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Stereoselective synthesis of a new class of potent and selective inhibitors of human Δ8,7-sterol isomerase

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ABSTRACT

Starting from Grundmann's ketone a new chemotype of inhibitors of the post-squalene part of cholesterol biosynthesis was developed. Stereoselective introduction of an angular methyl group at C-3a, followed by a plethora of functionalisations at C-4 and C-5 led to *cis*-configured amino alcohols as a new chemotype of inhibitors of cholesterol biosynthesis. In cell-based screening systems these compounds were identified to be selective inhibitors of human Δ8,7-sterol isomerase, inhibiting total cholesterol biosynthesis with IC_{50} values in the low nanomolar range. The most active compounds did not affect fungal Δ8,7-sterol isomerase (in ergosterol biosynthesis), neither showed noteworthy antimicrobial and cytotoxic effects.

1. Introduction

The invention of enzyme inhibitors represents a major strategy in the development of novel drugs, and almost one third of the current top 50 drugs are enzyme inhibitors.[1] The enzymes of cholesterol biosynthesis are part of these interesting targets. Cholesterol is essential for the inducement of many crucial functions of vertebral plasma membranes.[2] It is the most representative sterol present in these membranes and it is the product of a multistep biosynthetic pathway. Two major pathways for cholesterol biosynthesis, the Kandutsch–Russell[3,4] and the Bloch[5] pathway are known. 7-Dehydrocholesterol is the immediate biosynthetic precursor of cholesterol in the Kandutsch–Russell pathway, and its reduction to cholesterol is catalyzed by the enzyme 3β-hydroxy-steroid-Δ^7-reductase. Desmosterol is the direct biosynthetic precursor of cholesterol in the Bloch pathway and differs from cholesterol only in a double bond in the side chain. Conversion of desmosterol to cholesterol is catalyzed by the enzyme 3β-hydroxy-steroid-Δ^{24}-reductase in the final step of this pathway (Fig. 1).[6]

In mammals the preferred pathway for cholesterol biosynthesis starts with the Bloch pathway and ends with the last steps of the Kandutsch–Russell pathway. This switch between the pathways can occur since certain intermediates of the Bloch pathway can be converted to the corresponding ones of the Kandutsch–Russell pathway by action of the enzyme 3β-hydroxy-steroid-Δ^{24}-reductase (for details see Supplementary data).

Cholesterol is important for the formation of so called 'rafts' (DRMs—detergents resistant micro domains) which regulate several functions of the eukaryotic lipid membrane and are linked with the pathogenesis of certain diseases.[7,8] Cholesterol is also a precursor for steroid hormones and bile acids as well as it is relevant for the embryonic progress and morphogenesis.[9] Because of its eminent physiological role, disruptions in cholesterol metabolism cause various diseases. The most common are cardiovascular indispositions induced by an increased blood cholesterol level.[10]

The most prominent drugs marketed for treatment of hyperlipidaemia are the statins, inhibitors of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, an enzyme acting early in the pre-squalene part of cholesterol biosynthesis. Since therapy with statins is accompanied by a number of side-effects[11] like muscle toxicity, causing muscle weakness and cramps or even myopathy requiring hospitalization and life-threatening rhabdomyolysis, new cholesterol-lowering drugs having other molecular mechanisms are desirable. For this purpose the post-squalene part of the cholesterol biosynthesis pathway offers attractive targets.[12]

Contrariwise, the inborn lack of late enzymes of cholesterol biosynthesis is known to generate rare but serious disorders. Thus, specific inhibitors of such enzymes should be valuable tools for getting deeper insight into these disorders.[13,14] For example, CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome[15] and Conradi–Hünermann–Happle syndrome[16,17] are dysmorphogenetic syndromes of variable severity

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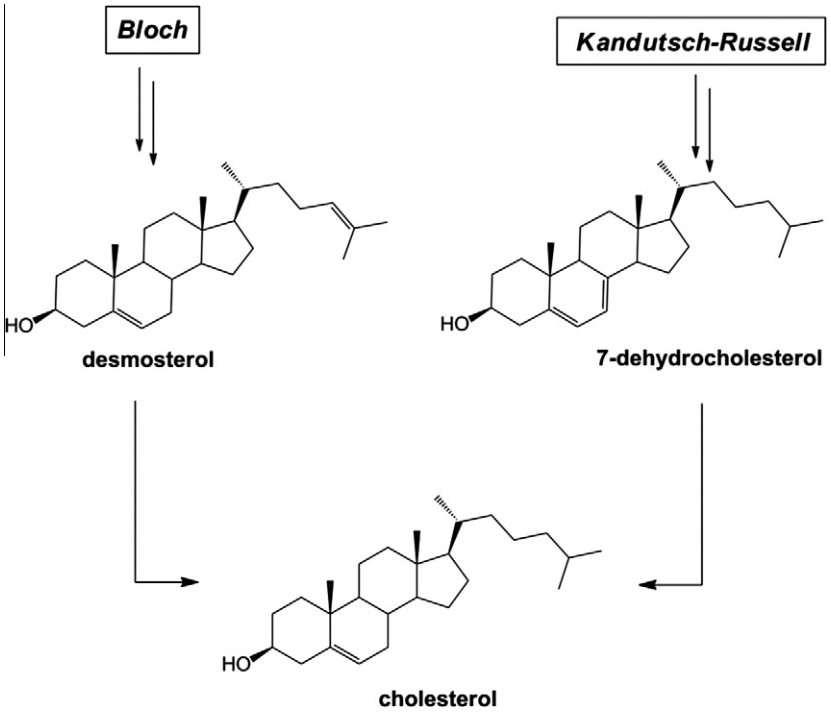


Figure 1. Chemical structures of the biosynthetic precursors of cholesterol: desmosterol (Bloch pathway) and 7-dehydrocholesterol (Kandutsch–Russel pathway).

due to mutations of the gene encoding the human 3β-hydroxysteroid Δ8,7-sterol isomerase (hSI; EC 5.3.3.5; also known as emopamil-binding protein, EBP).[18]

EBP is a vertebrate Δ8,7-sterol isomerase which has been shown to exhibit equally high binding affinity for both enantiomers of the calcium channel blocker emopamil.[19] Human Δ8,7-sterol isomerase catalyzes the shift of the double bond from C8–C9 to C7–C8 position in one of the last steps in both cholesterol biosynthesis pathways. In humans, such isomerisation occurs through a *trans* proton addition-elimination reaction[20,21] from either 5α-cholesta-8,24-dien-3β-ol (zymosterol, **1a**) to 5α-cholesta-7,24-dien-3β-ol (**2a**) for the Bloch pathway or alternatively from cholesta-8-en-3β-ol (zymostenol, **1b**) to lathosterol (**2b**) for the Kandutsch–Russell pathway (Fig. 2). In case of a selective inhibition of Δ8,7-sterol isomerase not the primary substrate zymosterol (**1a**), but zymostenol (**1b**) is the accumulating sterol. As mentioned above, the biosynthesis of cholesterol can switch from the Bloch to the Kandutsch–Russel pathway, and consequently, accumulating zymosterol (**1a**, Bloch pathway) can further be converted to zymostenol (**1b**, Kandutsch–Russel pathway) before the biosynthesis becomes definitely blocked.

The yeast counterpart ERG2p catalyses the corresponding step in ergosterol biosynthesis with the major difference that the isomerisation follows a *cis* proton addition-elimination reaction.[20,21] This stereoselectivity of both reaction mechanisms should allow for a selective inhibition of either the human or fungal Δ8,7-sterol isomerase (EBP or ERG2p) by appropriately tailored inhibitors.

