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Model studies in the lepadin series: synthesis of enantiopure decahydroquinolines by aminocyclization of 2-(3-aminoalkyl)cyclohexenones

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Abstract—Syntheses of enantiopure 3-acetoxy-2-methyldecahydroquinolines are accomplished by coupling cyclohexenyllithium **3** with α-amino epoxides and an aminocyclization of 2-(3-aminoalkyl)cyclohexenones (i.e., **5** and **9**) as the key steps. The procedure allows the incorporation of alkyl substituents at C(5) to give enantiopure 2,3,5-trisubstitued decahydroquinolines.

1. Introduction

Lepadin alkaloids are structurally characterized by the presence of a 2,3,5-trisubstituted *cis*-fused decahydroquinoline ring. The substitution pattern, which has a methyl group at C(2), a hydroxyl group, free or acylated, at C(3), and an eight carbon side chain at C(5), shows a variety of stereochemical arrangements, as shown in Figure 1. Eight lepadins (A–H) have been isolated from marine sources since 1991,[1–4] of which lepadins A–C have been found to possess significant in vitro cytotoxicity against several human cancer cell lines, whereas lepadins D–F have shown low cytotoxicity but significant and selective antiplasmodial and antitrypanosomal activity.

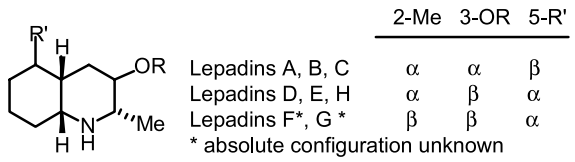

Figure 1.

Total enantioselective syntheses of lepadins A,[5] B,[5–7] C,[5] D–E,[7] and H,[7] as well as a formal route to *rac*-lepadin B[8] have been reported. The strategies described for the construction of 5-substituted 3-hydroxy-2-methyldecahydroquinolines in these synthetic approaches involve the elaboration of a polyfunctionalized piperidine followed by carbocyclic ring closure through aldol processes[5,6] or the construction of the piperidine ring from cyclohexanone derivatives either by an intramolecular enamine alkylation[7] or using a xanthate-mediated radical cyclization[8] (Scheme 1).

In this work, we report our studies on a new synthetic entry to the azabicyclic core of lepadins, either those that show a *cis* or *trans* relationship between the respective methyl and hydroxyl substituents at C(2) and C(3) of the decahydroquinoline ring (see Fig. 1). In our approach, we envisaged enantiopure cyclohexenones of type **I** (R′=H) as potential intermediates as they would bring about ring closure by forming the N–C(8a) bond. Here, we present the synthesis of these building blocks and the results obtained by their aminocyclization, either when R′=H or R′=alkyl.

2. Results and discussion

2.1. Synthetic aspects

The required starting materials are 2-bromocyclohex-2-enone ethylene acetal (**1**) and the (*S*) and (*R*) isomers of [(*S*)-1′-(dibenzylamino)ethyl]oxirane (**2a** and **2b**). The cyclohexenone derivative **1**, reported by Smith,[9] is a precursor of the α-ketovinyl anion equivalent **3**, often used in the formation of C–C bonds, for example, in reactions with alkyl halides,[9,10] ketones,[11] ethyl chloroformate,[9] and DMF.[12] Moreover, this vinyllithium derivative has been

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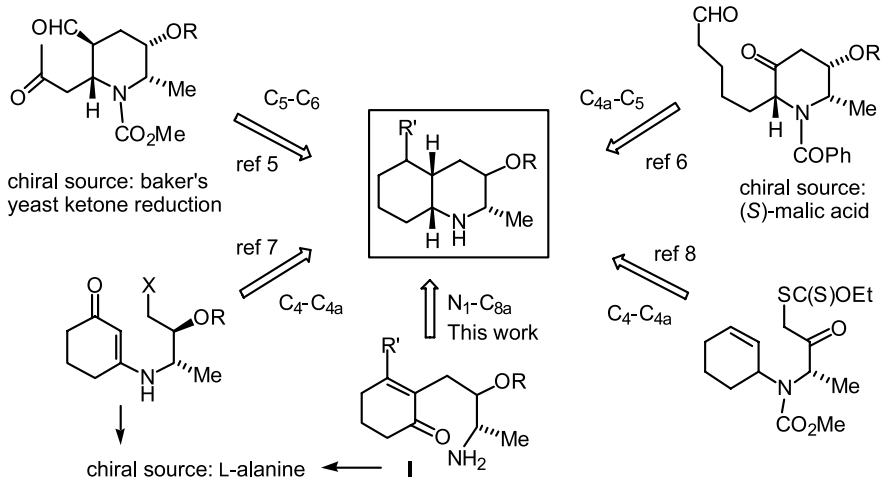
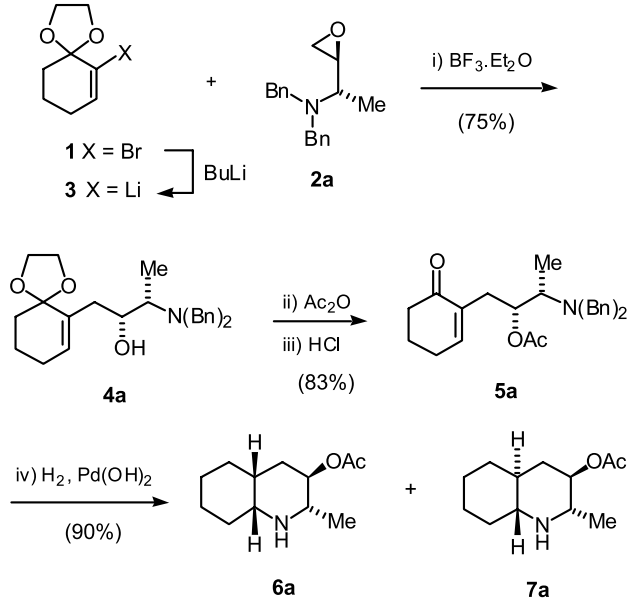


