-cyano-2-(3-oxypropyl)decahydroquinoline (13):** White solid (988 mg, 2.8 mmol, 96%), mp = 80-82 °C; R_f = 0.28 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 – 1.36 (m, 2H), 1.37 – 1.44 (m, 1H), 1.45 – 1.55 (m, 1H), 1.56 – 1.83 (m, 8H), 1.85 – 1.95 (m, 1H), 2.09 – 2.31 (m, 3H), 3.46 – 3.56 (m, 1H), 4.21 – 4.30 (m, 1H), 5.09 (d, *J* = 12.0 Hz, 1H), 5.23 (d, *J* = 12.0 Hz, 1H), 7.25 – 7.46 (m, 5H), 9.48 (s, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 23.3 (CH_2 × 2), 24.6 (CH_2), 25.0 (CH_2), 26.6 (CH_2), 30.5 (CH_2), 36.0 (CH_2), 41.1 (CH_2), 46.5 (CH), 55.1 (CH), 58.7 (C), 67.7 (CH_2), 119.7 (C), 128.5 (CH), 128.6 (CH × 2), 135.6 (C), 156.7 (C), 201.1 (CH); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2938, 2864, 2725, 2229, 1711, 1497, 1456, 1384, 1283, 1242, 1153, 1112; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{21}H_{26}N_2O_3^+$ 354.1938, found 354.1938 (Δ = 0 ppm).

***trans*-*N*-Benzyloxycarbonyl-8a-cyanodecahydroquinoline (3):** To a CH_2Cl_2 solution (7 mL) of aldehyde **7** (210 mg, 0.67 mmol, 1 eq) at -78 °C, was added dropwise a CH_2Cl_2 solution (0.8 mL) containing triethylsilane (128 μL, 0.80 mmol, 1.2 eq) and $BF_3{\cdot}OEt_2$ (99 μL, 0.80 mmol, 1.2 eq). As the addition has been finished, the cooling bath was removed and the reaction mixture was stirred at room temperature. Upon completion of the reaction monitored by TLC analysis, a saturated $NaHCO_3$ solution was slowly added into the reaction mixture at 0 °C, and then warmed up to room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product. Colorless oil (155 mg, 0.52 mmol, 78%), R_f = 0.33 (EtOAc/Hex = 1 : 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 – 1.36 (m, 1H), 1.42 – 1.60 (m, 4H), 1.61 – 1.73 (m, 4H), 1.74 – 1.89 (m, 3H), 3.14 (d, *J* = 13.1 Hz, 1H), 3.53 – 3.69 (m, 2H), 5.16 (s, 2H), 7.20 – 7.46 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 22.5 (CH_2), 23.3 (CH_2), 24.9 (CH_2), 25.7 (CH_2), 30.2 (CH_2), 35.0 (CH_2), 41.9 (2C, CH_2 and CH), 61.1 (C), 67.5 (CH_2), 118.3 (C), 128.0 (CH), 128.1 (CH), 128.4 (CH), 136.0 (C), 155.3 (C); IR (cm^{-1},

film) $\bar{\nu}_{max}$ = 2937, 2863, 2232, 1705, 1497, 1454, 1404, 1352, 1255, 1239, 1166, 1002 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{22}N_2O_2^+$ 298.1676, found 298.1686 (Δ = -3.4 ppm).

General Procedure for Preparation of the *trans*-acetamides:

Catalytic hydrogenation: To a 25 mL flask containing freshly activated Pd/C catalyst (10%, 342 mg, 10 mol%) was added MeOH solution (5 mL) of carbamate **3** (959 mg, 3.2 mmol, 1.0 eq). The reaction suspension was stirred overnight under a hydrogen balloon. Upon completion of the reaction monitored by TLC analysis, the suspension was filtered through celite and the filtrate was concentrated under reduced pressure to give a crude product (525 mg, 3.2 mmol, quantitative).

Acetylation: The crude product was used directly without further purification. To a CH_2Cl_2 solution (17 mL) of acetyl chloride (430 μL, 6.1 mmol, 1.0 eq) at -78 ºC, was slowly added Et_3N (850 μL, 6.1 mmol, 3.5 eq), and the solution was stirred for another 10 min at the low temperature. To the freshly prepared acetylating reagent, was cannulated the crude amine (287 mg, 1.7 mmol) in CH_2Cl_2 solution (2 mL). The solution was stirred for 1.5 h at -78 ºC. Upon completion of the reaction monitored by TLC analysis, a saturated $NaHCO_3$ solution was slowly added. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***trans*-*N*-Acetyl-8a-cyanodecahydroquinoline (4):** Yellow solid, (260 mg, 1.3 mmol, 74%), mp = 62-64 ℃, recrystallized from CH_2Cl_2, CCDC no. 1911884; R_f = 0.43 (pure EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 – 1.32 (m, 1H), 1.32 – 1.43 (m, 1H), 1.50 – 1.62 (m, 2H), 1.62 – 1.69 (m, 2H), 1.70 – 1.82 (m, 4H), 1.82 – 1.93 (m, 2H), 2.13 (s, 3H), 3.15 – 3.23 (m, 1H), 3.46 (dd, *J* = 7.8, 4.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 22.1 (CH_2), 22.9 (CH_2), 23.8 (CH), 24.0 (CH_2), 24.9 (CH_2), 29.7 (CH_2), 33.6 (CH_2), 40.4 (CH), 41.8 (CH_2), 60.1 (C), 117.9 (C), 170.7 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2936, 2864, 2233, 1653, 1410 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{12}H_{18}N_2O^+$ 206.1414, found 206.1425 (Δ = -5.3 ppm).

***rel*-(2*R*,4a*R*,8a*S*)-*N*-Acetyl-2-butyl-8a-cyanodecahydroquinoline (15a):** Yellow oil, (259 mg, 0.89 mmol, 69%), R_f = 0.44 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.04 – 1.16 (m, 1H), 1.18 – 1.36 (m, 9H), 1.45 – 1.58 (m, 2H), 1.58 – 1.77 (m, 7H), 1.79 – 1.90 (m, 1H), 2.00 – 2.10 (m, 2H), 2.13 (s, 3H), 3.32 (d, *J* = 12.6 Hz, 1H), 3.63 – 3.75 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.4 (CH_2), 22.5 (CH_2), 23.1 (CH_2 × 2), 23.7 (CH), 25.1 (CH_2), 27.4 (CH_2), 29.2 (CH_2), 30.5 (CH_2), 31.6 (CH_2), 35.3 (CH_2), 37.9 (CH_2), 39.0 (CH), 54.2 (CH), 58.2 (C), 118.4 (C), 171.4 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2933, 2861, 2230, 1657; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{30}N_2O^+$ 290.2353, found 290.2359 (Δ = -2.1 ppm).