After the identification of morpholines (e.g., tridemorph) as inhibitors of Δ8,7-sterol isomerase in fungi[22] and plants[23] a number of other inhibitors (e.g., **3**–**10**, Fig. 3) have been described that show more or less selective affinity for the human or the fungal enzyme.[24,25] Moreover, some of these inhibitors show multi-enzyme inhibition in the post-squalene part of sterol biosynthesis. Such a multi-enzyme inhibition can be advantageous in case of developing new antifungal agents by reducing fungal resistance. However it is estimated as a great drawback for inhibitors of cholesterol biosynthesis, since the resulting accumulation of particular precursors of cholesterol might cause severe side-effects.[13–17]

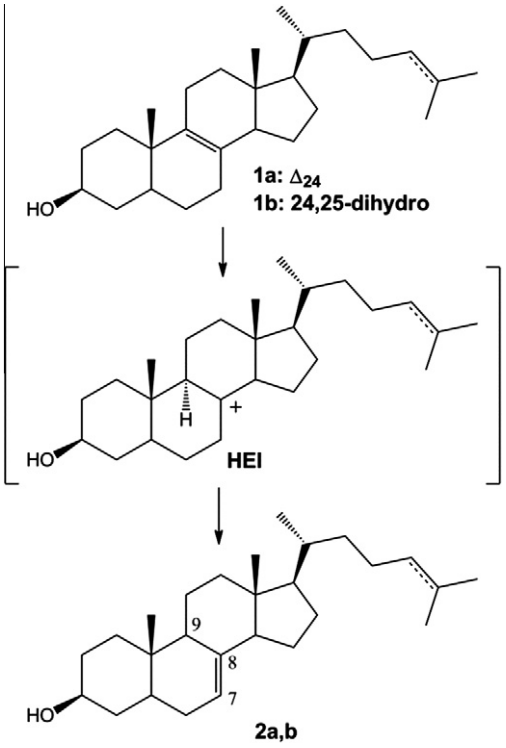


Figure 2. Human Δ8,7-sterol isomerase-catalysed isomerisation going through a carbocationic high energy intermediate (HEI).

The reason for this disadvantageous multi-enzyme inhibition is connected with the molecular mode of action of the inhibitors. Not only sterol Δ8,7-isomerisation passes through a carbocationic high energy intermediate (**HEI**; Fig. 2), but also the steps mediated by

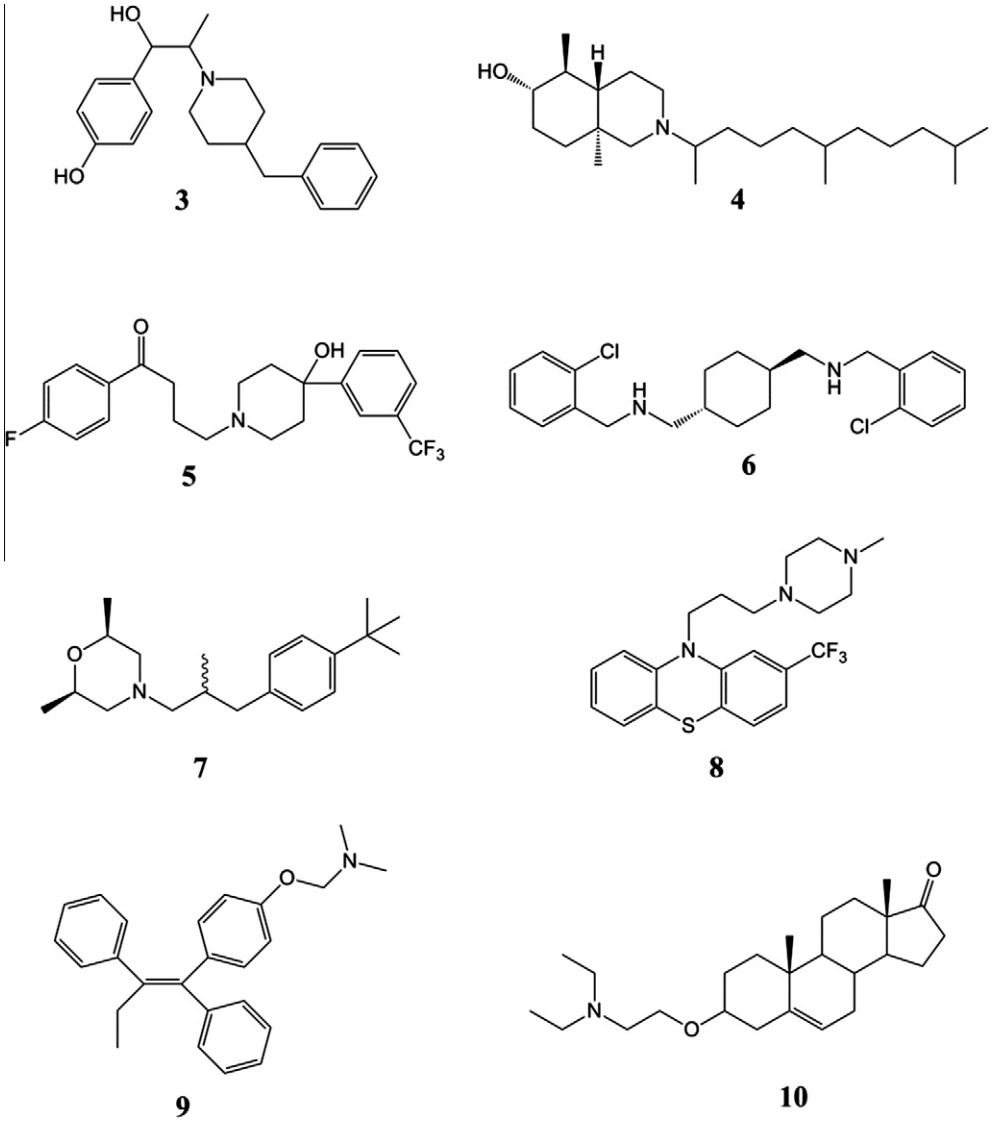


Figure 3. Structures of established Δ8,7-sterol isomerase (EBP or ERG2p) inhibitors.

the Δ7-sterol reductase, Δ24-sterol reductase, and Δ14-sterol reductases do so.[26] Suitable structures containing protonable nitrogen atoms, and in some cases thionium ions,[27,28] in pertinent positions of the scaffold are able to mimic the cationic HEIs, and inhibit the enzymes due to the resulting high affinity to the active site.[26] The established inhibitors shown in Figure 3 contain, without exception, protonable amine functions. Besides inhibition of Δ8,7-sterol isomerase, ifenprodil (**3**) and MDL28815 (**4**) also inhibit Δ14-sterol reductase,[29] trifluperidol (**5**), AY9944 (**6**), and fenpropimorph (**7**) show additional inhibition of Δ7-sterol reductase,[30,31] trifluoperazine (**8**), tamoxifen (**9**), and U18666A (**10**) additionally inhibit Δ24-sterol reductase.[32,33] Furthermore, a number of azasteroids are known to exert their antifungal activities through imitation of carbocationic HEIs in ergosterol biosynthesis.[27,28,34]

In continuation of our research on new inhibitors of ergosterol[28] and cholesterol[35] biosynthesis we designed a new chemotype of selective inhibitors of human Δ8,7-sterol isomerase. In order to achieve selective inhibition of the enzyme we invented HEI mimikries with high structural similarity to the steroidal substrate on the one side, and variable protonable amino groups localised in a domain matching ring B of the sterol on the other side. A versatile building block covering rings C+D of the sterol scaffold, as well as the lipophilic steroid side chain, is Grundmann's ketone[36] (**11**). Recently, this ketone was used by us as a precursor of cytotoxic azasteroid analogues.[37,38] Before attaching amino residues to the six-membered ring, the well-known problem of epimerisation at position C-3a of Grundmann's ketone (**11**) had to be abolished. In literature it is reported that this epimerisation can occur in presence of alkaline as well as acidic reagents and so causes a loss of stereochemical integrity.[39] A stereoselective introduction of an angular methyl group at position C-3a, under retention of the *trans* connection of both rings, would eliminate the possibility of

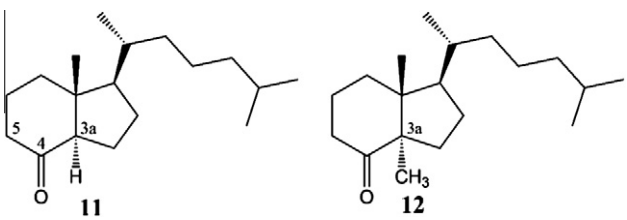


Figure 4. Grundmann's ketone (**11**) and modified ketone **12**.