Scheme 1. Synthetic approaches to lepadin alkaloids.

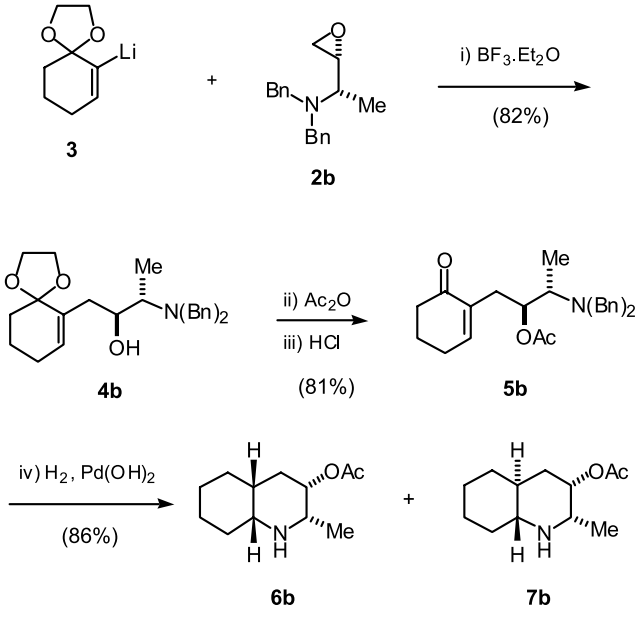
transmetallated with copper,[13] tin,[14] and palladium[15] reagents and then used in coupling processes. Finally, the lithium compound **3** reacts with TMSCl[16] and sulfinates to give vinylsilane and vinylsulfoxide[17] derivatives, respectively. To our knowledge, this versatile lithium derivative has not been used in reactions with epoxides, such as described in the present work. On the other hand, epoxides **2**[18] have been described by Reetz,[19] Barluenga and Concellón[20] and Beaulieu,[21] but there are no examples of their reactions with organolithium derivatives.[22]

The vinyllithium **3** formed on treatment of bromoacetal **1** with *n*-BuLi in THF reacted with epoxide **2a**[20] in presence of $BF_3 \cdot Et_2O$ (Ganem's conditions)[23,24] to give enantiopure alcohol **4a** (Scheme 2). After protection of the hydroxyl group as an acetate and subsequent deprotection of the acetal, the resulting cyclohexenone **5a** was submitted to a hydrogenation reaction, which involves a reduction of the double bond, a double debenzylation of the tertiary amine and an intramolecular reductive amination, to give the decahydroquinoline ring. In this process, in which two new



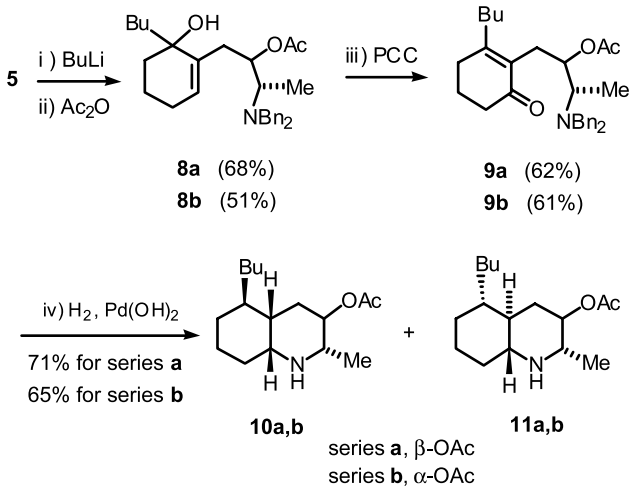
Scheme 2.

stereogenic centers are formed, the bicyclic compounds **6a** and **7a** were isolated in a 2:1 ratio. We then carried out the same sequence of reactions but starting from epoxide **2b**[20] (Scheme 3). In this series, the aminocyclization step starting from cyclohexenone **5b** gave a nearly equimolecular mixture of decahydroquinolines **6b** and **7b**. Thus, 5-dealkyllepadin derivatives with the same absolute configuration as lepadins D, E, and H (i.e., compound **6a**), and lepadins A, B, and C (i.e., compound **6b**) were achieved.