***rel*-(2*R*,4a*R*,8a*S*)-*N*-Acetyl-2-butyl-8a-cyanodecahydroquinoline (15b):** Yellow oil, (143 mg, 0.54 mmol, 78%), R_f = 0.28 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.04 – 1.17 (m, 1H), 1.17 – 1.41 (m, 5H), 1.47 – 1.58 (m, 2H), 1.58 – 1.79 (m, 7H), 1.79 – 1.92 (m, 1H), 1.98 – 2.11 (m, 2H), 2.13 (s, 3H), 3.32 (d, *J* = 12.9 Hz, 1H), 3.63 – 3.75 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.3 (CH_2), 22.6 (CH_2), 23.1 (CH_2 × 2), 23.8 (CH), 25.1 (CH_2), 29.6 (CH_2), 30.5 (CH_2), 35.3 (CH_2), 37.6 (CH_2), 38.9 (CH), 54.2 (CH), 58.2 (C), 118.4 (C), 171.4 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2936, 2864, 2231, 1656,

1452, 1400, 1340, 1166; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{26}N_2O^+$ 262.2040, found 262.2048 (Δ = -3.1 ppm).

Procedure for the Intramolecular Cyclization: To a THF solution (47 mL) of acetamide **4** (1.930 g, 9.4 mmol, 1.0 eq) at -78 ℃ was slowly added LiHMDS solution (1 M, 28 mL, 28 mmol, 3.0 eq) via a syringe. The reaction mixture was stirred at the low temperature for 1 h, and warmed up gradually to room temperature in 2 h. After slow addition of hydrochloric acid (1 N, 47 mL) and EtOAc (47 mL), the reaction was heated at reflux for 24 h. After separation of the organic layer, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***rel*-(5*S*,10*R*)-11,13-Dioxodecahydro-*H*-pyrrolo[2,1-j]quinoline (8):**[28] Yellow solid (2.060 g, 9.9 mmol, 90%), mp = 120-122 ℃; R_f = 0.59 (pure EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 – 1.14 (m, 1H), 1.25 – 1.40 (m, 1H), 1.40 – 1.54 (m, 2H), 1.54 – 1.75 (m, 6H), 1.75 – 1.85 (m, 1H), 1.85 – 1.99 (m, 1H), 2.18 (dddd, *J* = 12.8, 12.7, 12.7, 4.0 Hz, 1H), 2.77 (d, *J* = 20.9 Hz, 1H), 2.86 (ddd, *J* = 13.6, 11.5, 6.8 Hz, 1H), 3.30 (d, *J* = 20.9 Hz, 1H), 4.20 (dd, *J* = 13.8, 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.3 (CH_2), 22.4 (CH_2), 23.7 (CH_2), 25.8 (CH_2), 26.6 (CH_2), 33.8 (CH_2), 34.6 (CH_2), 42.0 (CH and CH_2), 71.3 (C), 169.7 (C), 208.4 (C); IR (cm^{-1}, film) ν = 1759, 1691, 1276, 1261; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{12}H_{17}NO_2^+$ 207.1254, found 207.1250 (Δ = 1.9 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Hexyl-11,13-dioxodecahydro-*H*-pyrrolo[2,1-j]quinoline (16a):** Yellow oil (249 mg, 0.85 mmol, 90%), R_f = 0.25 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.10 – 1.16 (m, 1H), 1.16 – 1.39 (m, 9H), 1.39 – 1.49 (m, 3H), 1.49 – 1.60 (m, 2H), 1.60 – 1.77 (m, 3H), 1.77 – 1.94 (m, 3H), 2.09 – 2.22 (m, 1H), 2.26 – 2.42 (m, 1H), 2.77 (d, *J* = 20.7 Hz, 1H), 3.34 (d, *J* = 20.7 Hz, 1H), 4.66 – 4.52 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.8 (CH_2), 22.5 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 37.1 (CH_2), 38.8 (CH_2), 42.0 (CH and CH_2), 47.0 (CH), 71.7 (C), 169.9 (C), 207.8 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2931, 2862, 1760, 1692, 1450, 1402; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{29}NO_2^+$ 291.2193, found 291.2199 (Δ = -2.1 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Butyl-11,13-dioxodecahydro-*H*-pyrrolo[2,1-j]quinoline (16b):** Yellow oil (173 mg, 0.66 mmol, 84%), R_f = 0.35 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.1 Hz, 3H), 1.02 – 1.18 (m, 1H), 1.26 – 1.42 (m, 5H), 1.42 – 1.52 (m, 3H), 1.52 – 1.63 (m, 2H), 1.63 – 1.79 (m, 3H), 1.79 – 1.96 (m, 3H), 2.08 – 2.25 (m, 1H), 2.36 (dddd, *J* = 12.7, 12.7, 12.7, 4.0 Hz, 1H), 2.79 (d, *J* = 20.7 Hz, 1H), 3.35 (d, *J* = 20.7 Hz, 1H), 4.55 – 4.68 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.8 (CH_2), 22.4 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 26.7 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 37.1 (CH_2), 38.4 (CH_2), 42.0 (CH and CH_2), 47.0 (CH), 71.7 (C), 169.8 (C), 207.8 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2933, 2867, 1760, 1693, 1459, 1401, 1293; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{25}NO_2^+$ 263.1880, found 263.1889 (Δ = -3.4 ppm).

