Synthesis of 9-azasteroid partial structures *via* Birch reduction as key step

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Dedicated to Prof. Lubor Fisera on the occasion of his 60th birthday

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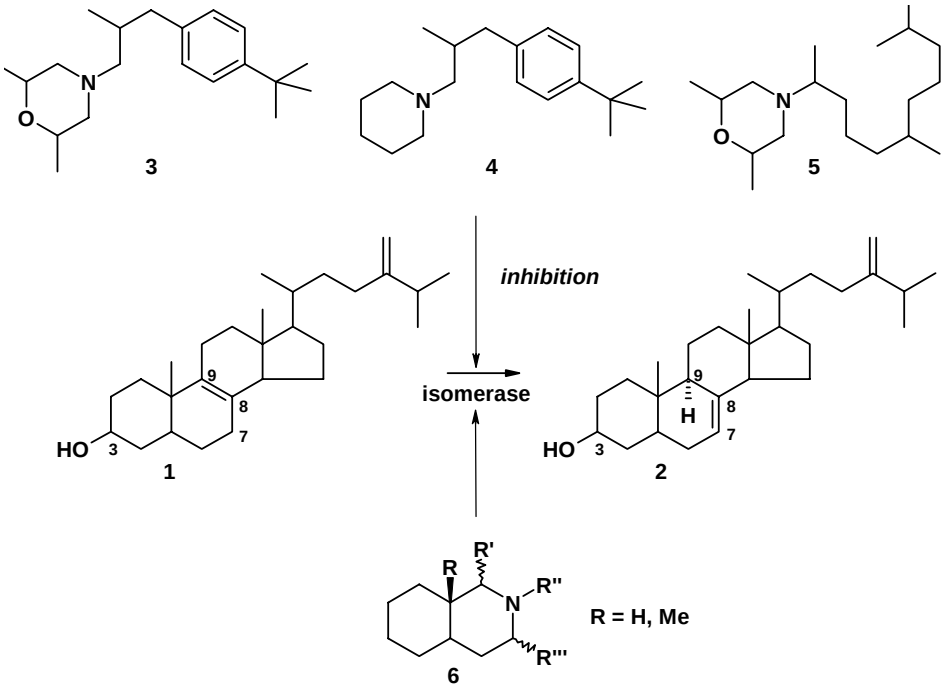
Abstract

A high-energy intermediate model for the inhibition of the ergosterol biosynthesis suggests 9-azasteroids as potential antimycotics. Key step for the approach described in this work involves a Birch reduction of substituted quinoline structures. The diastereoselectivity of this reaction was studied. Subsequent functionalization to incorporate the lipophilic properties of the steroidal core afforded *N*-substituted perhydro-quinolinols as mimics of the AB-ring system of steroids.

Keywords: Birch reduction, azasteroids, quinoline, ergosterol biosynthesis inhibition, fungicides

Introduction

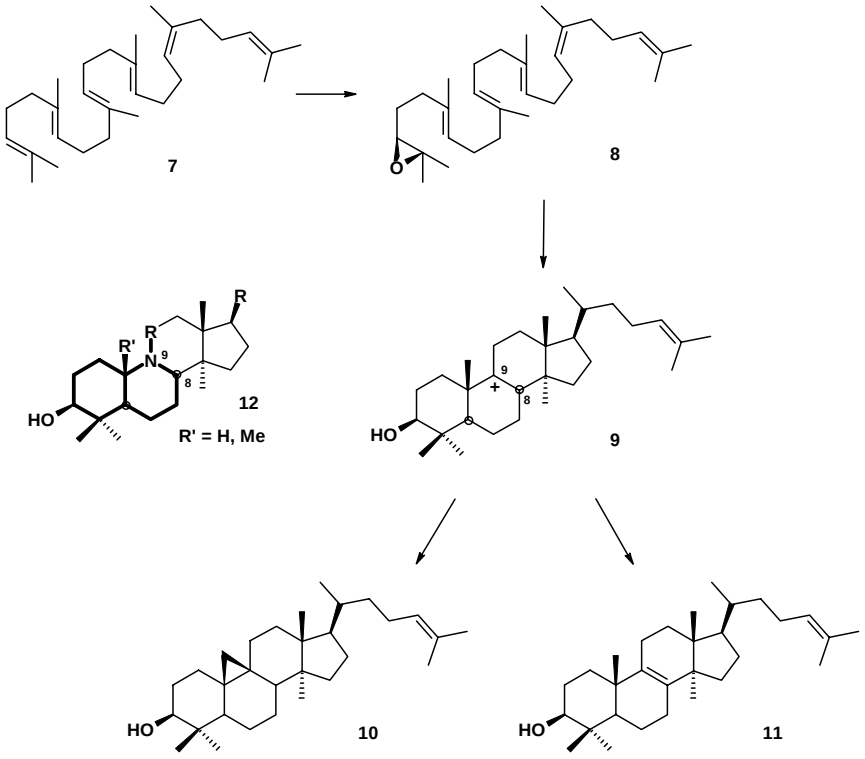
The ergosterol biosynthesis pathway represents an interesting target for the development of novel antimycotic agents. [1] During recent years, Δ^8-Δ^7-isomerase was a key target in the development of bioactive agents. [2] This enzyme is responsible for the isomerization of fecosterol **1** to episterol **2**. In particular perhydro-heterocyclic compounds with lipophilic chains such as phenpropimorph **3**, fenpropidine **4**, or tridemorph **5** were successfully established as commercial products (Scheme 1). In this context, we and others have started to investigate the potential of azasteroid partial structures **6** derived from the isoquinoline structural core as fungicides, which resemble the natural substrate of the enzymes involved to a greater extent. [3,4]



Scheme 1. Inhibition of Δ8-Δ7-isomerase.

