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Ring Expansion of Functionalized Octahydroindoles to Enantiopure *cis*-Decahydroquinolines†

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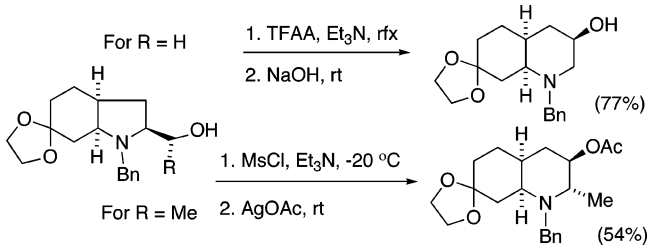

A new synthetic entry to enantiopure *cis*-decahydroquinolines is reported. Endo and exo derivatives of *cis*-1-benzyl-2-(hydroxymethyl)octahydroindol-6-one ethylene acetal undergo ring enlargement upon treatment with TFAA and then Et_3N (thermodynamic conditions) to give enantiopure 1-benzyl-3-hydroxydecahydroquinolin-7-one derivatives in 77 and 82% yield, respectively. For 2-(1-hydroxyethyl) analogues, the best synthetic result is obtained from the (2*S*,1′*R*) endo isomer, which under kinetic reaction conditions (MsCl, THF, −20 °C, then AgOAc at rt) gives the expanded product in 54% yield.

cis-Decahydroquinoline constitutes the azabicyclic skeleton of natural products such as lepadins[1] and several amphibian alkaloids,[2] as well as some pharmacologically interesting synthetic compounds.[3] Moreover, this heterocyclic motif occurs as a subunit of other azapolycyclic natural products (e.g., gephyrotoxins,[4] cylindricines,[5] and pseudoaspidopermidine and pandoline alkaloids[6]) (Figure 1). The extensive occurrence of this azabicyclic ring has stimulated the implementation of new procedures to gain access to functionalized enantiopure *cis*-decahydroquinolines that can be used as advanced intermediates in the synthesis of compounds embodying this skeleton-type.[7]

In this paper, we report the studies devoted to the ring enlargement of *cis*-octahydroindole derivatives to *cis*-decahydroquinolines. The diastereoselective ring expansion of monocyclic amines (azetidines,[8] pyrrolidines,[9,10] pyrrolines,[11] piperidines[12]) and bicyclic amines (2-azabicyclo[3.3.0]octanes,[13]

† Dedicated to the memory of the late Professor Marcial Moreno Mañas.

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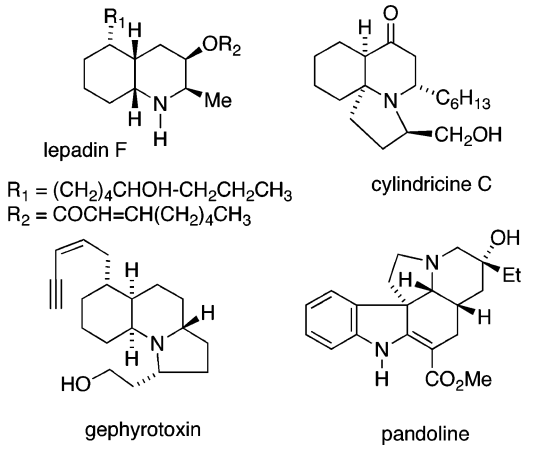
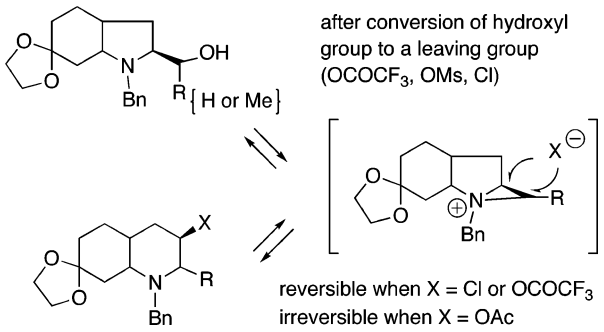


FIGURE 1. Natural and synthetic compounds embodying the *cis*-decahydroquinoline framework.