Scheme 3.

At this point, we explored the usefulness of cyclohexenones **5** as precursors of 5-alkylsubstituted decahydroquinolines (Scheme 4). Treatment of **5a** with *n*-BuLi gave a tertiary alcohol as an epimeric mixture, which was reacetylated upon the hydroxyl of the side chain, and the resulting **8a** was oxidized[25] to give the rearranged enone **9a**. The multi-step tranformation of **9a** under a hydrogen atmosphere (hydrogenation, debenzylation, and reductive aminocyclization) gave a mixture of trisubstituted decahydroquinolines **10a**



Scheme 4.

and **11a** in a nearly equimolecular ratio (71% overall yield), in which three new stereogenic centers were formed. Working with the epimeric epoxide **5b**, and following the same reaction sequence, decahydroquinolines **10b** and **11b** were formed in a 1:4 ratio (65% overall yield).

In all the cyclization processes (**5**→**6**+**7** and **9**→**10**+**11**), both in series **a** (3*R* configuration) and series **b** (3*S* configuration), the isolated decahydroquinolines show an *R* configuration at C(8a) (see Fig. 2). The configuration at C(4a) is controlled by the configuration of C(3) as well as by the presence or absence of a substituent at C(5). From the β-unsubstituted cyclohexenones (i.e., compounds **5**), the aminocyclization takes place with some diastereoselection if the acetoxy substituent can adopt a pseudo-equatorial disposition in the transition state leading to the reduced product, as occurs in **6a**, whereas in the epimeric series no stereocontrol was observed in the formation of the C(4a) stereocenter. Since it has not been established if the course of the reaction follows a pathway through an enimine intermediate or if there is a reduction of the double bond prior to the cyclization step, a clear understanding of the stereochemical course is not possible at this stage. More intriguing is the pathway of the aminocyclization leading to 2,3,5-trisubstituted decahydroquinolines **10** and **11**. The configuration at C(4a) and C(5) in all cases showed a trans relationship between the hydrogen atoms of these stereocenters suggesting that the double bond underwent a trans hydrogenation, as has been reported in some tetrasubstituted alkenes,[26] or, after a cis hydrogenation and formation of the subsequent imine, an epimerization took place at C(4a) through an enamine intermediate. Again, as occured in the 5-unsubstituted series, the ratio of trans decahydroquinolines (i.e., **11b**) to the cis epimers was higher in compounds with a 3*S* rather than 3*R* configuration.

2.2. NMR studies of decahydroquinolines 6, 7, 10, and 11 (series a and b)

The cis (**6** and **10**) and trans decahydroquinolines (**7** and **11**) are clearly differentiated by two NMR features: (i) the ^{1}H NMR chemical shift of H-8a, which appears more deshieled (δ 2.95) in the *cis*-than in the trans-derivatives (δ 2.20); (ii) the ^{13}C chemical shift of C(7) is more deshielded (~4–5 ppm) in the trans than in the cis derivatives.[27] In all cases, the preferred conformation of the cis decahydroquinolines has the H-8a axial with respect to the *N*-containing ring (*N-endo* conformer).

The absolute configuration of **6a** was deduced considering that: (a) the coupling constants for H-2 (dq, J=10, 6.5 Hz) and H-3 (td, J=10.5, 4.8 Hz) determined their axial location and hence, fixed the methyl at C(2) and the acetoxy at C(3) to an equatorial disposition; (b) the multiplicity of H-8a (br s) implied an equatorial relationship with respect to the cyclohexane ring, which discarded not only a trans junction of the decaline ring but also, taking into account the preferred conformation, implied an *R* configuration for C(8a). The ^{13}C chemical shifts also agree with this elucidation since the value of δ 20.3 for C(7) is diagnostic of a cis decahydroquinoline in a *N-endo* conformation. For trans compound **7a**, the axial proton H-8a is strongly coupled to two adjacent axial protons and one equatorial proton. Hence, its resonance signal appears as a deceptively simple triplet (J=10.4 Hz) of doublets (J=3.2 Hz) centered at δ 2.19. The NMR data for compounds **6b** and **7b** follow the same pattern of signals as that of their corresponding epimers at C(3), the major differences being in the chemical shift for H-3, which is now more deshielded since it is located in an equatorial arrangement, and in C-3 and C-4a, which resonate at a lower field, due to the axially