Another possible target to influence steroid biosynthesis is the cyclization reaction towards the steroidal ABCD ring system. Oxidation of squalene **7** to squalene-oxide **8** is followed by an electron cascade and cyclization reaction, which leads to the cationic species **9** after methyl group migration as a key branching point in the anabolism of steroids in fungi and plants: While the intermediate undergoes elimination to lanosterol **11** in fungi, the reactive compound cyclizes to cycloartenol **10** in plants (Scheme 2). [5]

One traditional inhibition strategy for enzymes accommodating such cationic species as high-energy intermediates (HEIs) is the incorporation of nitrogen at the site of the positive charge. The generally accepted concept behind this approach is the hypothesis, that such amine species are protonated under physiological conditions and consequently exhibit higher affinity to the functional groups within the active site of the enzyme stabilizing the positive center. [6] Consequently, azasteroids of the general type **12** incorporating key structural aspects of the steroidal ring system are potential inhibitors of proteins involved in this biosynthetic step.

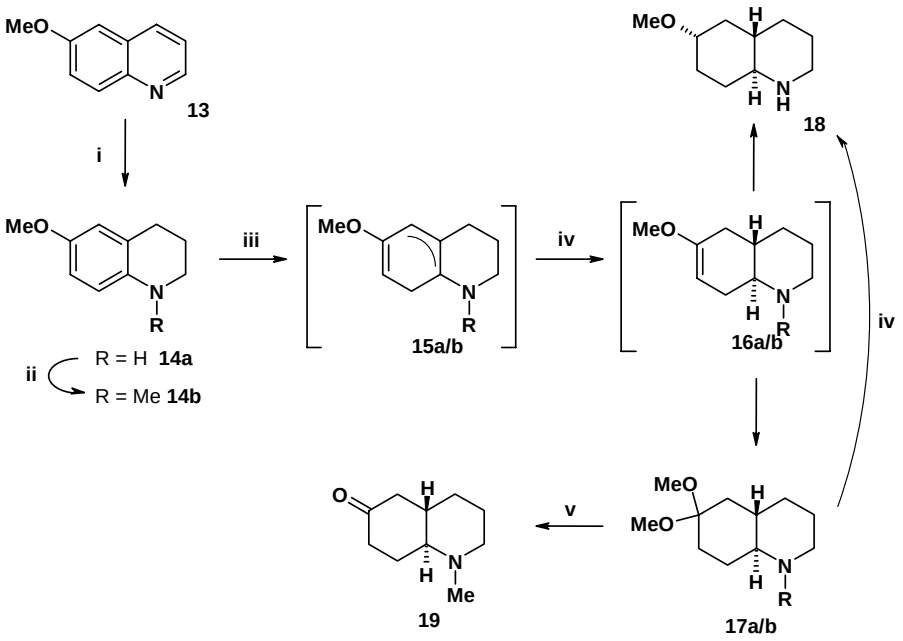


Scheme 2. Inhibition of the steroid cyclization.

Recently, we have disclosed two synthetic approaches to compounds **12** based on a diastereoselective Diels-Alder cyclization strategy. [7,8] Continuing our efforts for the construction of target compounds with various structural motifs, complete reduction of corresponding heteroaromatic precursors represent a straight forward strategy towards the AB-ring system. While reduction of the heteroaromatic core is an easy task the Birch reduction of the aromatic core is an interesting challenge. Though the Birch methodology is a well established method to access the corresponding dihydro compounds, low stability of the resulting enamine moiety derived from nitrogen containing heterocycles produce a series of problems. Consequently, procedures reported in the recent literature suffer from several disadvantages ranging from low yields, [9] only partial reduction of the heterocyclic system, [10] complex product mixtures, [11] high pressure techniques, [12] to rather complex and time consuming multi step approaches. [13] In the present publication we present our experiences in applying the one-pot Birch reaction developed for the synthesis of 4-dimethylaminocyclohexanone[14] to the quinoline system *en route* to the above target compounds. As key structural elements the hydroxyl group was implemented and the ring fusion was required to be *trans*. Furthermore we planned to introduce a side chain at the nitrogen atom as mimic for the lipophilic properties of the carbocyclic ring system in the parent steroidal system.

Results and Discussion

Starting from the readily available 6-methoxyquinoline **13** reduction of the heteroaromatic core was performed using Raney-Ni to give **14a** (R = H) in good yield (Scheme 3). Reductive alkylation with formaldehyde under hydrogenation conditions gave the *N*-methylated product **14b** (R = Me). Both substrates were used in the subsequent one-pot Birch reaction (Scheme 3).



Scheme 3. Model studies for the comprehensive reduction of the heteroaromatic core: (i) Raney-Ni. (ii) HCHO, Pd/C. (iii) Li/NH_3, MeOH. (iv) $NaCNBH_3$, pH 4. (v) HCl.

The Birch reduction was performed according to an optimized protocol reported by us recently. [14] This approach takes advantage of a one-pot comprehensive reduction of the heteroaromatic core avoiding isolation of the rather unstable intermediates **15** and **16**. However, we were able to isolate compound **16b** in a modified procedure to prove the reaction pathway outlined in Scheme 3.

The one-pot reaction is best carried out with lithium as electron source to give species **15** as an intermediate. In a one-pot procedure subsequent reduction to **16** was carried out using $NaCNBH_3$ at pH 4. As we had observed in our model study on dimethylanisidine[14] both enol ether **16** and ketal **17** can undergo further reduction leading to compound **18** as a by-product.