1-azabicyclo[2.2.2]octanes,[14] indolizidines,[15] indolines,[16] hexahydropyrrolo[3,4-d]isoxazoles[17]) with a hydroxymethyl substituent adjacent to the nitrogen atom is a well-known process,[18,19] but it is unprecedented in octahydroindole compounds. Considering the precedents, we envisaged that the transformation (Scheme 1) would occur via aziridinium intermediates[20] once the hydroxyl group is converted into a good leaving group. A ring opening at the fused carbon atom would then lead to a new heterocyclic derivative with an expanded ring. If the leaving group were a chloride or trifluoroacetate, in absence of another nucleophile in the reaction medium, the process would be reversible and the ratio of the expanded and nonexpanded compounds would reflect their thermodynamic stability. On the contrary, if X^- were an acetate and the chloride ion were taken out of the reaction medium using silver acetate, the ring opening of the aziridinium ion would be irreversible and the ratio of the formed compounds would arise from a kinetic control.

SCHEME 1. Synthetic Approach to Enantiopure *cis*-Decahydroquinolines



Our study of the stereospecific rearrangement of 2-hydroxymethyl- and 2-(α-hydroxyethyl)octahydroindoles to 3-substituted and 2,3-disubstituted decahydroquinolines began with the preparation of the rearrangement precursors (Scheme 2). The starting materials were the azabicyclic esters endo **1** and exo **2**, which were available from *O*-methyltyrosine in three steps (Birch reduction, aminocyclization promoted by MeOH−HCl, and benzylation).[21] Both esters were protected to give acetals **3** and **4** that, in turn, were reduced with $LiBH_4$ to the corresponding primary alcohols **5** and **6** in 80% overall yield in each series. On the other hand, the preparation of the secondary alcohols was carried out as follows: esters **3** and **4** were transformed to methyl ketones **7** (endo) and **8** (exo), respectively, in a two-step sequence involving the formation of their corresponding Weinreb amides[22] followed by coupling with methylmagnesium bromide. Then, ketones **7** and **8** were both reduced with $NaBH_4$ to give a mixture of secondary alcohols **9a** and **10a** (55:45 ratio)[23] in the endo series and **11a** and **12a** (63:37 ratio) in the exo series. At this point, improving the diastereoselectivity of the reduction was not a priority since the availability of all the diastereomers would help evaluate the scope and limitations of the enlargement process.

Two ^{13}C NMR features clearly differentiate the endo and exo series of *cis*-2-substituted octahydroindol-6-ones (Supporting Information, Table 1): (i) the chemical shift of the benzylic carbon resonates at a higher field in exo compounds (δ 51.5−54.0) than in the endo compounds (δ 59−63); (ii) the C-7 signal appears at lower values in the exo compounds (δ 29−32) than in the endo isomers (δ 37−39). It is worth noting that the stereochemistry at C-1′ for alcohols **9a**−**12a** was unequivocally established only after the stereochemical elucidation of the expanded decahydroquinolines (cf. vide infra). The conformationally mobile *cis*-octahydroindole system[21] has two conformers (*N*-outside and *N*-inside) in which H-7a is axial or equatorial, respectively, with respect to the carbocyclic ring. NMR studies allowed us to assign the conformational preference of the