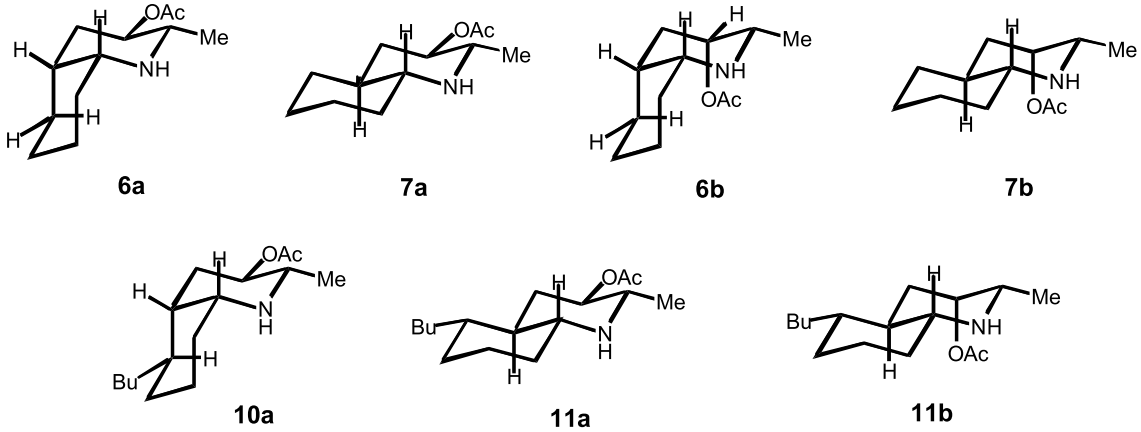


Figure 2. Preferred conformation of decahydroquinolines **6**, **7**, **10**, and **11**.

Table 1. ^{13}C NMR data for decahydroquinolines **6**, **7**, **10**, and **11**

	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-1′	C-2′	C-3′	C-4′	OAc
6a	56.5	73.0	36.4	36.8	26.5	26.1	20.3	31.9	54.3	18.9	—	—	—	—	170.6/21.3
6b	55.0	70.3	35.0	33.5	27.5	26.8	20.8	32.6	54.6	18.2	—	—	—	—	170.8/21.4
7a	55.7	75.7	37.5	41.6	31.8	25.6	25.3	32.6	60.9	18.5	—	—	—	—	170.4/21.2
7b	54.0	71.6	36.6	36.9	31.9	26.0	25.5	33.2	61.4	18.3	—	—	—	—	171.0/21.3
10a	56.5	72.7	32.5	41.8	33.0	29.7	21.3	32.7	55.5	18.8	31.9	28.1	23.1	14.1	170.5/21.1
11a	55.4	76.4	34.4	46.3	40.8	31.3	24.7	33.1	60.8	18.7	32.1	28.5	23.1	14.1	170.5/21.3
11b	53.7	71.6	33.5	40.9	40.7	31.9	24.9	33.4	61.1	18.2	31.7	28.4	23.1	14.1	171.0/21.3

All spectra were recorded at 100 MHz in $CDCl_3$ and the assignments were aided by HSQC experiments.

located acetoxy group (Table 1). For trisubstituted cis decahydroquinoline **10a**, the butyl substituent at C(5) controls the preferred conformation of the bicyclic ring, which agrees with the conformation showed for lepadins where the substituent at C(5) is always equatorially located. The stereochemistry at C(5) for the butyl substituted products (**10** and **11**) was determined considering that the equatorially located butyl side chain exerts a steric crowding on H-4*eq*, due to their 1,3-synperiplanar relationship, which is reflected in the ^{13}C and ^{1}H NMR spectra by an upfield chemical shift (~3 ppm) for C(4) and a downfield chemical shift (δ 2.25±0.05) for H-4*eq* as compared to the NMR data for compounds **6** and **7**.

In summary, a new synthetic entry to enantiopure polysubstituted decahydroquinolines has been reported. Although the observed stereoselectivity does not allow lepadin-type stereochemistries to be achieved, further studies in aminocyclization processes, starting from cyclohexenones of type **5**, are in progress with the aim of achieving the required stereochemistry of lepadin derivatives. Interestingly, the reported methodology could be applied to the synthesis of another type of natural decahydroquinolines, such as *trans*-195A,[28] 5-*epi*-*trans*-243A,[29] and related alkaloids isolated from dendrobatid frogs,[27c] which show the same pattern of relative configuration as compounds **11a** and **11b** in their four stereocenters.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. Analytical TLC was performed on SiO_2 (silica gel $60F_{254}$, Merck) or Al_2O_3 (ALOX N/UV_{254}, Polygram), and the spots were located with iodoplatinate reagent (compounds **4**, **5**, **8**, and **9**) or 1% aqueous $KMnO_4$ (compounds **6**, **7**, **10**, and **11**). Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel 60, SDS, 230–240 mesh ASTM) or Al_2O_3 (aluminium oxide 90, Merck). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Optical rotations were recorded with a Perkin-Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 or 300, or a Varian Mercury 400 instrument. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