The $NaCNBH_3$ reaction was highly selective giving *trans*-fused products exclusively. Since we did not obtain crystals suitable for X-ray diffraction from derivatives of the liquid products **17** and **19** the stereochemistry of this step was assigned utilizing the crystalline material **18**. Based on extensive NMR experiments and the structural data from the single crystal X-ray

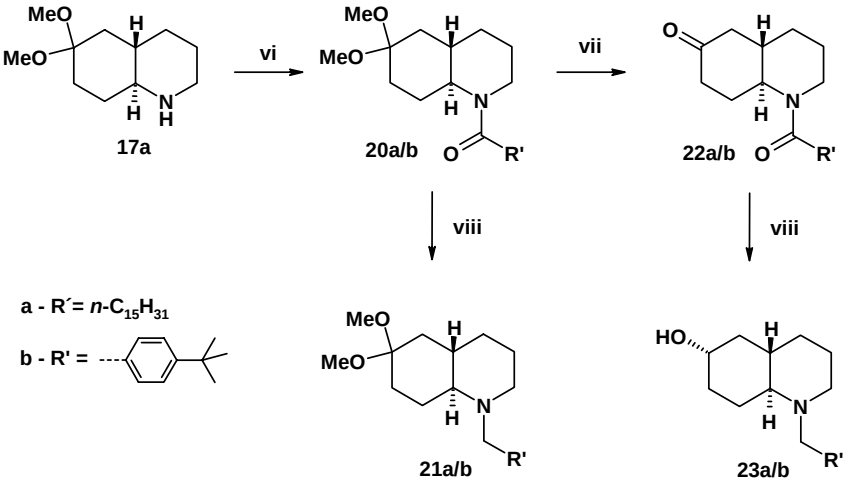
diffraction study the stereochemistry of all products resulting from the Birch reduction sequence was assigned.

Ketals **17a/b** were obtained in excellent yields and deprotection of the carbonyl group was performed according to standard conditions to give compound **19**.

Product **17a** served as precursor for the introduction of the lipophilic substituent at the nitrogen atom of the ring system. Two targets of biological interest were prepared: A long carbohydrate chain was intended to mimic the carbocyclic structure of the steroid, and the 4-*tert.*-butyl-benzyl group represents a typical hydrophobic substituent in a variety of inhibitors of the ergosterol biosynthesis with a related mode of action.

Following a straight forward strategy, acylation of substrate **17a** with the corresponding acid chloride in the presence of triethylamine as base afforded amides **20a** (R' = *n*-$C_{15}H_{31}$) and **20b** (R' = 4-*tert*-BuPh), respectively (Scheme 4).

At this stage reduction of the amide was carried out with RedAl® to form compounds **21a/b**. However, instead of proceeding *via* ketal cleavage and a subsequent second reduction step, the following shortcut in the total synthesis of the target products was developed: Deprotection of the ketal **20a/b** according to the protocol developed on the model compound **9** gave ketones **22a/b**. Finally, reduction of both the amide functionality and the ketone to the corresponding amino alcohols **23a/b** was performed using RedAl® in high to quantitative yields. This reagent turned out to be highly selective for the formation of an equatorial hydroxyl group.



Scheme 4. Synthetic strategy towards azasteroid partial structures bearing lipophilic chains: (vi) R'COCl/NEt3. (vii) H^+/H_2O. (viii) RedAl®.

Structural assignment is based on studying the coupling system for the annelation site protons in compound **18** using 2-dimensional NMR. Assignment of the *trans*-configuration and equatorial position of the methoxy group was confirmed by X-ray diffraction (Figure 1 and experimental section). Typical shifts and coupling constants for this model system were applied in the structural assignment of the other perhydroquinolines.

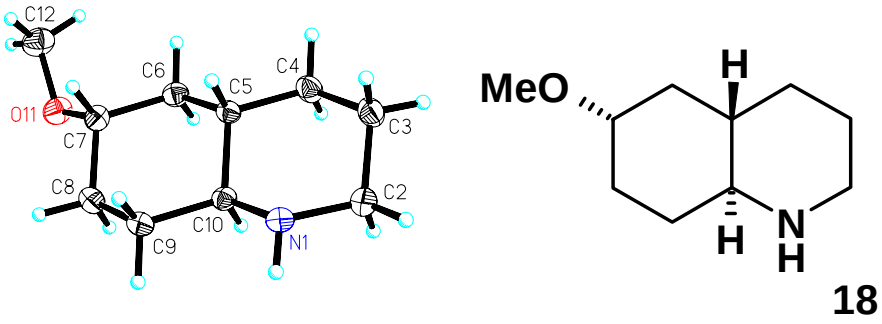


Figure 1. Structure determination of compound **18** by X-ray diffraction with crystallographic atom numbering and 20% ellipsoids.

In summary, we developed a diastereoselective route to *N*-substituted perhydro-quinolinols as potential inhibitors for the ergosterol biosynthesis based on a Birch reduction protocol. The target compounds represent azasteroid partial structures of the parent AB ring system in ergosterol and incorporate lipophilic chains mimicking the hydrophobic properties of the steroidal core.

Experimental Section

General Procedures. Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. Flash column chromatography was performed on silica gel 60 from Merck (40-63 μm). *Kugelrohr* distillation was carried out using a Büchi GKR-51 apparatus. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, University of Vienna. The NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) spectrometer and chemical shifts are reported in ppm using Me_4Si as internal standard.