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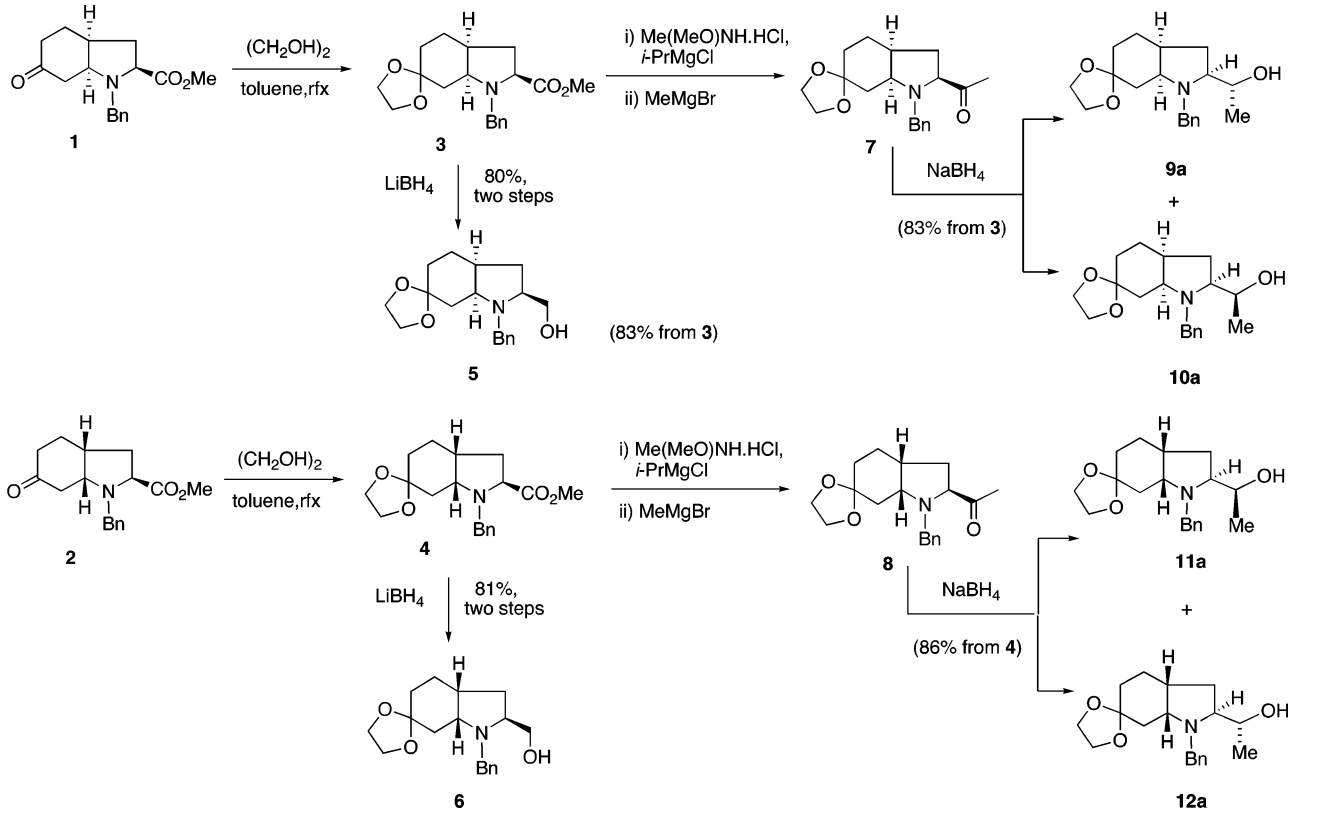
(23) Using LS−Selectride as the reducing agent, ketone **7** furnished stereoselectively alcohol **10a**.

SCHEME 2. Synthesis of *cis*-2-Hydroxymethyl- and 2-(α-Hydroxyethyl)octahydroindole Derivatives



described *cis*-2-substituted octahydroindol-6-one derivatives, in which the coupling constants H7−H7a (one of them of 11 Hz) are consistent with antiperiplanar couplings, indicating that the H-7a proton[24] is axially located with respect to the carbocyclic ring (Figure 2).

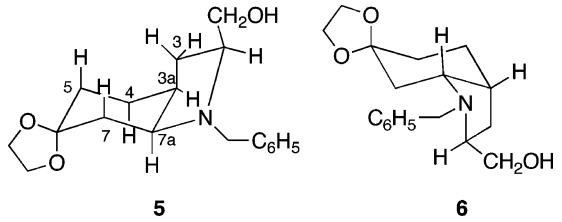
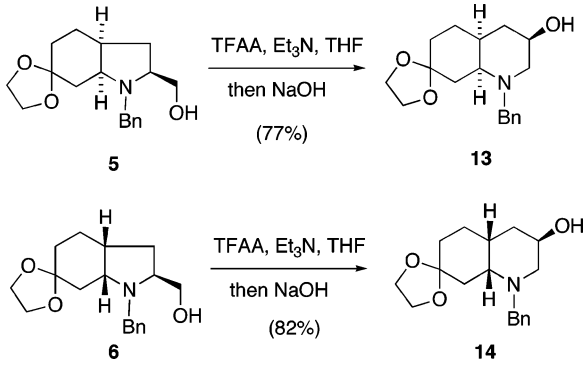


FIGURE 2. Preferred conformation of endo and exo compounds **5** and **6**.