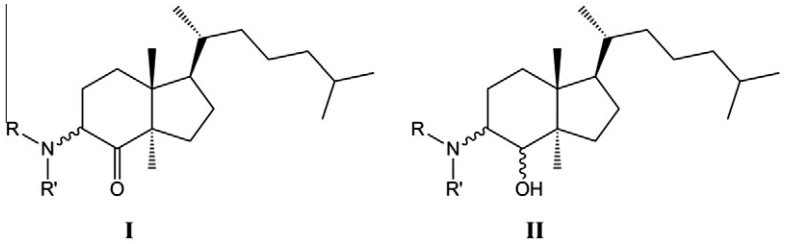


Figure 5. Target structures: α-aminoketones (**I**) and α-aminoalcohols (**II**).

epimerisation at this position and should also direct reactions performed at C-4 and C-5 (Fig. 4).

Starting from modified ketone **12** various stereoselective functionalisations at C-4 and C-5 should lead to an α-bromoketone, and further on to amino ketones **I** and *trans*- and *cis*-configured amino alcohols **II** (Fig. 5). In cell-based screening systems[20,32] these compounds were to be tested for their inhibition of cholesterol and ergosterol biosynthesis.

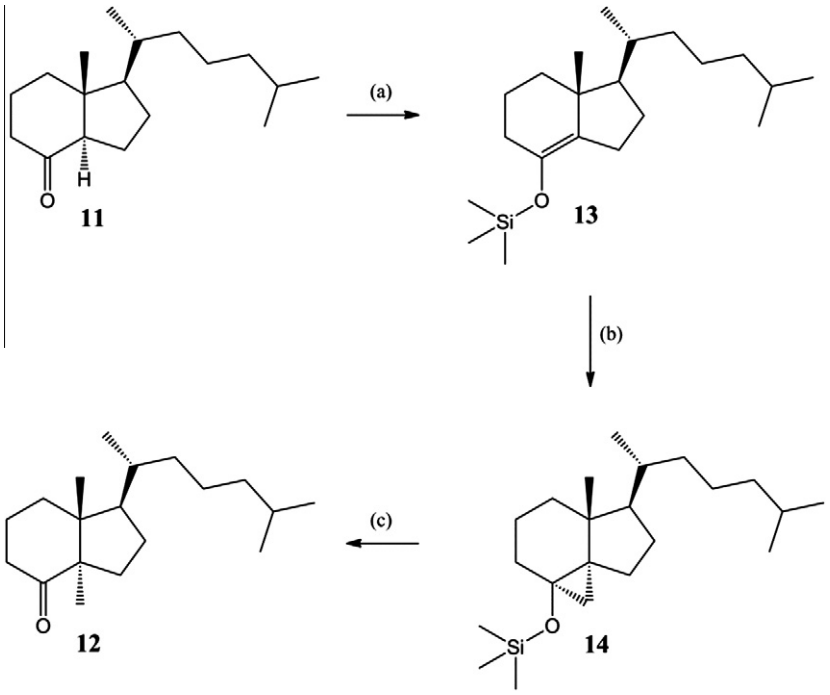
2. Chemistry

The synthesis of ketone **12** has previously been described rudimentarily by Corey et al.[41] and therefore the reaction conditions and work-up processes for the single steps had to be optimised. Conversion of Grundmann's ketone (**11**) to the trimethylsilyl enol ether **13** was done in dichloromethane with trimethylsilyl chloride (TMSCl) and lithium iodide in presence of hexamethyldisilazane ($(TMS)_2NH$) in good yield (64%).[42] The silyl enol ether **13** was converted to the cyclopropane derivative **14** (yield 80%) in a Simmons–Smith-like reaction by using the Furukawa reagent diethylzinc (Et_2Zn) and diiodomethane in diethyl ether.[43,44] The final alkaline hydrolysis[43] of the cyclopropane derivative **14** with sodium hydroxide in ethanol–water provided the *trans*-fused α-methylated ketone **12** in good yield (88%) (Scheme 1).

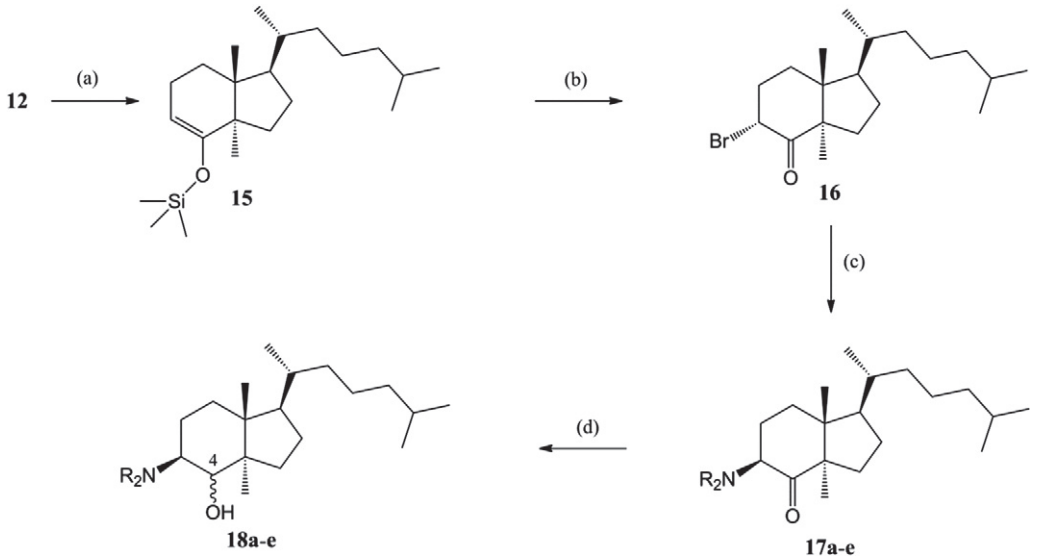
The first group of target structures (see Fig. 5, type **I**), the amino ketones **17a**–**e**, were prepared from bromoketone **16** (Scheme 2). This intermediate was obtained by treating ketone **12** in anhydrous THF with lithium diisopropylamide and trimethylsilyl chloride[45] to give the silyl enol ether **15** in good yield (83%), followed by stereoselective bromination (90% yield) with *N*-bromosuccinimide[46] in sodium acetate-buffered THF-water. The α-bromoketone **16** and the particular primary or secondary amine were refluxed in DMF[47] to give the amino ketones **17a**–**e** under clean inversion at C-5 (Scheme 2).

First attempts to simply reduce the carbonyl function of amino ketones **17a**–**e** with lithium aluminium hydride[48] in THF resulted partially in epimeric mixtures of the corresponding amino alcohols. Reductions of **17a**–**c** occurred stereoselectively to give the *cis*-configured 4*R*,5*S*-amino alcohols, whereas reductions of **17d** and **17e** were not stereoselective (Scheme 2).