1,2,3,4-Tetrahydro-6-methoxyquinoline (14a). A solution of 6-methoxyquinoline 13 (5.00 g, 31.4 mmol) in 130 mL of a 1:1 mixture of methanol and 1*N* KOH was treated with NiAl-alloy (10.92 g, 93 mmol) at such a rate to keep the reaction at reflux. After complete addition the solution was refluxed for additional 30 min and subsequently filtered through a bed of Celite. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by *Kugelrohr* distillation to give 4.31 g (84%) of 14a[16] as colorless crystals. Bp.: 85-90°C / 0.2 mbar; mp.: 41-43°C; ^{1}H NMR ($CDCl_3$): 1.96 (tt, 2H, J=6.4Hz/6.0Hz, H3), 2.78 (t, 2H, J=6.4Hz, H4), 3.28 (t, 2H, J=6.0Hz, H2), 3.55 (bs, 1H, N<u>H</u>), 3.78 (s, 3H, OCH_3), 6.46 (dd, 1H, J=11.0Hz/3.0Hz, H8), 6.58 (dd, 1H, J=11.0Hz/3.0Hz, H5), 6.60 (dd, 1H, J=11.0Hz/3.0Hz, H7). ^{13}C NMR ($CDCl_3$): 22.4 (t, C3), 27.1 (t, C4), 42.2 (t,

C2), 55.7 (q, OCH_3), 112.8 (d, C7), 114.8 (d, C5), 115.4 (d, C8), 122.7 (s, C4a), 138.8 (s, C8a), 151.7 (s, C6).

1,2,3,4-Tetrahydro-6-methoxy-1-methylquinoline (14b). A suspension of 14a (5.84 g, 35.78 mmol), 5% Pd/C (0.58 g), and 35% aqueous formaldehyde solution (30.7 g, 357.8 mmol) in methanol (250 mL) was charged into a *Parr* apparatus and hydrogenation was performed at a H_2 pressure of 6 bar overnight. The catalyst was separated by filtration through Celite and the remaining solution was concentrated to remove methanol. The residue was diluted with water and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by *Kugelrohr* distillation to give 5.10 g (92%) of 14b[17] as colorless oil which started to crystallize upon storage in a +4°C fridge. Bp.: 85-90°C / 0.03 mbar; ^{1}H NMR ($CDCl_3$): 2.02 (tt, 2H, J=6.4Hz/6.0Hz, H3), 2.81 (t, 2H, J=6.4Hz, H4), 2.88 (s, 3H, NCH_3), 3.16 (t, 2H, H2), 3.78 (s, 3H, OCH_3), 6.63 (dd, 3H, J=8.5Hz/3.5Hz, H8), 6.63 (dd, 3H, J=8.5Hz/3.5Hz, H5), 6.72 (dd, 3H, J=8.5Hz/3.5Hz, H7). ^{13}C NMR ($CDCl_3$): 22.4 (t, C3), 27.6 (t, C4), 39.3 (q, NCH_3), 51.2 (t, C2), 55.1 (q, OCH_3), 111.8, 112.0 (2d, C7,8), 114.6 (d, C5), 124.0 (s, C4a), 141.1 (s, C8a), 151.0 (s, C6).

***trans*-1,2,3,4,4a,5,8,8a-Octahydro-6-methoxy-1-methylquinoline (16b).** A 10% solution of 14b (2.00 g, 11.28 mmol) in dry THF was added to dry liquid NH_3 (55 mL) condensed into the reaction vessel. Small chips of lithium (0.78 g, 112.8 gAtom) washed with dry petroleum ether were cautiously added to maintain reflux. The reaction mixture was refluxed for 1 hour and then quenched with ethanol (10.40 g, 225.6 mmol). After the blue color had disappeared the ammonia was evaporated overnight. The residue was hydrolyzed with water (20 mL) and repeatedly extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated to give a quantitative amount of the isomeric forms 15b. The crude material was dissolved in a 1:1 mixture of dry THF and methanol (40 mL) and treated with $NaCNBH_4$ (1.43 g, 22.76 mmol) and a few crystals of bromocresol green at 0°C. The pH of the reaction was maintained at 4 by continuous addition of methanolic HCl. Subsequently, the mixture was hydrolyzed with 1*N* NaOH in brine and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel) to afford 0.80 g (39%) of 16b as colorless oil. ^{1}H NMR ($CDCl_3$): 0.71-2.28 (m, 10H, H2,3,4,5,8), 2.22 (s, 3H, NCH_3), 2.33-2.49 (m, 1H, H8a), 2.76-2.88 (m, 1H, H4a), 3.37 (s, 3H, OCH_3), 4.41-4.47 (m, 1H, H7). ^{13}C NMR ($CDCl_3$): 25.2 (t, C3), 29.2 (t, C8), 31.7 (t, C4), 34.4 (t, C5), 36.8 (d, C4a), 42.8 (q, NCH_3), 53.6 (q, OCH_3), 57.1 (t, C2), 64.4 (d, C8a), 90.4 (d, C7), 153.7 (s, C6).

General procedure for the one-pot Birch / $NaCNBH_4$ reduction

A solution of the precursor 14a/b (1 equiv.) in dry THF and dry MeOH was added to dry liquid ammonia condensed directly into the reaction vessel to form an approx. 10% reaction solution. Lithium chips were added slowly, maintaining the temperature at -35±5°C. After the initially vigorous reaction had ceased the mixture was refluxed until the blue color disappeared. Ammonia and the organic solvents were evaporated by a stream of nitrogen at approx. 50°C and the residue was treated with dry THF and MeOH. The resulting solution was cooled to -5±5°C

and brought to pH 4 by addition of methanolic HCl using bromocresol green as indicator. During the addition of $NaCNBH_3$ pH = 4 was maintained by treatment with methanolic HCl. When the pH showed no further change solid sodium bicarbonate and some NaOH were added and the solvents evaporated. The residue was treated with 1*N* NaOH saturated with NaCl and diethyl ether and the product isolated by repeated extraction. The combined ethereal layers were dried over sodium sulfate, filtered and concentrated. The crude product obtained by this general work-up was refluxed overnight in a mixture of MeOH and methanolic HCl.