Treatment of 2-(hydroxymethyl)octahydroindole derivative **5** with TFAA in THF followed by the addition of triethylamine[9] led to the ring-expanded product that after a hydrolytic workup (aqueous NaOH) allowed the isolation of decahydroquinoline **13** (Scheme 3). The NMR data (see below) of this compound prove that the configuration of C-3 in (−)-**13** is *R*, which supports the mechanism depicted in Scheme 1 (stereocontrolled process during the nucleophilic attack at C-2 of the aziridinium intermediate). The same protocol (TFAA/Et_3N/NaOH) also was applied to the exo isomer **6**, with decahydroquinoline (+)-**14** being isolated as a single isomer in 82% yield. Both decahydroquinolines show the same preferred conformation according to their NMR spectra. Thus, the coupling constants of H-4a and H-8a in each diastereomer are in accordance with an axial and an equatorial relationship, respectively, with respect to the *N*-containing ring (*N*-exo conformation).[25] The ^{13}C NMR data corroborate the above stereochemical elucidation because both **13** and **14** show a relative upfield shift for C-2 and C-8, a characteristic feature of *cis*-decahydroquinolines in the *N*-exo conformation (see Figure 3).

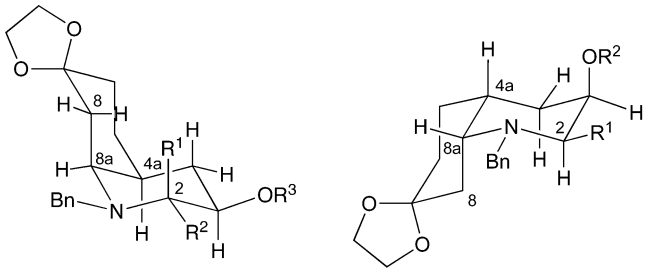
SCHEME 3. Synthesis of 3-Hydroxydecahydroquinolines



When we applied the same procedure (TFAA, THF, then Et_3N) to the secondary alcohols **9a**−**12a** under thermodynamic reaction conditions, the results were disappointing. After long reaction times (4−5 days at reflux temperature), only the starting material and degradation products were obtained.[26,27] The next attempt to expand the ring involved converting alcohols **9a**−**12a** to the secondary chlorides **9b**−**12b** that then were

(24) The chemical shift of H-3a and H-7a appears more deshielded in the exo derivatives than in the endo compounds, due to the syn relationship of the nitrogen lone pair with both protons in the exo series (Figure 2).

(25) For ^{13}C NMR studies in *cis*-decahydroquinolines, see Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Imamura, K.; Torres, J. A.; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5−21.

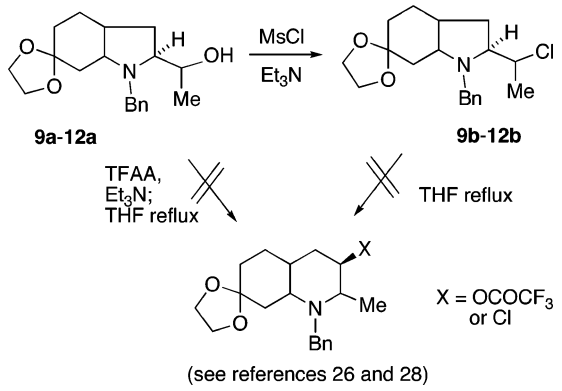


13 $R^1 = R^2 = H$; $R^3 = H$
17 $R^1 = H$; $R^2 = Me$; $R^3 = Ac$
18 $R^1 = Me$; $R^2 = H$; $R^3 = Ac$
21 $R^1 = H$; $R^2 = Me$; $R^3 = H$

14 $R^1 = R^2 = H$
15 $R^1 = Me$; $R^2 = H$
19 $R^1 = Me$; $R^2 = Ac$

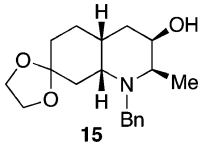
FIGURE 3. Stereochemistry of *cis*-decahydroquinolines.