3.1.1. 2-[(2*R*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4a). A solution of 6-bromo-1,4-dioxaspiro[4.5]dec-6-ene (**1**, 1.04 g, 4.75 mmol) in THF (3 mL) was added to a solution of *n*-BuLi (1.6 M in hexanes, 3.2 mL, 5.11 mmol) in THF (7 mL) at −78 °C. The reaction mixture was stirred for 90 min, treated with a solution of (2*S*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2a**, 489 mg, 1.83 mmol) in THF (6 mL) and $BF_3\cdot Et_2O$ (0.64 mL, 5.11 mmol), and continuously stirred at −78 °C for 2 h prior to being quenched with saturated $NaHCO_3$ solution (10 mL) and warmed to rt. The

product was extracted with Et_2O (3×20 mL), the combined organic layers were dried, concentrated, and the residue was chromatographed (SiO_2, elution with 9:1 hexane/EtOAc) to give 560 mg (75%) of **4a** as a colorless oil: R_f=0.31 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.0 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.15 (d, *J*=6.3 Hz, 3H), 1.60–1.80 (m, 5H), 1.95–2.05 (br, 2H), 2.52–2.61 (m, 1H), 2.85 (dm, *J*=14 Hz, 1H), 3.25 (br, 1H), 3.45 (d, *J*=13.8 Hz, 2H), 3.66–3.73 (m, 1H), 3.77 (d, *J*=13.8 Hz, 2H), 3.84–3.90 (m, 2H), 3.91–3.97 (m, 2H), 5.76 (t, *J*=3 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.4 (CH_3), 20.6 (CH_2), 25.4 (CH_2), 33.2 (CH_2), 36.2 (CH_2), 54.3 (CH_2), 57.7 (CH), 64.6 (CH_2), 64.7 (CH_2), 74.1 (CH), 107.5 (C), 126.7 (CH), 128.1 (CH), 128.7 (CH), 133.6 (CH), 140.3 (C). HRFABMS calcd for $C_{26}H_{34}NO_3$ (M^++1) 408.2539, found 408.2516.

3.1.2. 2-[(2*S*,3*S*)-3-Dibenzylamino-2-hydroxybutyl] cyclohex-2-enone ethylene acetal (4b). Operating as above, starting from 881 mg (4.02 mmol) of **1** and using (2*R*)-[1′(*S*)-(dibenzylamino)ethyl]oxirane (**2b**, 414 mg, 1.55 mmol), and after chromatography (SiO_2, 9:1 hexane/EtOAc) **4b** (518 mg, 82%) was isolated as an oil: R_f=0.28 (SiO_2, 9:1 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 1.05 (d, *J*=6.6 Hz, 3H), 1.62–1.72 (m, 5H), 1.95–2.05 (br, 2H), 2.17–2.25 (m, 1H), 2.52–2.62 (m, 1H), 3.33 (d, *J*=13.6 Hz, 2H), 3.64–3.76 (m, 1H), 3.88 (d, *J*=13.6 Hz, 2H), 3.90–3.98 (m, 4H), 5.93 (t, *J*=2 Hz, 1H), 7.16–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.6 (CH_3), 20.6 (CH_2), 25.3 (CH_2), 33.6 (CH_2), 34.3 (CH_2), 53.6 (CH_2), 58.2 (CH), 64.7 (CH_2), 64.8 (CH_2), 70.8 (CH), 107.8 (C), 127.0 (CH), 128.3 (CH), 128.9 (CH), 131.5 (CH), 139.2 (C).

3.1.3. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone (5a). To a solution of **4a** (101 mg, 0.25 mmol) in pyridine (0.8 mL) and Ac_2O (0.24 mL, 2.5 mmol) was added DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt. A saturated $NaHCO_3$ solution (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The dried organic extracts were concentrated to give the corresponding acetate, which was used directly in the following acetal hydrolysis step. The above crude acetal was dissolved in 1:1 H_2O/THF (4 mL) and stirred at rt for 1 h. The reaction mixture was basified with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×10 mL), and the resulting organic extracts were dried and concentrated. The residue was purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give **5a** as an oil (80 mg, 83%): R_f=0.27 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +7.8 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.08 (d, *J*=6.6 Hz, 3H), 1.75–1.83 (m, 1H), 1.83–1.93 (m, 2H), 1.94 (s, 3H), 2.16–2.28 (m, 2H), 2.31–2.38 (m, 2H), 2.75 (quint, *J*=6 Hz, 1H), 3.18 (dm, *J*=14 Hz, 1H), 3.41 (d, *J*=13.6 Hz, 2H), 3.78 (d, *J*=13.6 Hz, 2H), 5.17 (ddd, *J*=9.6, 7.6, 3.4 Hz, 1H), 6.53 (t, *J*=4 Hz, 1H), 7.17–7.41 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 8.8 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.2 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 53.9 (CH_2), 55.1 (CH), 74.3 (CH), 126.7 (CH), 128.1 (CH), 129.0 (CH), 136.4 (C), 139.9 (C), 146.4 (CH), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{26}H_{31}NO_3$: C, 77.00; H, 7.70; N, 3.45. Found C, 76.75; H, 7.85; N, 3.39.