***rel*-(2*R*,5*S*,10*R*)-2-Hexyl-11,13-dioxodecahydro-*H*-pyrrolo[2,1-j]quinoline (21a):** colorless oil (44 mg, 0.15 mmol, 54%), R_f = 0.53 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.2 Hz, 3H), 1.05 – 1.19 (m, 1H), 1.22 – 1.37 (m, 8H), 1.37 – 1.55 (m, 3H), 1.62 – 1.78 (m, 6H), 1.78 – 1.90 (m, 3H),

2.24 (dddd, *J* = 12.5, 12.3, 12.3, 3.2 Hz, 1H), 2.45 – 2.58 (m, 1H), 2.70 (d, *J* = 21.0 Hz, 1H), 3.17 – 3.31 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 21.2 (CH_2), 22.6 (CH_2), 24.5 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 27.6 (CH_2), 29.1 (CH_2), 30.0 (CH_2), 31.8 (CH_2), 32.8 (CH_2), 33.9 (CH_2), 42.5 (CH), 43.0 (CH_2), 52.8 (CH), 73.7 (C), 170.2 (C), 209.0 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2930, 2858, 1759, 1695, 1462, 1332, 1283; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{29}NO_2^+$ 291.2193, found 291.2204 (Δ = -3.8 ppm).

***rel*-(2*R*,5*S*,10*R*)-2-Butyl-11,13-dioxodecahydro-*H*-pyrrolo[2,1-j]quinoline (21b):** Yellow oil (76 mg, 0.29 mmol, 66%), R_f = 0.50 (EtOAc/Hex =1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.04 – 1.19 (m, 1H), 1.26 – 1.55 (m, 7H), 1.60 – 1.78 (m, 7H), 1.78 – 1.89 (m, 2H), 2.24 (dddd, *J* = 12.6, 12.6, 12.6, 3.9 Hz, 1H), 2.46 – 2.58 (m, 1H), 2.69 (d, *J* = 21.0 Hz, 1H), 3.17 – 3.32 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 21.2 (CH_2), 22.5 (CH_2), 24.5 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 29.9 (CH_2), 30.0 (CH_2), 32.5 (CH_2), 33.9 (CH_2), 42.4 (CH), 43.0 (CH_2), 52.8 (CH), 73.7 (C), 170.2 (C), 209.0 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 3008, 1758, 1695, 1277, 1261; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{25}NO_2^+$ 263.1880, found 263.1887 (Δ = -2.7 ppm).

General Derivation Procedure of the β-oxo tricyclic lactams:

Reduction: To a MeOH solution (5 mL) of ketone **8** (218 mg, 1.1 mmol, 1.0 eq) at an ice bath, was added $NaBH_4$ (99 mg, 2.6 mmol, 2.5 eq) in portions. The reaction mixture was stirred in the ice bath for 1 h, and quenched with saturated NH_4Cl solution. After evaporation of the volatile substance, the resulting solution was partitioned with EtOAc. The combined organic extracts were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic solution was concentrated under reduced pressure to give a crude product. The crude alcohol product was used directly without further purification.

Mesylation: To a solution of the crude alcohol from sodium borohydride reduction in CH_2Cl_2 (5 mL), cooled in an ice bath, was added Et_3N (320 μL, 2.6 mmol, 2.5 eq) via a syringe followed by MsCl (170 μL, 2.2 mmol, 2.0 eq). The reaction was stirred in the ice bath for 1.5 h. Upon completion of the reaction monitored by TLC analysis, a saturated $NaHCO_3$ solution was slowly added. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solid dehydrating agent, the extracts were concentrated under reduced pressure to give a crude product. The crude product was used directly without further purification.

Elimination: The crude mesylate was diluted with CH_2Cl_2 (8.5 mL) followed by the addition of DBU (0.4 μL, 2.8 mmol, 2.5 eq). The reaction mixture was stirred and heated at reflux for 8 h. Upon completion of the reaction monitored by TLC analysis, the reaction was quenched with saturated NH_4Cl solution. After separation from the organic extracts, the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***rel*-(5*S*,10*R*)-11,12-Didehydro-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (9):** Yellow oil (181 mg, 0.95 mmol, 86% over three steps), R_f = 0.29 (EtOAc/Hex = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 – 0.79 (m, 1H), 1.18 – 1.32 (m, 1H), 1.32 – 1.70 (m, 6H), 1.77 – 1.93 (m, 4H), 1.93 – 2.03 (m, 1H), 2.92 (ddd, *J* = 13.9, 10.9, 6.9 Hz, 1H), 3.92 (dd, *J* = 13.9, 8.6 Hz, 1H), 6.17 (d, *J* = 5.9 Hz, 1H), 7.36 (d, *J* = 5.9 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 22.2 (CH_2), 23.8 (CH_2), 24.5 (CH_2), 26.6 (CH_2), 29.3 (CH_2), 35.5 (CH_2),

36.6 (CH_2), 43.2 (CH), 71.2 (C), 127.6 (CH), 151.0 (CH), 176.2 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2864, 1683, 1456, 818, 764 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{12}H_{17}NO^+$ 191.1305, found 191.1306 (Δ = -0.5 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Butyl-11,12-didehydro-13-oxodecahydro-*H*-pyrrolo[2,1-j]-quinoline (17a):** Yellow oil (157 mg, 0.57 mmol, 67%) R_f = 0.23 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 – 0.78 (m, 1H), 0.84 (s, 3H), 1.12 – 1.38 (m, 8H), 1.38 – 1.52 (m, 3H), 1.52 – 1.69 (m, 4H), 1.69 – 1.86 (m, 2H), 1.86 – 2.09 (m, 4H), 2.09 – 2.24 (m, 1H), 4.25 – 4.44 (m, 1H), 6.15 (d, *J* = 5.7 Hz, 1H), 7.36 (d, *J* = 5.6 Hz, 1H); $^{13}C\{^1H\}$ (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.5 (CH_2), 23.4 (CH_2), 24.3 (CH_2), 26.7 (CH_2), 27.0 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 38.0 (CH_2), 39.2 (CH_2), 43.7 (CH), 48.8 (CH), 71.7 (C), 127.0 (CH), 150.7 (CH), 175.7 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2931, 2862, 1742, 1690, 1460, 1390, 1345; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{29}NO^+$ 275.2244, found 275.2245 (Δ = -0.4 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Butyl-11,12-didehydro-13-oxodecahydro-*H*-pyrrolo[2,1-j]-quinoline (17b):** Yellow oil (178 mg, 0.72 mmol, 94%) R_f = 0.32 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 – 0.78 (m, 1H), 0.87 (t, *J* = 6.9 Hz, 3H), 1.13 – 1.25 (m, 2H), 1.25 – 1.38 (m, 3H), 1.40 – 1.53 (m, 3H), 1.53 – 1.69 (m, 4H), 1.71 – 1.85 (m, 2H), 1.87 – 2.05 (m, 3H), 2.17 (ddd, *J* = 13.3, 10.5, 7.3 Hz, 1H), 4.31 – 4.42 (m, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 7.37 (d, *J* = 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 23.4 (CH_2), 24.3 (CH_2), 26.8 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 31.7 (CH_2), 37.6 (CH_2), 39.2 (CH_2), 43.7 (CH), 48.8 (CH), 71.8 (C), 127.1 (CH), 150.8 (CH), 175.7 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2934, 2864, 1685, 1276, 1261; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{25}NO^+$ 247.1931, found 247.1937 (Δ = -2.4 ppm).