SCHEME 4. Attempted Ring Expansion under Thermodynamic Conditions



heated in refluxing THF. In all cases, the unexpanded 2-(α-chloroethyl)octahydroindoles **9b**−**12b** were isolated (Scheme 4).[28] Because the configuration at C-1′ was retained, these results show that the process occurred through an aziridinium salt intermediate and that chlorides **9b**−**12b** were directly formed either by the opening of an aziridinium by the chloride ion or by a reversion process from an initially expanded product. Thus, under thermodynamic reaction conditions, we were unable to achieve 2,3-disubstituted decahydroquinolines from octahydroindoles **9a**−**12a**.[29]

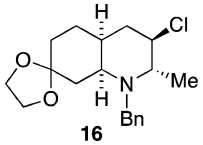
(26) Decahydroquinoline **15** was isolated in one run working from alcohol **11a**, although only in 5% yield. For ^{13}C NMR data, see Supporting Information, Table 2.



15

(27) The use of microwave conditions did not give satisfactory results either.

(28) Together with chloride **9b**, the expanded product **16** was formed according to the ^{13}C NMR spectrum of the reaction mixture. For NMR data of **9b**−**12b**, see Supporting Information.



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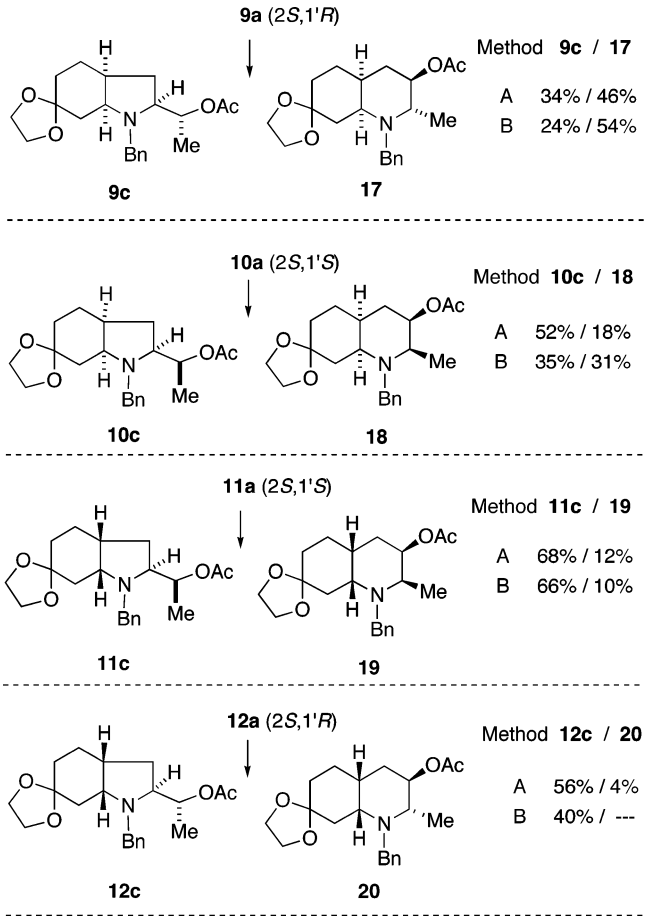
(29) There are scarcely any examples of ring enlargement via aziridinium ions from secondary alcohols, and they are always of the benzylic type (see refs 9b and 10b,c).

SCHEME 5. Ring Expansion under Kinetic Conditions[a]

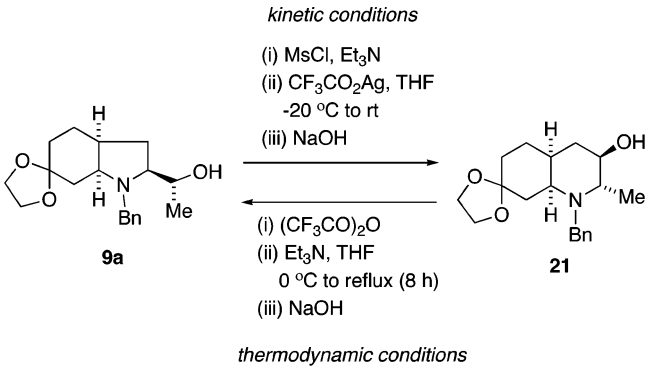


[a] Method A: (i) MsCl, Et_3N, THF reflux, 4 h. (**9b**−**12b** formed); (ii) AgOAc, THF reflux, 4 h. Method B: (i) MsCl, Et_3N, THF, −20 °C; (ii) AgOAc, rt, 1 h.