We could not find a structural explanation for the partially selective or non-selective reductions of ketones **17a**–**e**, and since the epimeric mixtures **18d** and **18e** could not be separated by silica column chromatography, sophisticated stereoselective transformations were elaborated to provide optionally each *trans*- and *cis*-configured amino alcohols **II** (Fig. 5) in a predictable manner. The central building block **23** for the preparation of *trans*-(4*S*,5*S*)-configured amino alcohols was obtained starting from ketone **12**

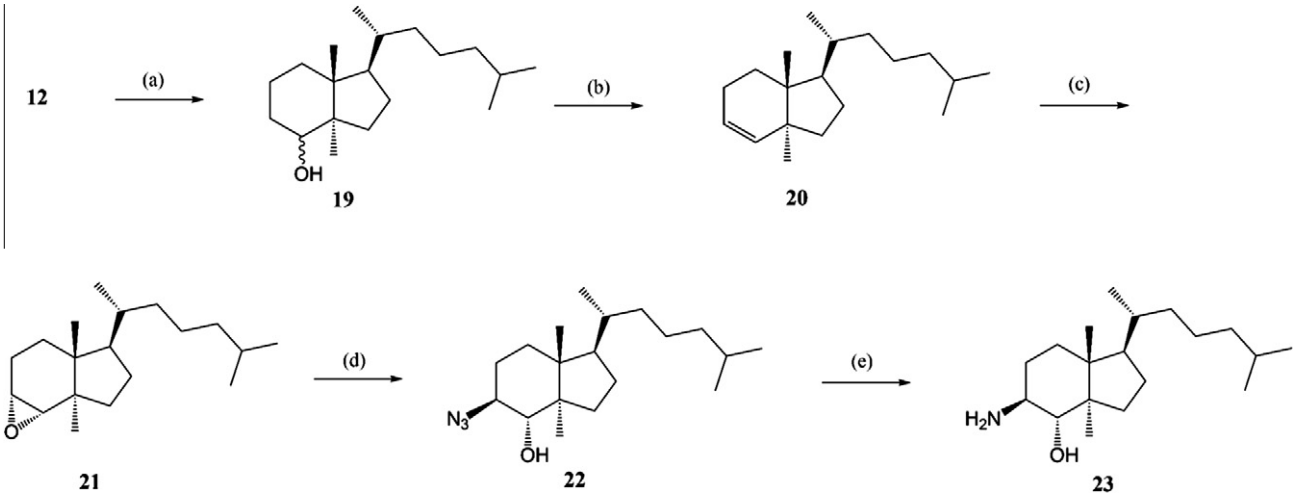


Scheme 1. Reagents and conditions: (a) trimethylsilyl chloride, 1,1,1,3,3,3-hexamethyldisilazane, lithium iodide, dichloromethane, rt, 24 h (64%); (b) 1 M diethylzinc solution in hexane, diiodomethane, diethyl ether, reflux, 12 h (80%); (c) 2 M aqueous sodium hydroxide solution, ethanol, reflux, 12 h (88%).



a	R_2N = *N*,*N*-dimethylamino	92 % (4*R*, *cis*)	**a**	R_2N = *N*,*N*-dimethylamino	50 %
b	R_2N = 4-methylpiperazin-1-yl	88 % (4*R*, *cis*)	**b**	R_2N = 4-methylpiperazin-1-yl	72 %
c	R_2N = (pyridin-3-yl)methylamino	96 % (4*R*, *cis*)	**c**	R_2N = (pyridin-3-yl)methylamino	68 %
d	R_2N = 2,6-dimethylmorpholin-4-yl	98 % (4*R*,*S*)	**d**	R_2N = 2,6-dimethylmorpholin-4-yl	59 %
e	R_2N = 2,3-dimethylanilino	97 % (4*R*,*S*)	**e**	R_2N = 2,3-dimethylanilino	82 %

Scheme 2. Reagents and conditions: (a) lithium diisopropylamide, trimethylsilyl chloride, THF, −78 °C → rt, 14 h (83%); (b) *N*-bromosuccinimide, sodium acetate, THF/water, rt, 12 h (90%); (c) amine, DMF, reflux, 12 h; (d) lithium aluminium hydride, THF, 0 °C, 30 min.

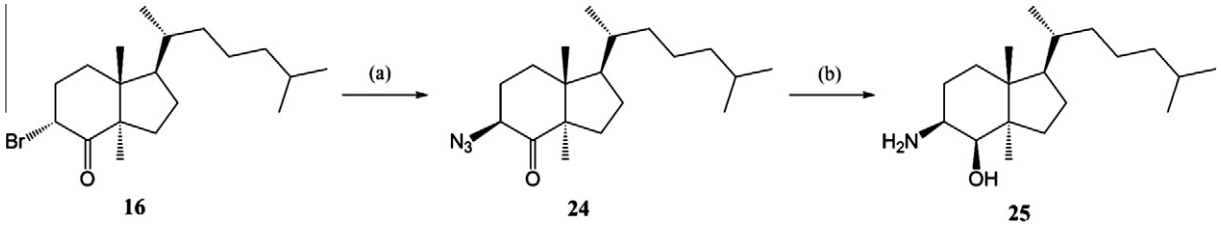


Scheme 3. Reagents and conditions: (a) lithium aluminium hydride, THF, 0 °C, 30 min (99%); (b) phosphorous oxychloride, pyridine, rt, 30 min (78%); (c) *m*-chloroperbenzoic acid, sodium bicarbonate, dichloromethane, 5 °C → rt, 2 h (93%); (d) sodium azide, DMF, 130 °C (microwave, 150 W, 4 psi), 2 h (86%); (e) lithium aluminium hydride, THF, 0 °C, 30 min (99%).

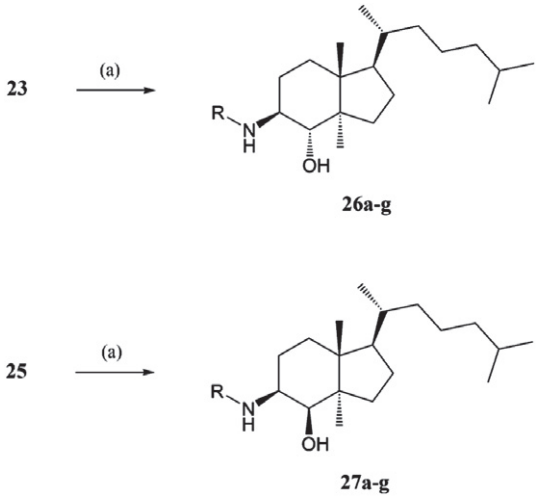
by lithium aluminium hydride reduction to give alcohol **19** (99% yield), followed by dehydration with phosphorous oxychloride[49] (78% yield) to give the olefin **20**. Stereoselective epoxidation of the olefin with *m*-chloroperbenzoic acid[50] gave the epoxide **21** in high yield (93%). Subsequent regio- and stereoselective microwave-accelerated ring opening with sodium azide[51] led to the azido alcohol **22** (86% yield), which finally was reduced with lithium aluminium hydride[52] to give the *trans*-(4*S*,5*S*)-configured amino alcohol **23** in almost quantitative yield (Scheme 3).

The epimeric *cis*-(4*R*,5*S*)-configured building block **25** for the preparation of amino alcohols of type **II** was obtained stereoselectively from α-bromo ketone **16** (Scheme 2) by substitution with sodium azide[53,54] under clean inversion at C-5 to give the α-azido ketone **24** in high yield (87%), followed by lithium aluminium hydride[52] reduction of both the azido and keto groups (99% yield) (Scheme 4).

The relative configurations of the residues at C-3a, C-4 and C-5 of the epimeric amino alcohols were elucidated by DPFGSE-NOE experiments, and since configuration at C-3a was known, these data also lead to the absolute configurations of the molecules (see Supplementary data). With **25**, irradiation at the resonance frequency of 4-H lead to an enhancement of the resonances of both the angular methyl group at C-3a and 5-H, clearly indicating that 4-H is located at the same side of the six-membered ring as these two groups. In the analogous experiment with the *trans*-amino alcohol **23** a nuclear Overhauser effect was observed neither with



Scheme 4. Reagents and conditions: (a) sodium azide, DMF, 0 °C, 2 h (87%); (b) lithium aluminium hydride, THF, 0 °C, 30 min (99%).



		26	27
a.	R = benzyl	85%	58%
b.	R = (5-iodofuran-2-yl)methyl	75%	86%
c.	R = 3-chlorobenzyl	79%	79%
d.	R = (furan-3-yl)methyl	84%	67%
e.	R = pent-4-en-1-yl	79%	56%
f.	R = 2,4-dichlorobenzyl	89%	73%
g.	R = 2,3-dichlorobenzyl	77%	85%

Scheme 5. Reagents and conditions: (a) aldehyde, sodium cyanoborohydride, acetic acid, methanol, 40 °C, 12 h.

the methyl group, nor with 5-H, in full accordance with the proposed configuration.