***rel*-(2*R*,5*S*,10*R*)-2-Hexyl-11,12-didehydro-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (22a):** Yellow oil (24 mg, 0.09 mmol, 84%), R_f = 0.53 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 – 0.88 (m, 3H), 1.18 – 1.36 (m, 8H), 1.37 – 1.52 (m, 3H), 1.55 – 1.74 (m, 4H), 1.76 – 1.93 (m, 5H), 2.42 – 2.54 (m, 1H), 3.15 – 3.27 (m, 1H), 6.06 (d, *J* = 5.9 Hz, 1H), 7.25 (d, *J* = 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2 × 2), 23.8 (CH_2), 26.7 (CH_2), 27.4 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 35.6 (CH_2), 43.6 (CH), 52.2 (CH), 72.3 (C), 129.1 (CH), 149.3 (CH), 176.5 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2932, 2859, 1688; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{29}NO^+$ 275.2244, found 275.2259 (Δ = -5.5 ppm).

***rel*-(2*R*,5*S*,10*R*)-2-Butyl-11,12-didehydro-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (22b):** Yellow oil (13 mg, 0.05 mmol, 26%), R_f = 0.48 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.19 – 1.51 (m, 8H), 1.56 – 1.74 (m, 4H), 1.74 – 1.94 (m, 6H), 2.42 – 2.55 (m, 1H), 3.14 – 3.28 (m, 1H), 6.07 (d, *J* = 5.9 Hz, 1H), 7.26 (d, *J* = 5.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 23.8 (CH_2), 26.8 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 32.0 (CH_2), 35.6 (CH_2), 43.7 (CH), 52.2 (CH), 72.4 (C), 129.1 (CH), 149.3 (CH), 176.6 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2865, 1689; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{25}NO^+$ 247.1931, found 247.1941 (Δ = -4.0 ppm).

Preparation of the 4-Nitrobenzoate derivatives: To the crude alcohol (300 mg, 0.84 mmol, 1 eq) from sodium borohydride reduction of ketone **8**, diluted within CH_2Cl_2 (8.4 mL) cooled in an ice bath, was added pyridine (280 μL, 3.4 mmol, 4.0 eq) via a syringe followed by addition of 4-nitrobenozoyl chloride (342 mg, 1.84 mmol, 2.2 eq) in one portion. The reaction was stirred under reflux conditions for 4 h. Upon completion

of the reaction monitored by TLC analysis, HCl solution (1 N, 5 mL) was added to quench the reaction. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. Removal of the solid dehydrating agent, followed by concentration of the extracts under reduced pressure gave a crude product, which was purified by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***rel*-(5*S*,10*R*,11*S*)-11-(4-Nitrobenzoyloxy)-13-oxodecahydro-*H*-pyrrolo[2,1-j]-quinoline (10):** Yellow solid (252 mg, 0.70 mmol, 84%), mp = 160-162 ℃ (decomposed), recrystallized from $CHCl_3$, CCDC no. 1911885; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 – 1.26 (m, 1H), 1.36 – 1.57 (m, 4H), 1.57 – 1.74 (m, 3H), 1.74 – 1.91 (m, 3H), 1.97 – 2.13 (m, 1H), 2.25 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.66 – 2.94 (m, 3H), 3.99 (dd, *J* = 13.8, 8.1 Hz, 1H), 5.78 (dd, *J* = 10.3, 8.3 Hz, 1H), 8.19 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.0 (CH_2), 22.2 (CH_2), 22.4 (CH_2), 25.8 (CH_2), 27.1 (CH_2), 31.5 (CH_2), 33.3 (CH_2), 36.7 (CH_2), 42.0 (CH), 64.4 (C), 71.9 (CH), 123.8 (CH), 130.8 (CH), 134.8 (C), 150.7 (C), 163.9 (C), 170.3 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2869, 1726, 1697, 1607, 1528, 1274, 1102, 750, 719; ESI-HRMS (*m/z*) : [M]$^+$ calcd for $C_{19}H_{22}N_2O_5^+$ 358.1523, found 358.1537 (Δ = -3.9 ppm).

***rel*-(2*R*,5*R*,10*S*,11*R*)-2-hexyl-11-(4-Nitrobenzoyloxy)-13-oxodecahydro-*H*-pyrrolo-[2,1-j]quinoline (20a):** Yellow solid, (86 mg, 0.19 mmol, 40%), mp = 166-168 ℃ (decomposed), recrystallized from CH_2Cl_2, CCDC no. 1920877; R_f = 0.15 (EtOAc/Hex = 1 : 4) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.14 – 1.39 (m, 9H), 1.39 – 1.61 (m, 6H), 1.61 – 1.83 (m, 4H), 1.88 – 2.01 (m, 1H), 2.05 – 2.23 (m, 2H), 2.39 (dd, *J* = 13.1, 5.1 Hz, 1H), 2.75 (dd, *J* = 15.9, 10.6 Hz, 1H), 2.89 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.27 – 4.40 (m, 1H), 5.72 (dd, *J* = 10.3, 8.3 Hz, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.2 (CH_2 × 2), 22.6 (CH_2), 25.9 (CH_2), 26.7 (CH_2), 27.4 (CH_2), 29.0 (CH_2 × 2), 31.7 (CH_2), 33.8 (CH_2), 36.6 (CH_2), 39.1 (CH_2), 42.2 (CH), 46.6 (CH), 65.1 (C), 72.2 (CH), 123.8 (CH), 130.7 (CH), 135.0 (C), 150.7 (C), 163.9 (C), 170.8 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2940, 2872, 1723, 1694, 1526, 1275 ; EI-HRMS (*m/z*) : [M]$^+$ calcd for $C_{25}H_{34}N_2O_5^+$ 442.2462, found 442.2474 (Δ = -2.7 ppm).