3.1.4. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl] cyclohex-2-enone ethylene acetal (5b). Operating as above, starting from 263 mg (0.64 mmol) of alcohol **4b**, and after chromatography (SiO_2, 8:2 hexane/EtOAc), acetate **5b** (196 mg, 81%) was isolated as an oil: R_f=0.25 (SiO_2, hexane/EtOAc, 8:2); $[\alpha]_D^{20}$ −32 (*c* 1.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.09 (d, *J*=7.2 Hz, 3H), 1.86–1.94 (m, 3H), 2.01 (s, 3H), 2.16–2.30 (m, 3H), 2.33–2.40 (m, 1H), 2.60 (dm, *J*=14 Hz, 1H), 2.89 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.8 Hz, 2H), 3.87 (d, *J*=13.8 Hz, 2H), 5.06 (ddd, *J*=10.2, 6.2, 2.6 Hz, 1H), 6.60 (t, *J*=4.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): 9.7 (CH_3), 21.2 (CH_3), 22.9 (CH_2), 26.1 (CH_2), 33.0 (CH_2), 38.2 (CH_2), 54.3 (CH_2), 55.4 (CH), 74.7 (CH), 126.6 (CH), 128.1 (CH), 128.8 (CH), 136.3 (C), 140.3 (C), 146.3 (CH), 170.3 (C), 198.8 (C). HRFABMS calcd for $C_{26}H_{32}NO_3$ (M^++1) 406.2382, found 406.2339.

3.1.5. Aminocyclization of 5a. A suspension of enone **5a** (50 mg, 0.12 mmol) and activated[30] $Pd(OH)_2$ in EtOH (2 mL) was stirred overnight under hydrogen. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give a residue, which was purified by chromatography (Al_2O_3, 9:1 hexane/EtOAc) to give **6a** (13 mg, 54%) and **7a** (9 mg, 36%), both as oils.

(2*S*,3*R*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6a**). R_f=0.51 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −20.7 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.4 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax* and H-7), 1.45 (m, H-4*ax*), 1.55 (m, H-8), 1.70 (m, H-8), 1.74 (m, 3H, H-4a, H-5*eq*, H-6*eq*), 1.87 (ddd, *J*=11.0, 3.6, 1.2 Hz, H-4*eq*), 2.05 (s, 3H, OAc), 2.70 (dq, *J*=10.0, 6.5 Hz, H-2*ax*), 2.95 (br s, H-8a), 4.58 (td, *J*=10.5, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1646.

(2*S*,3*R*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**7a**). ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.02 (qd, *J*=10.4, 3.2 Hz, H-5*ax*), 1.10 (masked, H-4*ax*), 1.12 (d, *J*=6.4 Hz, 3H, Me), 1.20–1.30 (m, 2H, H-8*ax* and H-4a), 1.35 (m, 2H, H-6*ax* and H-7*ax*), 1.65 (m, 2H, H-7*eq* and H-5*eq*), 1.8 (m, 2H, H-8*eq* and H-6*eq*), 2.04 (s, 3H, OAc), 2.05 (masked, H-4*eq*), 2.19 (td, *J*=10.4, 3.2 Hz, H-8a), 2.76 (dq, *J*=10, 6.4 Hz, H-2*ax*), 4.45 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1.

3.1.6. Aminocyclization of 5b. Operating as above, starting from 49 mg (0.12 mmol) of enone **5b**, and after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc), 11 mg (43%) of **6b** and 11 mg (43%) of **7b**, both as colorless oils, were isolated.

(2*S*,3*S*,4a*R*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline (**6b**). R_f=0.30 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +10.8 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 1.08 (d, *J*=6.6 Hz, 3H, Me), 1.20 (m, H-5*ax*), 1.40 (m, 3H, H-6*ax*, H-7), 1.50 (m, 2H, H-8*ax*, H-4*ax*), 1.72 (m, 4H, H-4a, H-5*eq*, H-6*eq*, H-8*eq*), 1.87 (ddd, *J*=12, 3.6, 1.5 Hz, H-4*eq*), 2.09 (s, 3H, OAc), 2.90 (qd, *J*=6.8, 2 Hz, H-2*ax*), 2.92 (br, H-8a), 4.75 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

(2*S*,3*S*,4a*S*,8a*R*)-3-Acetoxy-2-methyldecahydroquinoline

(**7b**). R_f=0.23 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ +28.6 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.94 (qd, *J*=12, 3 Hz, H-5*ax*), 1.06 (dd, *J*=6.8 Hz, 3H, Me), 1.21–1.34 (m, 5H, H-4*ax*, H-4a, H-6*ax*, H-7*ax*, H-8*ax*), 1.54 (dm, *J*=12 Hz, H-5*eq*), 1.69 (dm, *J*=12 Hz, H-6*eq*), 1.77 (dm, 2H, *J*=12 Hz, H-7*eq*, H-8*eq*), 1.88 (dd, *J*=10.8, 3.2 Hz, H-4*eq*), 2.12 (s, 3H, OAc), 2.22 (td, *J*=10, 3.2 Hz, H-8a), 2.92 (qd, *J*=6.4, 1.6 Hz, H-2*ax*), 4.88 (ddd, *J*=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{12}H_{22}NO_2$ (M^++1) 212.1651, found 212.1648.