The amino alcohols **23** and **25** were conveniently converted to a library of stereochemically pure secondary amines **26a–g** and **27a–g** by reductive *N*-alkylations[55] using various aldehydes and sodium cyanoborohydride (Scheme 5).

Since in a first screening for inhibition of cholesterol biosynthesis the *cis*-(4*R*,5*S*)-configured amino alcohols **27a–g**, especially the *N*-benzyl derivative (**27a**) and the *N*-pent-4-en-1-yl derivative (**27e**), showed significant inhibition of the Δ8,7-sterol isomerase, further modifications were accomplished in order to increase the activity of the *cis*-(4*R*,5*S*)-configured amino alcohols. Secondary amines **28a–c** were obtained by reductive N-alkylation[55] of primary amine **25** under the conditions as described above (Scheme 6). With regard to **27a** and **27e** these additional compounds feature increased electron density in the aromatic system and a different length of the aliphatic chain, respectively.

Another modification within this work was the synthesis of tertiary amines, again based on the two most promising structures **27a** and **27e**. N-Methylation was carried out using formaldehyde and sodium cyanoborohydride to give **29a** and **30** (Scheme 7). Additionally, different combinations of the most interesting *N*-residues (*N*-benzyl, *N*-pent-4-en-1-yl) were carried out by reductive N-alkylations of **27a** using either benzaldehyde or pent-4-enal and sodium cyanoborohydride to give the amino alcohols **29b** and **29c** (Scheme 7).

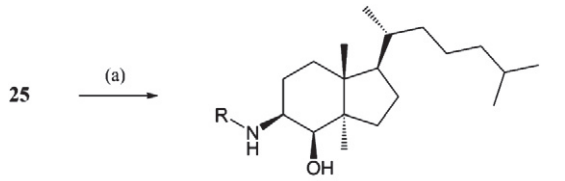
3. Biological assays

3.1. Antifungal activity and inhibition of ergosterol biosynthesis

All substances were subjected to a biological assay defining their MIC (Minimal Inhibitory Concentration; this value is defined as the lowest concentration that leads to a visibly detectable complete inhibition of growth) against 3 model strains (*Candida glabrata*, *Saccharomyces cerevisiae*, *Yarrowia lipolytica*) according to DIN 58940-84.[56,57] As we determined MIC values in the range from 25 to 50 μg/mL (MIC values of reference inhibitor clotrimazole: *C. glabrata* 2.5 μg/mL; *S. cerevisiae* 0.5 μg/mL; *Y. lipolytica* 1.0 μg/mL) it could be assumed that the compounds described here do not show noteworthy inhibition of cell growth, and hence do not affect ergosterol biosynthesis to a mentionable extent. For this reason investigations on the interaction of the compounds with ergosterol biosynthesis were abandoned.

3.2. Qualitative and quantitative test for inhibition of cholesterol biosynthesis

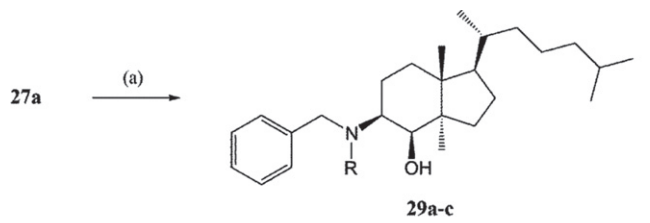
For qualitative screening of potential cholesterol biosynthesis inhibitors, two concentrations (1 and 50 μM) were initially pretested in a whole cell assay on HL-60 cells. This screening system, worked out by us previously,[40] allows for the identification of target enzymes in the post-squalene part of cholesterol biosynthesis by GC–MS analysis of the changes in the sterol pattern, as exemplified by the chromatograms shown in Figure 6. Whereas the untreated cells contained cholesterol as the only detectable sterol (chromatogram **A**), incubation with *cis*-amino alcohol **27a** (chromatogram **B**) led to a significant accumulation of zymostenol (**1b**), identified by comparing its relative retention time and MS data with those of an authentic sample.[40] Since **1b** is a substrate of human Δ8,7-sterol isomerase, the target enzyme was identified unambiguously. In contrast, the unselective inhibitor tamoxifen (**9**) led to an accumulation of both zymostenol (**1b**) and zymosterol (**1a**) in accordance with its dual mechanism[32,33,58] as inhibitor of both Δ8,7-sterol isomerase and Δ24-sterol reductase (chromatogram **C**). The amino ketones **17a–e** and the *trans*-amino alcohols **26a–g** did not induce noteworthy changes in the sterol pattern.



28a-c

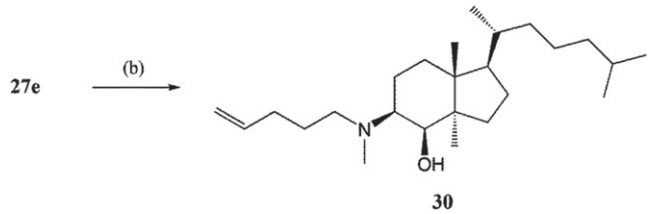
a	R = 4-methoxybenzyl	73%
b	R = 2,4-dimethoxybenzyl	57%
c	R = ethyl	75%

Scheme 6. Reagents and conditions: (a) aldehyde, sodium cyanoborohydride, acetic acid, methanol, 40 °C, 12 h.



29a-c

a	R = methyl	83%
b	R = benzyl	84%
c	R = pent-4-en-1-yl	82%



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Scheme 7. Reagents and conditions: (a) aldehyde, sodium cyanoborohydride, acetic acid, methanol, 40 °C, 12 h; (b) formaldehyde (38% aqueous solution), sodium cyanoborohydride, acetic acid, methanol, 40 °C, 12 h.

For quantitative screening we selected the substances that induced significant accumulation of zymostenol (**1b**) in the qualitative pre-screening. In this whole-cell assay[40] HL-60 cells are incubated with various concentrations of the test substances in the presence of 2-^{13}C-acetate. Due to the incorporation of 4–7 ^{13}C atoms into cholesterol molecules biosynthesised during the incubation period, newly synthesised cholesterol can be distinguished from unlabelled matrix cholesterol that was present in the cells before incubation, by GC–MS. From the dose–response curves obtained by determination of ^{13}C-labelled cholesterol and after normalisation to the protein content by a Bradford assay,[59] the IC_{50} values describing the overall effects of the inhibitors on cholesterol biosynthesis in the cellular system were calculated (Table 1).

3.3. MTT-test for cytotoxic effects

To determine possible cyctotoxic effects, the substances were subjected to the standard MTT test developed by Mosmann.[60] Cisplatin was used as a reference, the results are shown in Table 1.

4. Discussion

Starting from Grundmann's ketone (**11**) and via its derivative **12** with an angular methyl group at C-3a, we prepared a collection of secosteroids containing amino ketone and amino alcohol moieties as potential inhibitors of cholesterol biosynthesis. Since reduction of the α-aminoketones **17a–e** gave epimeric mixtures of amino alcohols **18a–e** in certain cases, we worked out fully stereoselective approaches to the primary amino alcohols **23** and **25**, from which the *trans*-(4*S*,5*S*)-configured amino alcohols **26a–g** and the *cis*-(4*R*,5*S*)-configured amino alcohols **27a–g**, **28a–c**, **29a–c** and **30** were readily accessible by standard reductive alkylation protocols.