To have an irreversible ring opening of the aziridinium intermediate, the chlorides **9b**−**12b** were treated with AgOAc in a THF solution at reflux temperature (Method A). Under these kinetic conditions, the ring-expanded decahydroquinolines **17**−**19** were formed in variable yields (Scheme 5), and **20** was detected only in the GC−MS analysis. The nonenlarged acetates **9c**−**12c** formed by the acetate attack on the carbon linked to the methyl group in the aziridinium intermediate also were isolated.[30] The best results from a synthetic point of view were obtained for the endo compound **9b**, because it was only in this series that the decahydroquinoline derivative was isolated as the main product. We then decided to carry out the process starting from alcohols **9a**−**12a**, working at −20 °C to avoid the formation of the corresponding chlorides,[10c] and promoting the ring opening of the aziridinium with AgOAc at rt (Method B). This decrease in temperature led to a slight increase in the ratio of the thermodynamically unfavored decahydroquinolines (see Scheme 5). As expected, the endo series of 2-(α-hydroxyethyl)octahydroindoles obtained the best result from alcohol **9a** that transformed into the decahydroquinoline **17** in 54−58% yield.[31,32] The reason was that the aziridinium intermediate was formed and opened without generating steric repulsion because

(30) It was confirmed in two series that the configuration at C-1′ of the side chain was identical to that of the starting alcohol. Treatment of **10a** and **11a** with acetic anhydride gave the same acetates **10c** and **11c** as those obtained through sequential treatment with MsCl and Et_3N, then AgOAc.

SCHEME 6



of the antiperiplanar relationship between the methyl group and the C(2)−C(3) bond. In contrast, the reason for the poor yields observed in the ring-expanded compounds in the exo series (**11a** and **12a**) is unclear even when taking into consideration that the transition states between **12a** and decahydroquinoline **20** are likely to be the most sterically demanding of the four pathways leading to expanded compounds. Figure 3 depicts the preferred conformation of all the synthesized 3-oxygenated *cis*-decahydroquinolines.

Finally, to obtain a better understanding of the ring-enlargement process, decahydroquinoline **21** (obtained under kinetic conditions from **9a**)[31] was submitted to the thermodynamic conditions of the aziridinium ring formation and opening (TFAA, then Et_3N followed by heating at reflux for 8 h, and ending with an aqueous NaOH treatment). Under these conditions, octahydroindole **9a** was formed, albeit as the only product (Scheme 6). This result confirms that 2-(α-hydroxyethyl)octahydroindoles are more stable than 2-methyl-3-hydroxyquinolines in the series of compounds examined (**9**−**12** vs **17**−**20**).

In summary, the study of the ring enlargement of *cis*-octahydroindole derivatives has given access to valuable functionalized enantiopure *cis*-decahydroquinolines (**13** and **14**, in excellent yields, and **17** in good yield), which could be used as building blocks in the synthesis of natural products. Moreover, it has been shown that subtle stereochemical differences in the octahydroindoles studied can have a significant impact on the ring-expansion pathway when the process is carried out under thermodynamic or kinetic conditions.