***trans*-Decahydro-6,6-dimethoxyquinoline (17a).** Precursor 14a (2.50 g, 15.32 mmol) was converted according to the general procedure in a mixture of 200 mL of liquid NH_3 and 50 mL of dry THF in the presence of 16 equiv. of dry methanol by treatment with 15 equiv. of lithium. The reaction was refluxed for additional 10 min after disappearance of the blue color. After evaporation the residue was dissolved in 50 mL of THF and 20 mL of methanol and reduced with 0.95 equiv. of $NaCNBH_3$. The crude product was purified finally by *Kugelrohr* distillation to give 2.77 g (91%) of 17a as colorless oil. Bp.: 65-70°C / 0.7 mbar; mp.: 157-159°C (picrate from MeOH). ^{1}H NMR ($CDCl_3$): 1.08 (dd, 1H, J=13Hz/13Hz, $H5_{ax}$), 1.00-1.20 (m, 1H, $H4_{ax}$), 1.00-1.40 (m, 1H, H4a), 1.20-1.30 (m, 1H, $H8_{ax}$), 1.25-1.40 (m, 1H, $H7_{ax}$), 1.40-1.60 (m, 1H, $H8_{eq}$), 1.40-1.95 (m, 2H, H3), 1.55-1.75 (m, 1H, $H4_{eq}$), 1.90 (td, 1H, J=13Hz/3Hz, $H5_{eq}$), 2.00-2.20 (m, 1H, $H7_{eq}$), 2.05-2.25 (m, 1H, H8a), 2.65 (ddd, 1H, J=12Hz/12Hz/3Hz, $H2_{eq}$), 3.00-3.10 (m, 1H, $H2_{ax}$), 3.14 (s, 3H, OCH_3), 3.19 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 26.4 (t, C3), 29.4 (t, C8), 30.8 (t, C7), 31.5 (t, C4), 37.9 (t, C5), 38.2 (d, C4a), 46.7 (t, C2), 46.9, 47.2 (2q, 2 OCH_3), 60.9 (d, C8a), 99.6 (s, C6). Calc. for picrate $C_{17}H_{24}N_4O_9$: C, 47.66; H, 5.65; N, 13.08. Found: C, 47.92; H, 5.47; N, 13.02.

***trans*-Decahydro-6,6-dimethoxy-1-methylquinoline (17b).** Precursor 14b (2.00 g, 11.28 mmol) was converted according to the general procedure in a mixture of 200 mL of liquid NH_3 and 50 mL of dry THF in the presence of 16 equiv. of dry methanol by treatment with 15 equiv. of lithium. The reaction was refluxed for an additional 10 min after disappearance of the blue color. After evaporation the residue was dissolved in 50 mL of THF and 20 mL of methanol and reduced with 1.00 equiv. of $NaCNBH_3$. The crude product was purified finally by *Kugelrohr* distillation to give 2.35 g (98%) of 17b as colorless oil. Bp.: 60-65°C / 0.7 mbar; mp.: 148-150°C (picrate from MeOH). ^{1}H NMR ($CDCl_3$): 0.85-2.20 (m, 10H, H3,4,4a,5_{ax},7,8), 2.25 (s, 3H, NCH_3), 3.15 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 2.30-3.10 (m, 4H, H2,8a,5_{eq}). ^{13}C NMR ($CDCl_3$): 25.6 (t, C3), 26.6 (t, C4), 31.1 (t, C8), 31.9 (t, C7), 37.4 (t, C5), 38.4 (d, C4a), 42.7 (q, NCH_3), 47.3, 47.5 (2q, OCH_3), 57.6 (t, C2), 68.3 (d, C8a), 99.5 (s, C6). Calc. for picrate $C_{18}H_{26}N_4O_9$: C, 48.89; H, 6.35; N, 12.61. Found: C, 48.64; H, 6.12; N, 12.71.

(4aα,6β,8aβ)-Decahydro-6-methoxyquinoline (18). To a solution of ketal 17a (0.30 g, 1.51 mmol) dissolved in dry methanol (3 mL) $NaCNBH_4$ (0.14 g, 2.27 mmol) was added. A flow of dry HCl gas was passed through this reaction mixture cooled to -5±5°C at a flux of approx. 4.7 mol/h for 10 min. The solution was poured into ice / 2*N* NaOH, saturated with NaCl, and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Purification by *Kugelrohr* distillation afforded 0.20 g (78%) of 18 as

colorless crystals as diastereomeric mixture of predominantly 6β-product accompanied by some 6α-isomer (<10%). Slow evaporation of a methanolic solution of this material gave crystals of the pure 6β-isomer suitable for x-ray diffraction. Bp.: 60-65°C / 0.5 mbar; mp.: 30-40°C. ^{1}H NMR ($CDCl_3$, assignment based on CH- and HH-COSY): 0.96 (q, J=11Hz, 1H, $H5_{ax}$), 1.00-1.20 (m, 2H, $H4_{ax}$, H4a), 1.25 (dt, J=9Hz/2.5Hz, 1H, $H7_{ax}$), 1.35-1.78 (m, 2H, $H3_{eq/ax}$), 1.65-1.80 (m, 2H, $H4_{eq}$, $H8_{ax}$), 1.85-2.05 (m, 1H, $H5_{eq}$), 1.98-2.18 (m, 1H, $H7_{eq}$), 2.11 (dt, J=12Hz/3.5Hz), 2.63 (dt, J=12Hz/3Hz, 1H, $H2_{eq}$), 3.00-3.20 (m, 1H, $H2_{eq}$), 3.08-3.28 (m, 1H, $H6_{ax}$), 3.33 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 26.4 (t, C3), 30.5 (t, C7), 31.4 (t, (C8), 31.9 (t, C4), 37.4 (t, C5), 40.3 (d, C4a), 46.9 (t, C2), 55.5 (q, OCH_3), 61.0 (d**,** C8a), 78.6 (d, C6).