These substances were subjected to several screening systems to determine their biological profile. The in vitro antifungal activities were assessed against the yeasts *C. glabrata, S. cerevisiae*, and *Y. lipolytica*. The compounds did not show noteworthy antifungal activity (MIC values higher than 25 μg/mL), and hence no inhibition of ergosterol biosynthesis could be adopted. The effect on cholesterol biosynthesis was determined in a HL-60 cells based whole-cell assay with GC–MS analysis of the changes in the sterol pattern. Whereas the amino ketones **17a–e** and the *trans*-configured amino alcohols **26a–g** were inactive in this assay, selective inhibition of human Δ8,7-sterol isomerase could be shown for a considerable number of *cis*-configured amino alcohols. The most promising substances from this qualitative investigation were subjected to a quantitative screening to determine their effects on overall cholesterol biosynthesis (Table 1). In addition, a MTT test was performed to define the cytotoxicity of the substances (Table 1).

From the results from Table 1 and the structures of the other, inactive compounds from the *cis*-amino alcohol series some conclusions on structure-activity relationships can be drawn. The activity of the inhibitors is greatly influenced by the size of the amino group. Whereas compounds bearing very small substituents (primary amine **25**, *N*,*N*-dimethylamine **18a**) have IC_{50} values in the submicromolar range, compounds bearing very bulky substituents like substituted benzyl residues are inactive. IC_{50} values in the low nanomolar range can be found for compounds bearing one medium-sized substituent (benzyl, pent-4-en-1-yl) in combination with hydrogen (secondary amine **27a**) or a methyl group (tertiary amines **29a** and **30**). Combination of two of the medium-sized groups leads to a decrease (**29c**) or complete loss of activity (*N*,*N*-dibenzyl derivative **29b**).

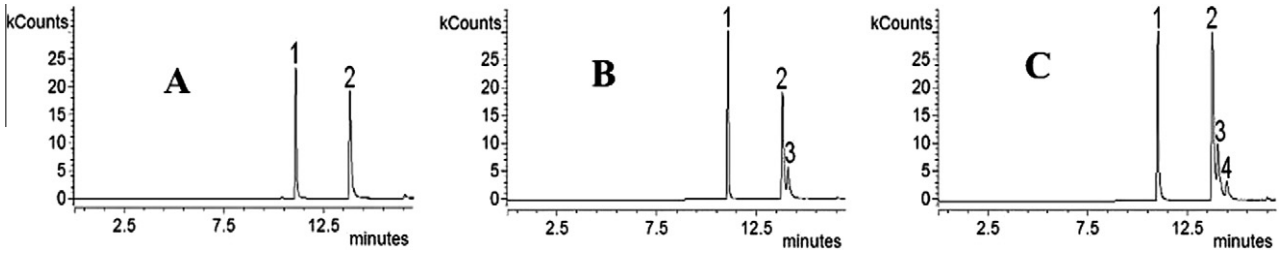

Figure 6. Extracted ion chromatograms of the accumulating sterols after incubation of HL-60 cells with inhibitors (with respective qualifier ions in brackets); (A) untreated control; (B) **27a** 1 μM; (C) tamoxifen (**9**) 1 μM; peak 1 cholestane (internal standard, 357 + 217 + 203), peak 2 cholesterol (458 + 368 + 329), peak 3 zymostenol (**1b**) (458 + 353 + 213), peak 4 zymosterol (**1a**) (456 + 441 + 351).

Table 1
IC_{50} values (nM) obtained in the MTT (see Section 3.3) test and in the assay for inhibition of overall cholesterol biosynthesis (see Section 3.2)

Compound	MTT test (nM)	IC_{50} value (nM)	Confidence interval (nM)	R^2
18a	17,000	576	462-720	0.899
25	11,000	581	477–638	0.948
27a	8000	15	14-18	0.959
27e	15,000	58	54–62	0.967
29a	7000	11	10-13	0.928
29b	27,000	>1000		
29c	17,000	82	71-95	0.965
30	7000	18	16-20	0.973
Cisplatin	5000	—	—	—

IC_{50} values (determined in triplicate) for the inhibition of total cell growth (MTT test) and total cholesterol biosynthesis through determination of ^{13}C incorporation into newly synthesised cholesterol. Confidence interval for the IC_{50} value, 95%; R^2, goodness of fit of the dose response curves.

Comparison of the corresponding IC_{50} values (MTT test vs cholesterol biosynthesis assay) of the most promising substances **27a**, **29a**, and **30** shows that there is a large difference in activity (factor 390–630), and therefore cytotoxicity should not matter. As these most active compounds obviously do not affect the yeast ergosterol biosynthesis, highly selective inhibitors of human Δ8,7-sterol isomerase that inhibit total cholesterol biosynthesis with IC_{50} values in the low nanomolar range could be developed.

An inborn lack of the Δ8,7-sterol isomerase is known to generate rare but serious disorders, so the inhibitors described here are not likely to be drug candidates. But due to their potent and specific inhibition of this enzyme they should be valuable tools for investigations aimed at a better understanding of disorders caused by defects in the gene encoding Δ8,7-sterol isomerase.

5. Experimental section

5.1. Analysis and materials

All solvents were of HPLC or p.a. grade, otherwise they were distilled before use over appropriate drying agents. Unless stated otherwise, the chemicals were purchased from Sigma–Aldrich (Schnelldorf, Germany) and Acros (Geel, Belgium), and were used without further purification. MSTFA and TSIM were from Marcherey & Nagel (Düren, Germany) Bondesil PSA was from Varian, 24-well plates were from Peske (Aindling–Arnhofen, Germany). Cholestane was obtained from Steraloids Inc. (Birmingham, UK), Bradford colour solution for protein determination was from Carl Roth GmbH + Co. KG (Karlsruhe, Germany), RPMI 1640 medium and fetal bovine serum (FBS) were from PAA Laboratories GmbH (Cölbe, Germany), medium for *HL-60* cells (lipid free medium) and lipoprotein deficient serum (LPDS) were purchased from PAN Biotech (Aidenbach, Germany). The yeast-culture mediums consisted of yeast extract 10 g/L, peptone 20 g/L and glucose 20 g/L. Each yeast culture was splitted once a week to keep the cultures in log phase. Each yeast culture was maintained at 28 °C. The 0.5 Mc Farland standard was prepared from 0.05 mL solution A (0.117 g $BaCl_2 \times 2H_2O$ in 10 mL of water) and 9.95 mL 10% (w/v) H_2SO_4. The *Candida glabrata*, *Candida cerevisiae* and *Yarrowia lipolytica* test cultures were purchased from DSMZ (Deutsche Sammlung für Mikroorganismen und Zellkulturen, Braunschweig, Germany). HL-60 cells were purchased from DSMZ and were maintained in RPMI 1640 medium containing 10% FBS without antibiotics at 37 °C in a humidified atmosphere containing 5% CO_2.

For syntheses, all anhydrous reactions were carried out under an inert atmosphere using Schlenk techniques. Reactions were monitored by TLC using pre-coated plastic sheets POLYGRAM® SIL G/UV_{254} from Marcherey & Nagel. Merck Silica Gel 60 (particle size 0.040–0.063 mm) was used for silica column chromatography (SCC). Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Structure assignment for all prepared compounds was done by using ^1H NMR, ^{13}C NMR, as well as DEPT, HMQC, and HMBC techniques. NMR spectra were recorded on JEOL Eclipse plus NMR workstations (Jeol GSX 400 or JNMR GX 500 instrument), respectively, at 500.1599 or 399.7820 MHz for ^1H and 125.7653 or 100.5253 MHz for ^{13}C. Spectra were calibrated by using residual undeuterated solvent as an internal reference ($CHCl_3$ with ^1H at 7.26 ppm, ^{13}C at 77.00 ppm). Mass spectra were recorded on a Hewlett–Packard 5989A, using electron impact ionisation (EI) at 70 eV and chemical ionisation with methane (CI). Electron impact high resolution mass spectra (EI-HRMS) were recorded on GC Mate II Jeol. The substances were directly injected. IR spectra were obtained on Perkin-Elmer Paragon 1000 spectrometer. The UV spectrophotometer Hitachi U 1100 was from Hitachi (Krefeld, Germany). Melting points were determined on a Büchi 540 apparatus.