Experimental Section

(3*R*,4a*S*,8a*S*)-1-Benzyl-3-hydroxy-7-oxodecahydroquinoline Ethylene Acetal (13). To a solution of alcohol **5** (223 mg, 0.74 mmol) in THF (2 mL) cooled to −78 °C, TFAA (0.21 mL, 1.47 mmol, 2 equiv) was added, and the reaction mixture was stirred for 3 h at this temperature. Et_3N (0.5 mL, 3.68 mmol, 5 equiv) was added, and after 15 min, the reaction mixture was heated at reflux for 20 h. The mixture was cooled to 25 °C and 2.5 N NaOH (15 mL, 50 equiv) was added. After this mixture was stirred for 3 h, the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried and concentrated to give an oil that was purified by chromatography (SiO_2, 1−5% MeOH in CH_2Cl_2) to give 173 mg (77%) of **13** as a colorless oil: $R_f = 0.35$ (SiO_2, CH_2Cl_2/MeOH 95:5); $[\alpha]^{20}_D$ −44 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, gCOSY, $CDCl_3$) 1.45 (dm, J = 10.5 Hz, 1H, H-5eq), 1.47 (m, 1H, H-6eq), 1.50 (q, J = 10.5 Hz, 1H, H-4ax), 1.55 (m, 1H, H-6ax), 1.58 (m, 1H, H-4eq), 1.61 (ddd, J = 12.5, 4.5, 2.0 Hz, 1H, H-8eq), 1.73 (tt, J = 13.5, 5.0 Hz, 1H, H-5ax), 1.82 (t, J = 12.5 Hz, 1H, H-8ax), 1.97 (dm, J = 10.5 Hz, 1H, H-4a), 2.10 (t, J = 10.5 Hz, 1H, H-2ax), 2.62 (ddd, J = 10.5, 5.0, 1.5 Hz, 1H, H-2eq), 3.00 (dt, J = 12.5, 4.5 Hz, 1H, H-8a), 3.45 and 3.66 (2d, J = 12.5 Hz, 1H each, NCH_2Ar), 3.68 (dddd, J = 10.5, 10.5, 5.0, 5.0, 1H, H-3ax), 3.80−3.90 (m, 4H, OCH_2), 7.20−7.30 (m, 5H, ArH); ^{13}C NMR (75 MHz, gHSQC) 26.9 (C-5), 27.0 (C-8), 29.9 (C-6), 32.8 (C-4a), 33.1 (C-4), 52.0 (C-2), 57.0 (C-8a), 58.3 (NCH_2), 64.1 and 64.2 (OCH_2), 68.1 (C-3), 109.9 (C-7), 126.8, 128.1, 129.5, 139.3 (Ar). Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N 4.62. Found: C 70.86, H 8.03, N 4.38.

(3*R*,4a*R*,8a*R*)-1-Benzyl-3-hydroxy-7-oxodecahydroquinoline Ethylene Acetal (14). Similar to the above procedure, alcohol **6** (464 mg, 1.53 mmol) in THF (4 mL) was treated with TFAA (0.43 mL, 3.04 mmol, 2 equiv) and then with Et_3N (1.07 mL, 7.65 mmol, 5 equiv). After workup, the crude material was purified by chromatography (SiO_2, 1−5% MeOH in CH_2Cl_2) to give **14** (380 mg, 82%) as a white solid: $R_f = 0.40$ (SiO_2, CH_2Cl_2/MeOH 95:5); mp 101−103 °C; $[\alpha]^{20}_D$ +39 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.47 (m, 1H, H-6eq), 1.52 (m, 1H, H-5eq), 1.55 (m, 1H, H-4), 1.60 (m, 1H, H-6ax), 1.68 (m, 2H, H-4, H-8eq), 1.80 (tt, J = 13.5, 5.0 Hz, 1H, H-5ax), 1.87 (t, J = 12.5 Hz, 1H, H-8ax), 2.31 (dm, J = 10.5 Hz, 1H, H-4a); 2.52 and 2.57 (2d, J = 12.0 Hz, 1H each, H-2), 3.15 (dt, J = 12.5, 4.5 Hz, 1H, H-8a), 3.48 and 3.71 (2d, J = 13.0 Hz, 1H each, NCH_2Ar), 3.84 (br s, 1H, H-3eq), 3.90−3.95 (m, 4H, OCH_2), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC), 25.6 (C-8), 26.6 (C-5), 29.8 (C-6), 28.8 (C-4a), 30−5 (C-4), 50.6 (C-2), 57.7 (C-8a), 58.5 (NCH_2), 64.1 and 64.3 (OCH_2), 65.4 (C-3), 109.8 (C-7), 127.2, 128.4, 128.7, 139.0 (Ar). Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26, H 8.31, N, 4.62. Found: C 70.89, H 8.50, N 4.44.