***rel*-(2*R*,5*R*,10*S*,11*R*)-2-Butyl-11-(4-nitrobenzoyloxy)-13-oxodecahydro-*H*-pyrrolo-[2,1-j]quinoline (20b):** Yellow solid, (121 mg, 0.29 mmol, 79%), mp = 194-198 ℃ (decomposed), recrystallized from $CHCl_3$, CCDC no. 1920876; R_f = 0.72 (EtOAc/Hex = 2 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.19 – 1.39 (m, 5H), 1.41 – 1.59 (m, 5H), 1.62 – 1.83 (m, 5H), 1.91 – 2.01 (m, 1H), 2.06 – 2.24 (m, 2H), 2.39 (dd, *J* = 13.0, 5.2 Hz, 1H), 2.75 (dd, *J* = 15.8, 10.6 Hz, 1H), 2.90 (dd, *J* = 15.9, 8.0 Hz, 1H), 4.29 – 4.40 (m, 1H), 5.73 (dd, *J* = 10.4, 8.2 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 2H), 8.32 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.2 (CH_2 × 2), 22.5 (CH_2), 25.9 (CH_2), 27.5 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 33.8 (CH_2), 36.7 (CH_2), 38.8 (CH_2), 42.2 (CH), 46.6 (CH), 65.2 (C), 72.2 (CH), 123.8 (CH), 130.7 (CH), 135.0 (C), 150.7 (C), 164.0 (C), 170.8 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2934, 2868, 2360, 1726, 1694, 1528, 1407,1347, 1273, 1101 ; EI-HRMS (*m/z*) : [M]$^+$ calcd for $C_{23}H_{30}N_2O_5^+$ 414.2149, found 414.2148 (Δ = 0.2 ppm).

Preparation of the tricyclic lactams: The conjugated tricyclic lactams were hydrogenated to the saturated tricyclic products according to the mentioned catalytic hydrogenation procedure.

***rel*-(5*S*,10*R*)-13-Oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (5):** Yellow oil (201 mg, 1.0 mmol, 94%), R_f = 0.18 (EtOAc/Hex = 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 – 1.23 (m, 1H), 1.23 – 1.38 (m, 3H), 1.40 – 1.49 (m, 2H), 1.49 – 1.59 (m, 2H), 1.59 – 1.70 (m, 3H), 1.70 – 1.85 (m, 3H), 1.86 – 1.98 (m, 1H), 2.15 – 2.27 (m, 1H), 2.40 – 2.56 (m, 1H), 2.68 – 2.84 (m, 1H), 3.88 (dd, *J* = 13.7, 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.3 (CH_2), 22.5 (CH_2), 23.5 (CH_2), 24.9 (CH_2), 26.0 (CH_2), 27.3 (CH_2), 30.6 (CH_2), 33.3 (CH_2), 33.8 (CH_2), 42.1 (CH), 64.0 (C), 175.8 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 3475, 2934, 2863, 1684, 1460, 1417 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{12}H_{19}NO^+$ 193.1461, found 193.1456 (Δ = 2.6 ppm).

***rel*-(2*R*,5*S*,10*R*)-2-Hexyl-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (5a):** Yellow oil (25 mg, 0.09 mmol, 100%), R_f = 0.45 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.7 Hz, 3H), 1.08 – 1.20 (m, 1H), 1.21 – 1.52 (m, 13H), 1.53 – 1.79 (m, 9H), 1.85 (dd, *J* = 12.4, 8.2 Hz, 1H), 2.08 (dd, *J* = 16.1, 8.9 Hz, 1H), 2.36 – 2.51 (m, 2H), 3.09 – 3.19 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.1 (CH_2), 22.6 (CH_2), 23.5 (CH_2), 24.4 (CH_2), 26.1 (CH_2), 27.2 (CH_2), 27.7 (CH_2), 29.1 (CH_2), 30.4 (CH_2), 31.5 (CH_2), 31.8 (CH_2 × 2), 33.2 (CH_2), 42.4 (CH), 51.6 (CH), 66.1 (C), 176.3 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2931, 2858, 1685; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{31}NO^+$ 277.2400, found 277.2404 (Δ = -1.4 ppm). The ^{13}C NMR data are in agreement with those reported in the literature.[13,20b]

***rel*-(2*R*,5*S*,10*R*)-2-Butyl-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (5b):** Colorless oil (13 mg, 0.05 mmol, 100%), R_f = 0.38 (EtOAc/Hex = 1 : 2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.09 – 1.24 (m, 2H), 1.24 – 1.39 (m, 6H), 1.39 – 1.53 (m, 3H), 1.54 – 1.72 (m, 6H), 1.72 – 1.82 (m, 2H), 1.83 – 1.91 (m, 1H), 2.06 – 2.15 (m, 1H), 2.38 – 2.54 (m, 2H), 3.10 – 3.22 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.1 (CH_2), 22.6 (CH_2), 23.5 (CH_2), 24.4 (CH_2), 26.1 (CH_2), 27.2 (CH_2), 30.0 (CH_2), 30.4 (CH_2), 31.6 (CH_2 × 2), 33.2 (CH_2), 42.5 (CH), 51.7 (CH), 66.2 (C), 176.3 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2933, 2862, 1684; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{27}NO^+$ 249.2087, found 249.2096 (Δ = -3.6 ppm). The ^{13}C NMR data are in agreement with those reported in the literature.[20a,20b]