3.1.7. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-en-1-ol (8a). To a cooled (−78 °C) solution of **5a** (105 mg, 0.258 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M in hexanes, 0.8 mL, 1.29 mmol) and the reaction mixture was stirred for 4 h, the temperature slowly rising to rt. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic extracts were concentrated and the residue was dissolved in pyridine (1 mL) and treated with Ac_2O (0.25 mL, 2.58 mmol) and DMAP (5 mg, 0.04 mmol). The reaction mixture was stirred overnight at rt, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 15 mL). The dried organic extract was concentrated and purified by chromatography (SiO_2, hexane/EtOAc 8:2) to give the epimeric alcohols **8a** and 1-*epi*-**8a** (81 mg, 68%), in a 1:1 ratio according to the NMR spectrum, which were used directly in the next step.*Compound* **8a**. R_f=0.82 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.92 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=7.0 Hz, 3H), 1.18–1.38 (m, 4H), 1.49–1.80 (m, 7H), 1.82–1.93 (m, 2H), 1.98 (s, 3H), 2.75 (quint, *J*=7 Hz, 1H), 2.95 (dm, *J*=12 Hz, 1H), 3.44 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.29–5.40 (m, 2H), 7.18–7.40 (m, 10H). *Compound* 1-*epi*-**8a**. R_f=0.64 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.89 (t, *J*=6.6 Hz, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.18–1.38 (m, 4H), 1.40–1.70 (m, 7H), 1.74–1.88 (m, 2H), 2.00 (s, 3H), 2.44–2.54 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.48 (d, *J*=13.6 Hz, 2H), 3.73 (d, *J*=13.6 Hz, 2H), 5.30 (m, 1H), 5.39 (t, *J*=3.9 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.8. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-1-butylcyclohex-2-enol (8b). Operating as above, starting from 147 mg (0.36 mmol) of cyclohexenone **5b**, and after chromatography (SiO_2, hexane/EtOAc 8:2), 85 mg (51%) of **8b** was obtained: R_f=0.58 (SiO_2, 8:2 hexane/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.09 (d, *J*=7 Hz, 3H), 1.20–1.40 (m, 5H), 1.42–1.78 (m, 6H), 1.84–1.96 (m, 2H), 2.05 (s, 3H), 2.18–2.28 (m, 1H), 2.85 (quint, *J*=7 Hz, 1H), 3.37 (d, *J*=13.5 Hz, 2H), 3.90 (d, *J*=13.5 Hz, 2H), 5.13–5.22 (m, 1H), 5.45 (t, *J*=3.7 Hz, 1H), 7.18–7.40 (m, 10H).

3.1.9. 2-[(2*R*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9a). To a solution of epimeric alcohols **8a** (81 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added PCC (57 mg, 0.26 mmol) and SiO_2 (57 mg), and the mixture was stirred overnight at rt. The residue obtained after evaporation of the solvent was purified by chromatography (SiO_2, hexane/EtOAc 9:1) to give **9a** as a viscous oil (50 mg, 62%): R_f=0.36 (SiO_2, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −5.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 0.91 (t, *J*=6.8 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.20–1.50 (m, 4H), 1.70–1.8 (m, 2H), 1.92 (s, 3H), 1.98–2.33 (m, 6H), 2.34–2.42 (m, 1H), 2.71 (quint, *J*=6.8 Hz, 1H), 3.08 (dd, *J*=13.6, 4.4 Hz, 1H), 3.45 (d, *J*=13.6 Hz, 2H), 3.75 (d, *J*=13.6 Hz, 2H), 5.20 (ddd, *J*=8.8, 6.8, 5.2 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 8.9 (CH_3), 14.1 (CH_3), 21.2 (CH_3), 22.4 (CH_2), 22.9 (CH_2), 28.3 (CH_2), 30.1 (CH_2), 30.8 (CH_2), 34.7 (CH_2), 37.7 (CH_2), 54.0 (CH_2), 55.2 (CH), 75.0 (CH), 126.7 (CH), 128.1 (CH), 128.9 (CH), 131.3 (C), 140.1 (C), 160.9 (C), 170.4 (C), 198.7 (C). Anal. Calcd for $C_{30}H_{39}NO_3\cdot H_2O$: C, 75.12; H, 8.62; N, 2.92. Found C, 75.48; H, 9.02; N, 2.58.