5.2. Determination of the MIC values

For the determination of antifungal activity against *C. glabrata*, *C. cerevisiae* and *Y. lipolytica*, all substances were dissolved in absolute ethanol to give standard solutions with a concentration of 0.8 mg/mL. The solutions were diluted stepwise with ethanol to give the test concentrations of 50, 25 and 12.5 μg/mL. All dilutions were done like described in the SANCO guideline.[57] The dilutions were added to the 24-well plate, each row containing, respectively, two wells with the same concentration. Additionally, each well plate contained a control row consisting of two wells to which only 2.0 mL of medium had been added (sterility control), two wells to which only 10 μL of ethanol had been added (negative control) and two wells containing a concentration of 0.5 μg/mL clotrimazole (positive control). Each testing day additionally one row on a single plate was treated with ketoconazole (4, 2, 1, 0.5, 0.25, 0.125 μg/mL) as 'MIC control'. The subsequent general process and the visual determination of the MIC values were described in literature before.[28]

5.3. GC–MS analysis

5.3.1. Qualitative analysis of the sterol fractions

For qualitative analysis a Varian GC 3800 equipped with a CTC Combi Pal autosampler coupled to a Varian Saturn 2000 ion trap with a Varian Factor Four EZ Guard VF 5 MS 30 m × 0.25 mm × 0.25 μm column was used. The 1177 injector was held at 250 °C and operated in splitless mode for 1 min. The transfer line was held at 270 °C. The oven program started at 50 °C held for 1 min, and ramped to 260 °C with 50 °C per min, followed by a gradient of 4 °C per min to 310 °C held for 0.5 min. The MS was operated in full scan mode from 9 to 12 min at a mass range from 50 to 450 *m*/*z* and from 12 to 18 min at a mass range from 100 to 650 *m*/*z*. For substance identification three qualifier ions were chosen for each sterol (Fig. 6).

5.3.2. Quantitative analysis of labelled cholesterol

Quantitative analysis was carried out with a Varian GC 3800 equipped with a CTC Combi Pal autosampler coupled to a Varian Saturn 1200 triple quad. The column used was again a Varian Factor Four EZ Guard VF 5 MS 30 m × 0.25 mm × 0.25 μm. The 1177 injector was held at 250 °C and operated in splitless mode for 1 min. The transfer line was held at 270 °C. The oven program started at 50 °C held for 1 min, and ramped to 260 °C with 50 °C per min, followed by a gradient of 4 °C per min to 310 °C held for 0.5 min. Quantification of the labelled cholesterol was carried out

by analysing the ions 372–379 and 462–469 *m*/*z*. For cholestane (I.S.) 217 and 357 *m*/*z* were chosen as quantifier ions.

5.4. Incubation and work-up procedures for the identification of the target enzyme and for quantification of the inhibition of cholesterol biosynthesis

For the qualitative screening, two test concentrations (1 and 50 μM) were established. The substances were dissolved in ethanol and the initial weight was calculated for the matter that there was a final concentration of 50 μM if 10 μL of this solution were added to 990 μL of lipid-free medium containing 1% LPDS without antibiotics. An aliquot of this 50 μM solution was diluted by 1:50 in order to obtain the second needed concentration of 1 μM if 10 μL of this solution were added to 990 μL of lipid free medium containing 1% LPDS without antibiotics.

HL-60 cells (10^6 cells) were incubated in 24-well plates in 1 mL (990 μL of lipid free medium containing 1% LPDS + 10 μL of respective inhibitor solution). After a 24 h incubation period (conditions: 37 °C in a humidified atmosphere containing 5% CO_2) the content of each well was transferred into a 2 mL plastic tube and the wells were washed with 750 μL of phosphate-buffered saline (PBS). The cells were collected by centrifugation at 540×*g* for 5 min, washed once with 1 mL of PBS, and centrifuged again. After decantation 1 mL of 1 M NaOH was added to each tube, saponification was carried out at 70 °C for 60 min. Fifty microlitres of internal standard solution (cholestane in TBME, 10 μg/mL) and 700 μL of TBME were added and the tubes were shaken vigorously for 1 min and then centrifuged at 9200×*g* for 5 min. The organic layer was separated with a pipette, and extraction was repeated with another 750 μL of TBME in the same manner. The combined organic extracts were stirred vigorously over 35 mg of dried sodium sulphate and 5 mg of Bondesil PSA and then centrifuged for 5 min at 9200×*g*. One millilitre of the purified extract was transferred into an autosampler vial and evaporated to dryness under mild stream of nitrogen. To each vial, 950 μL of TBME and 50 μL of *N*-trimethylsilylimidazole (TSIM) were added. Silylation reaction was carried out for 1 h at room temperature. The trimethylsilyl ethers were analysed as described in Section 5.3.1.

For the determination of labelled cholesterol (quantitative screening), the protocol was altered in the following manner: To each incubation well 10 μL of a sterile sodium 2-^{13}C-acetate solution (6.25 mg/mL) were added before addition of the inhibitor solution, leading to a final ^{13}C-acetate concentration of 62.5 μg/mL. After saponification 3 × 25 μL aliquots were taken for protein determination according to Bradford,[59] using bovine serum albumin as standard. After work-up and silylation, GC–MS analysis was performed as described in Section 5.3.2. The percentage inhibition (Fig. 7, formula) relative to untreated control samples (0% inhibition) was plotted against the logarithmic inhibitor concentration using Graph Pad Prism 4. A bottom level constant equal to 0 was set as constraint using a sigmoidal dose–response model with a various slope. All samples were normalised to their protein content taking into account the number of cells. For each concentration the percentage was determined in triplicate.

5.5. MTT test

For the determination of the cytotoxicity of the tested substances against human leukemia HL-60 cells a standard MTT test according to Mosmann was used. Cisplatin was utilised as reference.

5.6. Syntheses

5.6.1. (1*R*,3a*R*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-one (12)

Compound **14** (345 mg, 0.98 mmol) was dissolved in a mixture of ethanol (10 mL) and an aqueous solution of sodium hydroxide

$$\%inhibition = \left[1 - \left(\frac{A_S \times A_{I,S,C} \times PC_C}{A_C \times A_{I,S,S} \times PC_S}\right)\right] \times 100$$

Figure 7. Calculation formula for the percentage inhibition; A_S area sample; $A_{I.S.C.}$ area internal standard control; PC_C protein content control; A_C area control; $A_{I.S.S.}$ area internal standard sample; PC_S protein content sample.

(2 M, 10 mL). The reaction mixture was stirred under reflux for 12 h. After evaporating ethanol under reduced pressure, the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with a aqueous hydrochloric acid (2 M, 30 mL) and water (30 mL), dried over sodium sulphate, and evaporated under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 9:1) to afford ketone **12** as a colourless oil (242 mg, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.55–2.40 (m, 2H, H-5, H-6), 2.27–2.20 (m, 1H, H-5), 1.93–1.67 (m, 5H, H-1′, H-2, H-3, H-7), 1.55–1.46 (m, 1H, H-5′), 1.45–1.19 (m, 5H, H-1, H-2′, H-3′, H-6), 1.15–1.05 (m, 4H, H-2, H-4′, H-7), 1.06 (s, 3H, CH_3-3a), 1.01–0.96 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, *J* = 6.3 Hz), 0.86 (d, 3H, H-6′, *J* = 6.2 Hz), 0.85 (d, 3H, CH_3-5′, *J* = 6.2 Hz), 0.84 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 216.0 (CO), 60.8 (3a-C), 49.6 (7a-C), 47.0 (1-CH), 39.79 (5-CH_2), 38.0 (3-CH_2), 36.2 (7-CH_2), 35.3 (1′-CH), 31.5 (4′-CH_2), 28.9 (6-CH_2), 28.3 (5′-CH), 25.5 (2-CH_2), 24.6 (3′-CH_2), 23.2 (6′-CH_3), 22.9 (CH_3-5′), 21.8 (2′-CH_2), 19.9 (CH_3-3a), 19.1 (CH_3-7a), 18.2 (CH_3-1′). HRMS Found 278.4701 (Calcd 278.4727). IR (NaCl, film, cm^{-1}): 2931, 2862, 1723, 1451, 1379, 1105, 887, 860. $[\alpha]_D^{20}$ −42 (0.5; $CHCl_3$).