***trans*-Octahydro-1-methylquinolin-6(*2H*)-one (19).** Ketal 17b (0.50 g, 2.76 mmol) was dissolved in a 1:1 mixture of diethyl ether and 2*N* HCl and stirred at room temperature overnight. After addition of NaOH to maintain a pH > 8 the layers were separated and the aqueous phase was extracted with diethyl ether. The combined ethereal layers were dried over sodium sulfate, filtered, and concentrated to give 0.35 g (82%) of pure 19 as yellow oil. ^{1}H NMR ($CDCl_3$): 0.73-2.40 (m, 13H, H2,3,4,4a,5,7,8), 2.26 (s, 3H, NCH_3), 2.77-2.88 (m, 1H, H8a). ^{13}C NMR ($CDCl_3$): 25.0 (t, C3), 29.7 (t, C8), 32.2 (t, C4), 39.3 (t, C7), 41.1 (d, C4a), 42.6 (q, NCH_3), 46.0 (t, C5), 57.0 (t, C2), 66.3 (d, C8a), 209.4 (s, C6).

General procedure for acylation of precursor 17a

A 10% solution of ketal 17a (1 equiv.) and dry triethylamine (1.2 equiv.) in dry diethyl ether was treated with a 10% solution of the corresponding acid chloride (1.1 equiv.) in dry diethyl ether and stirred overnight at room temperature. The reaction mixture was hydrolyzed with water, extracted with diethyl ether, dried over sodium sulfate, filtered, and concentrated.

***trans*-Decahydro-6,6-dimethoxy-1-(1-oxohexadecyl)-quinoline (20a).** Compound 17a (2.00 g, 10.03 mmol) was treated with palmitinic acid chloride according to the above procedure to give 4.28 g (97%) of 20a as colorless crystals after chromatographic purification (silica gel). Mp.: 48-52°C. ^{1}H NMR ($CDCl_3$): 0.75-0.88 (t, 3H, J=6.4Hz, H16'), 1.00-1.35 (m, 2H, H15'), 1.40-1.50 (m, 2H, H3), 1.40-1.65 (m, 2H, H3'), 1.20-1.40, 1.90-2.10 (m, 2H, H8), 0.90-1.30 (m, 22H, H4, H3'-12'), 1.20-1.55, 1.80-2.15 (m, 2H, H7), 1.00-1.35 (m, 2H, H13'), 1.60-1.90 (m, 1H, H4a), 1.80-2.05 (m, 2H, H5), 1.95-2.4 (m, 2H, H2'), 0.95-1.25, 3.09, 3.13 (2s, 2x3H, OCH_3), 3.15-3.45 (m, 1H, H8a), 3.00-3.15, 3.50-3.65 2(m, 2H, H2). ^{13}C NMR ($CDCl_3$): 13.8 (q, C16'), 22.4 (t, C15'), 22.5 (t, C3), 25.2 (t, C3'), 29.1 , 29.2 , 29.2 , 29.5 , 29.4 (10t, C4, C4'-12'), 31.0 (t, C7), 31.6 (t, C13'), 33.0 (d, C4a), 33.7 (t, C2'), 38.3 (t, C2), 38.5 (t, C5), 47.0 , 47.5 (2q, OCH_3), 60.1 (d, C8a), 99.4 (s, C6), 172.2 (s, C=O). Calc. for $C_{27}H_{51}NO_3$: C, 74.09; H, 11.74; N, 3.20. Found: C, 73.86; H, 11.61; N, 3.32.

***trans*-1-(4-(1,1-Dimethylethyl)-benzoyl)-decahydro-6,6-dimethoxyquinoline (20b).** Precursor 17a (2.00 g, 10.03 mmol) were treated with 4-(1,1-dimethylethyl)-benzoylchloride according to the general procedure to give 2.81 g (78%) of 20b as colorless crystals after recrystallization from diisopropyl ether. Mp.: 120-125°C. ^{1}H NMR ($CDCl_3$): 1.23 (s, 9H, $C(CH_3)_3$), 0.90-2.40 (m, 9H, H3,4,4a,7,8), 3.12, 3.09 (2s, 2x3H, OCH_3), 3.15-3.53 (m, 5H, H2,8a,5), 7.24 (d, J=8Hz, 2H,

PhH), 7.31 (d, J=8Hz, 2H, PhH). ^{13}C NMR ($CDCl_3$): 23.1 (t, C3), 26.0 (t, C8), 31.1 (t, C4), 31.1 (q, C($\underline{C}H_3)_3$), 33.2 (t, C7), 34.6 (s, $\underline{C}(CH_3)_3$), 38.8 (d, C4a), 38.8 (t, C5), 42.4 (t, C2), 47.4, 47.7 (q, OCH_3), 59.9 (d, C8a), 99.6 (s, C6), 125.1 (d, PhC3), 126.7 (d, PhC2), 134.3 (s, PhC1), 152.4 (s, PhC4), 171.7 (s, C=O). Calc. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.80; H, 9.43; N, 3.88.