3.1.10. 2-[(2*S*,3*S*)-2-Acetoxy-3-(dibenzylamino)butyl]-3-butylcyclohex-2-enone (9b). Operating as above, starting from 71 mg (0.15 mmol) of alcohol **8b** and after chromatography (SiO_2, 9:1 hexane/EtOAc), enone **9b** (41 mg, 61%) was isolated as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (t, *J*=7.2 Hz, 3H), 1.10 (d, *J*=6.8 Hz, 3H), 1.20–1.32 (m, 2H), 1.32–1.44 (m, 2H), 1.81–1.88 (m, 2H), 1.96 (s, 3H), 1.96–2.03 (m, 2H), 2.16–2.42 (m, 6H), 2.34–2.42 (m, 1H), 2.68 (dd, *J*=13.8, 11.0 Hz), 2.89–2.96 (m, 1H), 3.39 (d, *J*=13.6 Hz), 3.90 (d, *J*=13.6 Hz), 5.08 (ddd, *J*=11.0, 5.8, 2.4 Hz, 1H), 7.18–7.40 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$, HSQC) 9.7 (CH_3), 14.1 (CH_3), 21.1 (CH_3), 22.4 (CH_2), 23.0 (CH_2), 28.4 (CH_2), 30.1 (CH_2), 30.9 (CH_2), 34.8 (CH_2), 37.8 (CH_2), 54.5 (CH_2), 55.8 (CH), 75.9 (CH), 126.7 (CH), 128.1 (CH), 128.7 (CH), 131.7 (C), 140.22 (C), 160.1 (C), 170.1 (C), 198.8 (C).

3.1.11. Aminocyclization of 9a. Following the above procedure for the aminocyclization of **5a** using enone **9a** (38 mg, 0.08 mmol) and carrying out the hydrogenation process for 36 h, the crude product was purified by chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc) to give 7 mg (33%) of **10a** and 8 mg (38%) of **11a**, both as colorless oils.

(2*S*,3*R*,4a*S*,5*R*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**10a**). R_f=0.59 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −34.5 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.90 (m, 1H, H-1′), 0.90 (t, *J*=6.8 Hz, 3H, H-4′), 1.10 (d, *J*=6.4 Hz, Me), 1.12 (masked, H-8*ax*), 1.20 (m, 4H, H-6 and H-2′), 1.25 (m, 2H, H-3′), 1.30 (m, H-4*ax*), 1.40 (m, H-4a), 1.48 (m, 2H, H-7), 1.5 (m, H-8*eq*), 1.70 (m, 2H, H-5*ax*, H-1′), 2.04 (s, 3H, OAc), 2.27 (ddd, *J*=12.4, 3.6, 2.8 Hz, H-4*eq*), 2.76 (dq, *J*=10, 6.5 Hz, H-2*ax*), 2.97 (br s, H-8a), 4.49 (td, *J*=10.4, 4.4 Hz, H-3*ax*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ (M^++1) 268.2198, found 268.2202.

(2*S*,3*R*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11a**). R_f=0.28 (Al_2O_3, 8:2 hexane/EtOAc); $[\alpha]_D^{20}$ −4.3 (*c* 0.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.88 (t, *J*=6.8 Hz, 3H, H-4′), 0.90 (masked, 1H, H-6*ax*), 0.94 (m, 2H, H-4*ax*, H-4a), 1.05 (masked, 2H, H-5 and H-1′), 1.07 (d, *J*=6.4 Hz, 3H, Me), 1.15 (m, 1H, H-8*ax*), 1.25 (m, 4H, H-2′, H-3′), 1.30 (m, 1H, H-7*ax*), 1.45 (m, 1H, H-1′), 1.75 (m, 3H, H-6, H-7, H-8), 2.05 (s, 3H, OAc), 2.20 (ddd, *J*=11, 9, 3 Hz, H-8a), 2.29 (dm, *J*=12 Hz, H-4*eq*), 2.70 (dq, *J*=10.4, 6.4 Hz, H-2*ax*), 4.41 (td, *J*=10.4, 4.8 Hz, H-3*ax*); ^{13}C NMR see Table 1.

HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ + 1$) 268.2198, found 268.2203.

3.1.12. Aminocyclization of 9b. Operating as in the cyclization of **9a**, from enone **11** (22 mg, 0.05 mmol) was obtained **11b** as an oil (6 mg, 52%) after chromatography (Al_2O_3, from 9:1 to 7:3 hexane/EtOAc).[31]

(2*S*,3*S*,4a*R*,5*S*,8a*R*)-3-Acetoxy-5-butyl-2-methyldecahydroquinoline (**11b**). R_f=0.13 (Al_2O_3, 8:2 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, COSY) 0.87 (t, J=6.8 Hz, 3H, H′-4), 0.98 (m, 4H, H-4a, H-5, H-6, H-1′), 1.06 (d, J=6.8 Hz, 3H, Me), 1.15 (m, 2H, H-4*ax*, H-8*ax*), 1.25 (m, 4H, H-2′ and H-3′), 1.30 (m, H-7*ax*), 1.45 (m, 1H, H-1′), 1.77 (m, 3H, H-8*eq*, H-7*eq*, H-6*eq*), 2.11 (s, 3H, OAc), 2.20 (dt, J=10, 3.2 Hz, H-4*eq*), 2.27 (td, J=10, 3 Hz, H-8a), 2.90 (qd, J=6.4, 1.6 Hz, H-2*ax*), 4.91 (ddd, J=3.2, 3.2, 1.6 Hz, H-3*eq*); ^{13}C NMR see Table 1. HRFABMS calcd for $C_{16}H_{30}NO_2$ ($M^+ + 1$) 268.2198, found 268.2194.

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