Ring Expansion of Alcohol 9a. A solution of alcohol **9a** (50 mg, 0.16 mmol) in THF (1 mL) was treated with MsCl (16 μL, 0.19 mmol, 1.2 equiv) and Et_3N (90 μL, 0.64 mmol, 4 equiv) under an argon atmosphere at −20 °C for 1 h. AgOAc was added (80 mg, 0.48 mmol, 3 equiv) and the resulting mixture was warmed to rt over a period of 1 h. The reaction mixture was filtered through a bed of Celite and diluted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ (10 mL), dried, and concentrated to give a mixture of acetates **9c** and **17**. Purification and separation of the compounds were performed by chromatography (SiO_2, CH_2Cl_2/EtOAc 9:1) to afford 14 mg (24%) of **9c** and 31 mg (54%) of **17** (see Supporting Information for analytical data).

(2*S*,3a*S*,7a*S*)-1-Benzyl-2-[(1′*R*)-(1-acetoxyethyl)]octahydroindol-6-one Ethylene Acetal (9c). Colorless oil. $R_f = 0.38$ (SiO_2, CH_2Cl_2/EtOAc 8:2); $[\alpha]^{20}_D$ −10.7 (*c* 0.4, $CHCl_3$); IR 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.23 (d, J = 6.4 Hz, 3H, CH_3), 1.26 (m, 2H, H-5), 1.44 (d, J = 8.4 Hz, 2H, H-7), 1.60 (m, 2H, H-4), 1.76 (m, 2H, H-3), 2.07 (s, 3H, OAc), 2.20 (m, 1H, H-3a), 2.90 (q, J = 8.4 Hz, 1H, H-7a), 2.91 (ddd, J = 8.4, 8.0, 4.0 Hz, 1H, H-2), 3.63 and 3.86 (2d, J = 14.0 Hz, 1H each, NCH_2Ar), 3.66−3.83 (m, 4H, OCH_2), 5.05 (qd, J = 6.4, 4.0 Hz, 1H, H-1′), 7.20−7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$), see Table 1. HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2170.

(2*S*,3*R*,4a*S*,8a*S*)-3-Acetoxy-1-benzyl-2-methyl-7-oxodecahydroquinoline Ethylene Acetal (17). Colorless oil. $R_f = 0.84$ (SiO_2, CH_2Cl_2/EtOAc 8:2). $[\alpha]^{20}_D$ −37 (*c* 1.0, $CHCl_3$); IR 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, gCOSY) 1.03 (d, J = 6.4 Hz, 3H, Me), 1.45−1.74 (m, 7H, H-4, H-5, H-6, and H-8eq), 1.91 (t, J = 12.4 Hz, 1H, H-8ax), 2.06 (s, 3H, OAc), 2.10 (dm, J = 12.0 Hz, 1H, H-4a), 2.84 (dq, J = 10.0, 6.0 Hz, 1H, H-2ax), 2.93 (dt, J = 12.4, 4.4 Hz, 1H, H-8a), 3.63 and 3.90 (2d, J = 14.8 Hz, 1H each, NCH_2Ar), 3.81−3.94 (m, 4H, OCH_2), 4.60 (td, J = 11.0, 5.2 Hz,

(31) The use of silver trifluoroacetate instead of silver acetate slightly increased the yield of the expanded compound, which gave alcohol **21** (58%) after a basic workup (see Scheme 6).

(32) The use of tetrabutylammonium acetate did not improve the course of the reaction. From **9a**, a mixture of acetates **17** (38%) and **9c** (34%) were isolated, whereas from **10a**−**12a**, more complex reaction mixtures were formed with the decahydroquinolines **18**, **19**, and **20** being obtained in a yield lower than 10%.

1H, H-3ax), 7.18−7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT, gHSQC) 16.8 (Me), 21.3 (OAc), 26.6 (C-5), 28.1 (C-8), 29.6 (C-4), 29.7 (C-6), 31.4 (C-4a), 52.6 (NCH_2), 53.0 (C-2), 55.8 (C-8a), 64.0 and 64.1 (OCH_2), 75.5 (C-3), 109.8 (C-7), 126.5, 127.7, 128.2, 141.2 (Ar), 170.6 (CO). HRFABMS: calcd for $C_{21}H_{30}NO_4$ 360.2175 (MH^+), found 360.2171.

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Supporting Information Available: Experimental and NMR data for all compounds reported. Tables of ^{13}C NMR chemical shifts of octahydroindoles and decahydroquinolines reported. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds as well as COSY and HSQC spectra when available. This material is available free of charge via the Internet at http://pubs.acs.org.

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