General procedure for reduction of the amide functionality

The corresponding amide (1 equiv.) was dissolved in a mixture of dry toluene and/or dry diethyl ether and treated with a 3.5*M* solution of RedAl® in toluene at the below specified temperature. The reaction temperature was maintained for 5 hours and then cooled to room temperature. The mixture was hydrolyzed with 2*N* NaOH and extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give the crude product.

***trans*-1-Hexadecyl-decahydro-6,6-dimethoxyquinoline (21a).** Amide 20a (2.00 g, 4.58 mmol) was dissolved in 100 mL of a 1:1 mixture of solvents and treated with RedAl® (4.17 g, 14.09 mmol) at 90°C according to the above procedure. The crude product was purified by flash column chromatography (silica gel) to give 1.85 g (96%) of 21a as coloress liquid. ^{1}H NMR ($CDCl_3$): 0.86 (t, J=6 Hz, 3H, CH_3), 1.01-2.79 (m, 43H), 2.90-3.02 (m, 1H, $H2_{eq}$), 3.12 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 13.9 (q, C16'), 22.5 (t, C15'), 31.7 (t, C14'), 24.3, 25.4, 26.2, 27.6, 29.2, 29.5, 31.1, 32.0, 37.4, 38.5 (19C, C3,4,4a,5,7,8,1'-13'), 47.2 (q, OCH_3), 47.4 (q, OCH_3), 53.1 (d, C8a), 65.1 (t, C2), 99.3 (s, C6). Calc. for $C_{27}H_{53}NO_2$: C, 76.54; H, 12.61; N, 3.31. Found: C, 76.72; H, 12.48; N, 3.42.

***trans*-1-(4-(1,1-Dimethylethyl)-phenylmethyl)-decahydro-6,6-dimethoxyquinoline (21b).** Compound 20b (80 mg, 0.22 mmol) was dissolved in 5 mL of diethyl ether and treated with RedAl® (0.33 g, 1.12 mmol) at 90°C according to the general procedure to give 70 mg (93%) of 21b as faint yellow oil without further purification. Mp.: 161-165°C (picrate from methanol). ^{1}H NMR ($CDCl_3$): 0.90-2.40 (m, 13H, $H2_{ax}$,3,4,4a,5,7,8,8a), 1.30 (s, 9H, $C(CH_3)_3$), 2.78-2.92 (m, 1H, $H2_{ab}$), 3.15, 3.20 (2s, 2x3H, OCH_3), 3.17 (dd, J=14Hz, 1H, NCH_2Ph), 4.06 (dd, J=14Hz, 1H, NCH_2Ph), 7.22 (d, 2H, J=8Hz, PhH), 7.32 (d, 2H, J=8Hz, PhH). ^{13}C NMR ($CDCl_3$): 25.4 (t, C3), 26.9 (t, C8), 31.3 (q, C($\underline{C}H_3)_3$), 31.3 (t, C4), 32.1 (t, C7), 34.3 (s, $\underline{C}(CH_3)_3$), 37.7 (d, C4a), 38.7 (t, C5), 47.4, 47.6 (q, OCH_3), 53.5 (t, Ph$\underline{C}H_2$N), 57.1 (t, C2), 66.2 (d, C8a), 99.5 (s, C6), 124.8 (d, PhC3), 128.6 (d, PhC2), 136.0 (s, PhC1), 149.3 (s, PhC4). Calc. for picrate $C_{28}H_{39}N_4O_9$: C, 58.42; H, 6.83; N, 9.73. Found: C, 58.68; H, 6.84; N, 9.78.

***trans*-Octahydro-1-(1-oxohexadecyl)-quinolin-6(*2H*)-one (22a).** Ketal 20a (0.50 g, 1.14 mmol) was dissolved in a mixture of 10 mL acetone and 2 mL 2*N* HCl and refluxed overnight. Then the pH was adjusted to 7 by addition of sodium bicarbonate and the solvent was evaporated. The residue was treated with water and diethyl ether, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (silica gel) to give 0.33 g (74%) of 15a as yellow crystals. Mp.: 51-54°C. ^{1}H NMR ($CDCl_3$): 0.85-0.9 (m, 3H, CH_3), 1.0-2.6 (m, 42H). ^{13}C NMR ($CDCl_3$): 13.9 (q, C16'), 22.5 (t, C15'), 31.8 (t, C14'), 25.3,

25.6, 28.5, 29.1, 29.3, 29.4, 29.5, 30.8, 33.9, 36.9, 38.6, 39.7 (18C, C3,4,4a,5,7,8,2'-13'), 47.19 (d, C8a), 58.27 (t, C2), 172.62 (s, NC=O), 208.86 (s, C=O). Calc. for $C_{25}H_{45}NO_2$: C, 76.67; H, 11.58, N, 3.58. Found: C, 76.51; H, 11.78; N, 3.49.