***rel*-(2*R*,5*R*,10*S*)-2-Hexyl-13-oxodecahydro-*H*-pyrrolo[2,1-j]-quinoline (18a):** Yellow oil (124 mg, 0.45 mmol, 95%), R_f = 0.14 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.4 Hz, 3H), 1.10 – 1.34 (m, 11H), 1.34 – 1.52 (m, 5H), 1.52 – 1.62 (m, 2H), 1.62 – 1.87 (m, 5H), 1.87 – 1.98 (m, 1H), 1.98 – 2.10 (m, 1H), 2.10 – 2.26 (m, 1H), 2.39 – 2.54 (m, 1H), 4.13 – 4.28 (m, 1H); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.5 (CH_2), 22.6 (CH_2), 23.9 (CH_2), 25.4 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 27.7 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 31.7 (CH_2), 36.2 (CH_2), 39.3 (CH_2), 42.5 (CH), 46.5 (CH), 64.9 (C), 176.1 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2931, 2861, 1689, 1459, 1403, 1355; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{31}NO^+$ 277.2400, found 277.2413 (Δ = -4.7 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Butyl-13-oxodecahydro-*H*-pyrrolo[2,1-j]quinoline (18b):** Yellow oil (164 mg, 0.66 mmol, 95%), R_f = 0.12 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.8 Hz, 3H), 1.15 – 1.36 (m, 9H), 1.38 – 1.52 (m, 4H), 1.53 – 1.63 (m, 1H), 1.65 – 1.83 (m, 5H), 1.94 (dd, *J* = 12.1, 7.6 Hz, 1H), 1.99 – 2.10 (m, 1H), 2.19 (dd, *J* = 16.5, 8.8 Hz, 1H), 2.42 – 2.55 (m, 1H), 4.16 – 4.26 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 22.6 (CH_2), 23.9 (CH_2), 25.4 (CH_2), 26.1 (CH_2), 27.7 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 36.1 (CH_2), 38.9 (CH_2), 42.5 (CH), 46.5 (CH), 64.9 (C), 176.2 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2864, 1686, 1458, 1403, 1261; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{27}NO^+$ 249.2087, found 249.2099 (Δ = -4.8 ppm).

The $LiAlH_4$ reduction: To a solution of lactam (**9**, 180 mg, 0.93 mmol, 1.0 eq.) in THF (9.3 mL) in an ice bath under argon, was slowly added $LiAlH_4$ (141 mg, 3.7 mmol, 4.0 eq) in portions. The reaction mixture was stirred under reflux conditions overnight. Upon completion of the reaction monitored by TLC analysis, the reaction mixture was cooled down in an ice bath. Addition of water (1 mL), NaOH (15%, 1 mL), and water (1 mL) in sequence resulted in the formation of white solid precipitates, which were filtered off by a short celite pad to give a filtrate. The filtrate was concentrated under reduced pressure to give a crude product. The crude product was purified by a short chromatography on silica gel, using EtOAc/n-hex as the eluant to give the titled product.

***rel*-(5*S*,10*R*)-Decahydro-*H*-pyrrolo[2,1-j]quinoline (1):** Yellow oil (126 mg, 0.70 mmol, 76%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 – 1.11 (m, 2H), 1.11 – 1.25 (m, 1H), 1.25 – 1.35 (m, 2H), 1.35 – 1.47 (m, 2H), 1.48 – 1.72 (m, 8H), 1.87 – 2.02 (m, 1H), 2.24 – 2.37 (m, 1H), 2.46 – 2.58 (m, 1H), 2.64 (d, *J* = 12.3 Hz, 1H), 2.99 – 3.14 (m, 1H), 3.61 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.1 (CH_2), 21.6 (CH_2), 23.5 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 27.0 (CH_2), 30.8 (CH_2), 35.9 (CH_2), 43.2 (CH), 51.1 (CH_2), 51.4 (CH_2), 67.5 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2930, 2859, 1447, 1274, 1082, 765; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{12}H_{21}N^+$ 179.1669, found 179.1675 (Δ = -3.3 ppm).

***rel*-(2*R*,5*R*,10*S*)-2-Butyl-decahydro-*H*-pyrrolo[2,1-j]quinoline (C2-*epi*-Lepadiformine C, 19b):** Yellow oil (153 mg, 0.65 mmol, 98%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 0.98 – 1.20 (m, 5H), 1.20 – 1.35 (m, 6H), 1.35 – 1.47 (m, 2H), 1.47 – 1.68 (m, 7H), 1.68 – 1.76 (m, 1H), 1.76 – 1.91 (m, 2H), 1.91 – 2.02 (m, 1H), 2.86 – 3.00 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.1 (CH_2), 22.5 (CH_2), 23.0 (CH_2), 23.6 (CH_2), 26.3 (CH_2), 26.7 (CH_2), 28.9 (CH_2), 31.1 (CH_2), 32.6 (CH_2), 36.4 (CH_2), 37.2 (CH_2), 43.4 (CH), 47.7 (CH_2), 57.7 (CH), 68.1 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2930, 2860, 1450, 1275 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{16}H_{29}N^+$ 235.2295, found 235.2301 (Δ = -2.6 ppm).

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-8a-cyano-2-(2-propenyl)decahydroquinoline (11):** To a CH_2Cl_2 solution (33 mL) of allyltrimethylsilane (2.6 mL, 16.4 mmol, 2.4 eq) and $BF_3{\cdot}OEt_2$ (1.0 mL, 8.2 mmol, 1.2 eq) at -90 ºC was added dropwise CH_2Cl_2 solution (7 mL) of aldehyde **7** (2.143 g, 6.8 mmol, 1 eq) at -78 ºC. The cooling bath was removed and the reaction mixture was stirred at room temperature. Upon completion of the reaction monitored by TLC analysis, a saturated $NaHCO_3$ solution was slowly added into the reaction mixture at 0 ºC, and then warmed up to room temperature. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product as an inseparable mixture with encarbamate **3'** (~ 4 : 1). The crude product can be used directly for the subsequent transformations. For the purpose of isolation of the title product, the crude product was allowed to stand at room temperature for several days, for encarbamate **3**' is prone to be gradually decomposed at room temperature. Subsequent flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant gave the pure product as white solid (1.766 g, 77%) mp = 58-60 ºC; R_f = 0.44 (EtOAc/Hex = 1 : 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 – 1.42 (m, 3H), 1.44 – 1.54 (m, 1H), 1.56 – 1.73 (m, 5H), 1.73 – 1.86 (m, 3H), 2.27 – 2.38 (m, 1H), 2.57 – 2.69 (m, 1H), 3.49 – 3.58 (m, 1H), 4.26 – 4.34 (m, 1H), 4.97 – 5.06 (m, 2H), 5.11 (d, *J* = 12.1 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.50 – 5.63 (m, 1H), 7.28 – 7.43 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 23.2 (CH_2), 23.3 (CH_2), 25.1 (CH_2), 26.1 (CH_2), 30.5 (CH_2), 35.9 (CH_2), 36.6 (CH_2), 49.5 (CH),

55.3 (CH), 58.7 (C), 67.6 (CH_2), 117.8 (CH_2), 119.9 (C), 128.3 (CH × 2), 128.5 (CH), 134.9 (CH), 135.7 (C), 156.9 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2938, 2864, 1712, 1641, 1456, 1383, 1273, 1152, 1112, 1000, 915; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{21}H_{26}N_2O_2^+$ 338.1989, found 338.1984 (Δ = 1.5 ppm).

General Procedure for the Wittig Olefination: To a THF solution (40 mL) of methyltriphenyl-phosphonium bromide (1.774 g, 5.0 mmol, 3.0 eq) at an ice bath, was slowly added NaHMDS solution (1 M, 4.1 mL, 4.1 mmol, 2.5 eq) via a syringe. The reaction mixture was stirred at the low temperature for 1 h. To the freshly prepared Wittig reagent at the ice bath was added a THF solution (2 mL) of aldehyde **13** (592 mg, 1.7 mmol, 1.0 eq), and warmed up gradually to room temperature in 2 h. Upon completion of the reaction monitored by TLC analysis, the reaction was quenched with saturated NH_4Cl. After separation of the organic layer, the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removal of the solid dehydrating agent, the organic layer was concentrated under reduced pressure to give a crude product. Purification of the crude product by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***cis-rel*-(2*R*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-8a-cyano-2-(3-hexenyl)decahydroquinoline (14a):** Yellow oil (477 mg, 1.3 mmol, 84%), *cis/trans* = 10:1, ***cis*-14a** : R_f = 0.56 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 – 0.95 (m, 3H), 1.24 – 1.42 (m, 3H), 1.44 – 1.55 (m, 2H), 1.59 – 1.81 (m, 8H), 1.85 – 1.98 (m, 4H), 1.99 – 2.11 (m, 1H), 3.53 (d, *J* = 13.3 Hz, 1H), 4.19 – 4.27 (m, 1H), 5.08 – 5.20 (m, 3H), 5.23 – 5.33 (m, 1H), 7.27 – 7.43 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.3 (CH_3), 20.4 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 24.8 (CH_2), 25.1 (CH_2), 26.1 (CH_2), 30.5 (CH_2), 31.9 (CH_2), 36.1 (CH_2), 46.6 (CH), 55.6 (CH), 58.7 (C), 67.6 (CH_2), 119.8 (C), 127.5 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 132.2 (CH), 135.8 (C), 157.0 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 3008, 2937, 2864, 2229, 1711, 1457, 1383, 1283, 1242, 750, 698; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{24}H_{32}N_2O_2^+$ 380.2458, found 380.2468 (Δ = -2.6 ppm).

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-8a-cyano-2-(3-butenyl)decahydroquinoline (14b):** White solid (462 mg, 1.3 mmol, 77%), mp = 93-95 °C, recrystallized from CH_2Cl_2, CCDC no. 1920894; R_f = 0.58 (EtOAc/Hex = 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 – 1.42 (m, 3H), 1.44 – 1.56 (m, 2H), 1.57 – 1.89 (m, 9H), 1.92 – 2.13 (m, 2H), 3.53 (d, *J* = 13.2 Hz, 1H), 4.18 – 4.27 (m, 1H), 4.82 – 4.97 (m, 1H), 5.09 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.53 – 5.66 (m, 1H), 7.25 – 7.47 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 23.3 (CH_2 × 2), 25.1 (CH_2), 26.0 (CH_2), 30.5 (CH_2), 31.2 (CH_2), 31.5 (CH_2), 36.0 (CH_2), 46.6 (CH), 55.5 (CH), 58.7 (C), 67.6 (CH_2), 115.0 (CH_2), 119.8 (C), 128.3 (CH), 128.5 (CH × 2), 135.8 (C), 137.3 (CH), 157.0 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2938, 2864, 2363, 1711, 1641, 1455, 1382, 1283, 1242, 998, 913 ; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{22}H_{28}N_2O_2^+$ 352.2145, found 352.2155 (Δ = -2.8 ppm).

General Procedure for the Aerobic Hydrogenation: To a 25 mL flask charged with the alkene (**14a**, 216 mg, 0.61 mmol, 1.0 eq) and riboflavin tetrabutyrate (8 mg, 12 μmol, 2 mol%), was added acetonitrile (4.9 mL), hydrazine hydrate (N_2H_4-H_2O, 60 μL, 1.2 mmol, 2.0 eq). The solution was stirred under an oxygen balloon at room temperature overnight. Evaporation of the volatile substance afforded the resulting crude reside, which was purified by flash chromatography on silica gel, EtOAc/*n*-Hex as the eluant to give the titled product.

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-2-hexyl-8a-cyanodecahydroquinoline (3a):** Colorless oil (625 mg, 1.63 mmol, 96%) R_f = 0.51 (EtOAc/Hex =1 : 6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 0.99 – 1.09 (m, 1H), 1.17 (brs, 5H), 1.20 – 1.27 (m, 3H), 1.27 – 1.38 (m, 3H), 1.45 – 1.52 (m, 1H), 1.56 – 1.69 (m, 4H), 1.69 – 1.81 (m, 4H), 1.87 – 2.00 (m, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 4.14 – 4.24 (m, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 7.25 – 7.44 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.5 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 25.1 (CH_2), 26.4 (CH_2), 27.5 (CH_2), 29.0 (CH_2), 30.5 (CH_2), 31.7 (CH_2), 32.3 (CH_2), 36.1 (CH_2), 46.6 (CH), 56.3 (CH), 58.7 (C), 67.5 (CH_2), 119.8 (C), 128.2 (CH), 128.4 (CH), 128.5 (CH), 135.9 (C), 157.1 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2933, 2861, 2229, 1712, 1457, 1382, 1284, 1244; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{24}H_{34}N_2O_2^+$ 382.2615, found 382.2612 (Δ = 0.8 ppm).