***trans*-1-(4-(1,1-Dimethylethyl)-benzoyl)-octahydroquinolin-6(*2H*)-one (22b).** Ketal 20b (3.47 g, 9.65 mmol) was dissolved in 100 mL of diethyl ether, treated with 150 mL of 2*N* sulfuric acid, and stirred at room temperature for 6 hours. The mixture was repeatedly extracted with diethyl ether, the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The crude product was recrystallized from diisopropyl ether to give 2.42 g, (77%) of 22b as colorless crystals. Mp.: 124-126°C. ^{1}H NMR ($CDCl_3$): 1.20-2.72 (m, 11H, H3,4,4a,5,7,8), 1.30 (s, 9H, $C(CH_3)_3$), 3.26-3.62 (m, 2H, H8a. H-2), 4.00-4.10 (m, 1H, $H2_{ax}$), 7.26-7.47 (m, 4H, PhH). ^{13}C NMR ($CDCl_3$): 22.7 (t, C3), 26.3 (t, C4), 28.3 (t, C8), 31.0 (q, $C(\underline{C}H_3)_3$), 34.5 (s, $\underline{C}(CH_3)_3$), 36.8 (d, C4a), 39.7 (t, C7), 42.2 (t, C5), 47.0 (t, C2), 58.2 (d, C8a), 125.1 (d, PhC3), 126.5 (d, PhC2), 133.6 (s, PhC1), 152.6 (s, PhC4), 171,7 (s, O=CN), 208.7 (s, C=O). Calc. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.40; H, 8.45; N, 4.38.

(4aα,6β,8aβ)-1-Hexadecyl-decahydroquinolin-6-ol (23a). According to the outlined protocol ketone 22a (0.22 g, 0.56 mmol) was dissolved in 20 mL of a 1:1 solvent mixture and treated with RedAl® (1.36 g, 4.60 mmol) at 60°C. Chromatographic purification (silica gel) gave 0.16 g (74%) of 23a as yellow crystals. Mp.: 55-56°C. ^{1}H NMR ($CDCl_3$): 0.85 (t, 3H, J=6Hz, CH_3), 0.9-2.75 (m, 47H), 2.85-2.96 (m,1H, $H2_{eq}$), 3.5-3.7 (m, 1H, H6). ^{13}C NMR ($CDCl_3$): 14.0 (q, C16'), 22.5 (t, C15'), 23.9 (t, C3), 27.7 (t, C2'), 28.1 (t, C2'), 31.8 (t, 14'), 25.6, 29.2, 29.5, 32.2, 34.5 (t, 13C, C4,7,8,4'-13'), 39.6 (t, C5), 41.8 (d, C4a), 53.2 (t, C2), 53.4 (t, C1'), 64.6 (d, C8a), 69.5 (t, C6). Calc. for $C_{25}H_{48}NO$: C, 79.09; H, 13.01; N, 3.69. Found: C, 78.83; H, 13.25; N, 3.78.

(4aα,6β,8aβ)-1-(4-(1,1-Dimethylethyl)-phenylmethyl)-decahydroquinolin-6-ol (23b). Ketone 22b (1.20 g, 3.83 mmol) was converted with RedAl® (6.80 g, 22.97 mmol) according to the general procedure in 40 mL of dry toluene at 90°C. The crude product was purified by *Kugelrohr* distillation to give 1.15 g (100%) of 23b as colorless wax. Bp.: 130-140°C / 0.02 mbar. ^{1}H NMR ($CDCl_3$): 0.95-2.38 (m, 13H, $H2_{ax}$,3,4,4a,5,7,8,8a), 1.30 (s, 9H, $C(CH_3)_3$), 2.79-2.91 (m, 1H, $H2_{eq}$), 3.58-3.77 (m, 1H, H6), 3.21 (d, J_{ab}=13Hz, 1H, $PhC\underline{H}_2N$), 4.04 (d, J_{ab}=13 Hz, 1H, $PhC\underline{H}_2N$), 7.18-7.43 (m, 4H, PhH). ^{13}C NMR ($CDCl_3$): 25.2 (t, C3), 28.5 (t, C8), 31.1 (q, $C(\underline{C}H_3)_3$), 32.1 (t, C4), 34.0 (s, $\underline{C}(CH_3)_3$), 34.2 (t, C7), 39.5 (d, C4a), 41.6 (t, C5), 53.2 (t, $Ph\underline{C}H_2N$), 56.9 (t, C2), 65.5 (d, C8a), 69.0 (d, C6), 124.6 (d, PhC3), 128.7 (d, PhC2), 135.3 (s, PhC1), 149.1 (s, PhC4). Calc. for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.48; H, 10.07, N, 4.61.

X-Ray structure determination of 18. A prismatic crystal of 0.40 x 0.15 x 0.10 mm was used for X-ray data collection with a Philips PW1100 four-circle diffractometer and graphite monochromatized Mo Kα radiation, λ = 0.71073 Å. Crystal data are: $C_{10}H_{19}NO$, M_r = 169.26, monoclinic, space group $P2_1/c$, a = 14.017(3), b = 5.369(1), c = 14.711(3) Å, β = 116.07(1)°, V = 994.5(3) Å^3, Z = 4, D_x = 1.131 g cm^{-3}, μ = 0.072 mm^{-1}, T = 293(2) K. Cell dimensions from ±ω-scans of 25 reflections. The intensities of 2764 reflections ($\theta \leq 25°$, ω-2θ scans) were measured, corrected for *LP* but not for absorption, and were then merged to 1748 independent F^2. The

structure was solved with direct methods using the program SHELXS86. Structure refinement on F^2 was carried out with the program SHELXL93. [18] Non-hydrogen atoms were refined anisotropically. The N-bonded hydrogen atom was fully refined. C-bonded hydrogen atoms were inserted in idealized positions and were refined riding with their carrier atoms. Final refinement gave R_1 = 0.055/0.150 for observed/all reflections and 115 parameters. CCDC 108184 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure determination showed that the methoxy group and the N-bonded H-atom adopt equatorial positions relative to the decahydroquinoline moiety (Fig. 1). The N-H group forms a weak hydrogen bond with the N atom of a neighboring molecule, N---N = 3.346(3) Å. This gives rise to continuous hydrogen bond chains …N-H---N-H---N-H… parallel to the b-axis.

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