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Benzyloxycarbonyl-2-butyl-8a-cyanodecahydroquinoline (3b):** White solid (211 mg, 0.60 mmol, 98%), mp = 96-98 °C, recrystallized from CH_2Cl_2, CCDC no. 1952224; R_f = 0.47 (EtOAc/Hex = 1 : 6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.1 Hz, 3H), 0.96 – 1.09 (m, 1H), 1.09 – 1.24 (m, 3H), 1.24 – 1.40 (m, 3H), 1.40 – 1.53 (m, 2H), 1.54 – 1.69 (m, 4H), 1.69 – 1.82 (m, 4H), 1.86 – 2.00 (m, 1H), 3.46 – 3.56 (m, 1H), 4.14 – 4.24 (m, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 7.24 – 7.44 (m, 5H); ^{13}C{^{1}H} (101 MHz, $CDCl_3$) 14.0 (CH_3), 22.3 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 25.1 (CH_2), 26.3 (CH_2), 29.6 (CH_2), 30.5 (CH_2), 32.0 (CH_2), 36.0 (CH_2), 46.6 (CH), 56.2 (CH), 58.6 (C), 67.5 (CH_2), 119.8 (C), 128.2 (CH), 128.4 (CH × 2), 135.9 (C), 157.1 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2936, 2864, 2229, 1711, 1457, 1382, 1281, 1242; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{22}H_{30}N_2O_2^+$ 354.2302, found 354.2303 (Δ = -0.3 ppm).

General Procedure for Preparation of the *syn*-acetamides:

A mixed solution of carbamate (**3b**, 182 mg, 0.51 mmol, 1.0 eq) in $HBr_{(aq)}$ (48%, 2.5 mL) and acetic acid (10 mL) was stirred at 60 °C for 6 h. Upon completion of the reaction monitored by TLC analysis, the solution was concentrated under reduced pressure to give a crude residue. The crude product was acetylated according to the mentioned procedure directly without further purification.

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Acetyl-2-hexyl-8a-cyanodecahydroquinoline (4a):** Colorless oil (81 mg, 0.28 mmol, 53%), R_f = 0.51 (EtOAc/Hex = 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.08 – 1.20 (m, 2H), 1.20 – 1.34 (m, 8H), 1.34 – 1.52 (m, 3H), 1.57 – 1.78 (m, 7H), 1.78 – 1.86 (m, 1H), 2.10 – 2.18 (m, 4H), 3.54 (d, *J* = 13.3 Hz, 1H), 3.81 – 3.90 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.4 (C), 119.5 (C), 57.9 (C), 56.4 (CH), 46.6 (CH), 35.5 (CH_2), 32.9 (CH_2), 31.7 (CH_2), 30.4 (CH_2), 28.9 (CH_2), 27.8 (CH_2), 26.3 (CH_2), 25.2 (CH_2), 24.7 (CH), 23.3 (CH_2), 23.2 (CH_2), 22.5 (CH_2), 13.9 (CH_3); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2863, 2229, 1674, 1458, 1367, 1274; EI-HRMS (*m/z*) : $[M]^+$ calcd for $C_{18}H_{30}N_2O$ 290.2353, found 290.2357 (Δ = -1.4 ppm).

***rel*-(2*R*,4a*S*,8a*R*)-*N*-Acetyl-2-butyl-8a-cyanodecahydroquinoline (4b):** Yellow solid (115 mg, 0.44 mmol, 86%), mp = 78-80 °C, recrystallized from CH_2Cl_2, CCDC no. 1947269; R_f = 0.31 (EtOAc/Hex = 1 : 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.08 – 1.20 (m, 2H), 1.20 – 1.54 (m, 7H), 1.54 – 1.65 (m, 3H), 1.65 – 1.78 (m, 4H), 1.78 – 1.92 (m, 1H), 2.05 – 2.20 (m, 4H), 3.53 (d, *J* = 13.1 Hz, 1H), 3.78 – 3.90 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.4 (CH_2), 23.1 (CH_2), 23.3 (CH_2), 24.7 (CH), 25.2 (CH_2), 26.3 (CH_2), 30.0 (CH_2), 30.4 (CH_2), 32.7 (CH_2), 35.4 (CH_2), 46.5 (CH), 56.3 (CH), 57.9 (C), 119.5 (C), 175.3 (C); IR (cm^{-1}, film) $\bar{\nu}_{max}$ = 2935, 2864, 2362, 1673, 1457, 1382, 1277; EI-HRMS

(*m/z*) : $[M]^+$ calcd for $C_{16}H_{26}N_2O^+$ 262.2040, found 262.2047 (Δ = -2.7 ppm).

Supporting Information:

The Supporting Information is available free of charge on the ACS Publications website.

^1H and ^{13}C-NMR spectra of all compounds (PDF)

The X-ray Crystallographic Data of **2**, **3'**, **3b**, **4**, **4b**, **10 14b**, **20a**, and **20b** (CIF)

All calculated geometry coordinates from DFT calculation for stability comparison.

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Notes

The authors declare no competing financial interest.

Dedicated to Professor Iwao Ojima on occasion of his 75th birthday.

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(15) See the Supporting Information for the ORTEP representation of the X-ray structure.

(16) The addition sequence was important in this reaction. As long as the free aminonitrile was mixed with a base, it usually suffered with low yields. Such a phenomenon also suggested possible spontaneous dissociation of the nitrile group, especially in the basic conditions.

(17) As we anticipated, despite intense efforts to convert the angular nitrile group of CDHQ **3**, attempts to attain the carbonyl functionality from the nitrile for further transformations were unsuccessfully. These efforts included basic or peroxide-mediate hydrolysis, reducing agents, Rh-mediated hydrolysis and organolithiums. These reactions led either to recovery of the starting materials, low yield of the aldehyde product, or to complete destruction if in forcing conditions.

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(24) Addition of the co-solvent is necessary because of the poor solubility of the substrates in HBr. Employment of ethereal solvents will result in the decomposition of the solvents.

(25) The catalytic hydrogenation over Pd/C proceeded very slowly in ethyl acetate.

(26) The crude product is prone to be decomposed at room temperature.

(27) Two sets of the ^{13}C-NMR peaks have been reported due to the observation of equilibrium between acyclic form (i.e. aldehyde) as the major contributor and cyclic form as the minor one (i.e. aminal).

(28) The numbering method follows the lepadiformine system for convenience.