5.6.2. [(1*R*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-4-yloxy]-trimethylsilane (13)

To a stirred solution of Grundmann's ketone **11** (500 mg, 1.91 mmol) in anhydrous dichloromethane (10 mL) under nitrogen atmosphere was added 1,1,1,3,3,3-hexamethyldisilazane (335 μL, 2.05 mmol), lithium iodide (280 mg, 2.10 mmol) and trimethylsilyl chloride (500 μL, 4.12 mmol) at room temperature. The reaction mixture was obstructed from light and stirred for 24 h. Then triethylamine (2 mL) and a mixture of diethyl ether (50 mL) and a saturated aqueous solution of sodium bicarbonate (50 mL) were added. The organic layer was separated and the remaining aqueous layer was extracted with diethyl ether (2 × 40 mL). The combined organic extracts were washed once with an aqueous hydrochloric acid (1 M, 50 mL) and once with water (50 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to silica column chromatography (SCC) (petroleum ether/ethyl acetate 99:1) to afford the silyl enol ether **13** as a colourless oil (411 mg, 64%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22–2.07 (m, 1H, H-5), 2.03–1.91 (m, 1H, H-5), 1.90–1.81 (m, 1H, H-1′), 1.79–1.50 (m, 5H, H-3, H-6, H-7), 1.41–1.32 (m, 1H, H-5′), 1.31–1.09 (m, 4H, H-1, H-2, H-2′, H-6), 1.07–0.84 (m, 6H, H-2′, H-2, H-3′, H-4′), 0.77 (d, 3H, CH_3-1′, *J* = 6.6 Hz), 0.76–0.72 (m, 3H, H-6′, with underneath s, 3H, CH_3-7a at 0.75 ppm), 0.71 (d, 3H, CH_3-5′, *J* = 6.2 Hz), 0.00 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.1 (4-CH), 126.6 (3a-C), 55.8 (7a-C), 42.2 (1-CH), 38.1 (3-CH_2), 36.0 (5-CH_2), 34.5 (7-CH_2), 33.4 (1′-CH), 27.9 (4′-CH_2), 26.5 (6-CH_2), 26.1 (5′-CH), 22.3 (2-CH_2), 22.1 (2′-CH_2), 21.3 (3′-CH_2), 21.1 (CH_3-7a), 18.6 (6′-CH_3), 17.4 (CH_3-5′), 16.9 (CH_3-1′), 0.0 (3C, $Si(CH_3)_3$). HRMS Found 336.6389 (Calcd 336.6384). IR (NaCl, film, cm^{-1}): 3032, 2967, 2915, 1450, 1378, 890. $[\alpha]_D^{20}$ +13 (0.5; $CHCl_3$).

5.6.3. [(1*R*,3a*S*,4*R*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-7a-methylhexahydrocyclopropa[d]inden-4-yl-oxy]-trimethylsilane (14)

To a stirred solution of **13** (410 mg, 1.23 mmol) in anhydrous diethyl ether (20 mL) under nitrogen atmosphere was added

diethylzinc (1 M solution in hexanes, 4.20 mL, 4.20 mmol) and diiodomethane (362 μL, 4.50 mmol). The reaction mixture was stirred under reflux for 18 h and then pyridine (1.20 mL) was added dropwise. The resulting suspension was filtered and the filtrate was diluted with water (30 mL). After separating the organic layer, the remaining aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic extracts were washed once with an aqueous hydrochloric acid (1 M, 50 mL) and once with water (50 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to silica column chromatography (SCC) (petroleum ether/ethyl acetate 98:2) to afford the cyclopropane derivative **14** as a colourless oil (345 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00–1.80 (m, 2H, H-5), 1.72–1.62 (m, 1H, H-6), 1.55–1.47 (m, H-1′), 1.45–1.11 (m, 10H, H-1, H-2, H-2′, H-3, H-5′, H-6, H-7), 1.10–0.89 (m, 5H, H-2′, H-3′, H-4′), 0.78 (d, 3H, CH_3-1′, J = 6.5 Hz), 0.75 (d, 3H, H-6′, J = 6.0 Hz), 0.74 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.58 (s, 3H, CH_3-7a), 0.49 (d, 1H, CH_2-cyclopropane, J = 5.8 Hz), 0.22 (d, 1H, CH_2-cyclopropane, J = 5.8 Hz), 0.00 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 59.0 (4-CH), 57.9 (1-CH), 40.3 (3a-C), 38.1 (7a-C), 37.6 (5-CH_2), 34.6 (3-CH_2), 34.2 (6-CH_2), 32.5 (1′-CH), 31.2 (7-CH_2), 28.7 (CH_2-cyclopropane), 26.7 (4′-CH_2), 26.6 (5′-CH), 22.3 (2-CH_2), 21.3 (2′-CH_2), 21.1 (CH_3-7a), 19.3 (3′-CH_2), 17.8 (6′-CH_3), 17.7 (CH_3-5′), 16.7 (CH_3-1′), 0.0 (3C, $Si(CH_3)_3$). HRMS Found 350.6496 (Calcd 350.6538). IR (NaCl, film, cm^{-1}): 2960, 2910, 1457, 1370, 897, 863. $[\alpha]_D^{20}$ −19 (0.5; $CHCl_3$).

5.6.4. [(1*R*,3a*R*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yloxy]-trimethylsilane (15)

To a stirred solution of ketone **12** (874 mg, 3.13 mmol) in anhydrous THF (60 mL) under nitrogen atmosphere was added dropwise lithium diisopropylamide (2 M solution in hexane, 4.20 mL, 4.41 mmol) at −78 °C. The reaction mixture was stirred for 2 h and then trimethylsilyl chloride (0.55 mL, 4.82 mmol) was added dropwise. The reaction mixture was allowed to warm up to ambient temperature and was stirred for further 12 h. After evaporating THF under reduced pressure, the residual was taken up in diethyl ether (50 mL) and water (100 mL) was added. The biphasic mixture was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed once with a saturated aqueous solution of sodium bicarbonate (50 mL) and once with water (50 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 9:1) to afford the silyl enol ether **15** as a colourless oil (910 mg, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.61 (dd, 1H, H-5, J = 2.2 Hz, J = 5.3 Hz), 2.13–1.95 (m, 2H, H-6, H-7), 1.93–1.86 (m, 1H, H-6), 1.84–1.66 (m, 2H, H-3, H-2), 1.59–1.45 (m, 2H, H-1′, H-3), 1.41–1.30 (m, 4H, H-1, H-3′, H-5′), 1.29–1.22 (m, 2H, H-2, H-7), 1.21–1.04 (m, 3H, H-2′, H-3′), 1.04–0.97 (m, 1H, H-2′), 0.95 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.93 (s, 3H, CH_3-3a), 0.86 (d, 3H, H-6′, J = 5.8 Hz), 0.85 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.75 (s, 3H, CH_3-7a), 0.12 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.6 (4-C), 100.5 (5-CH), 50.8 (3a-C), 45.3 (7a-C), 45.2 (1-CH), 39.1 (6-CH_2), 35.8 (3-CH_2), 35.0 (1′-CH), 30.5 (7-CH_2), 28.7 (4′-CH_2), 27.6 (5′-CH), 26.3 (2-CH_2), 23.7 (3′-CH_2), 22.4 (CH_3-5′), 22.2 (6′-CH_3), 21.1 (CH_3-3a), 20.4 (2′-CH_2), 18.1 (CH_3-7a), 17.6 (CH_3-1′), 0.10 (3C, $Si(CH_3)_3$). HRMS Found 350.6514 (Calcd 350.6538). IR (NaCl, film, cm^{-1}): 2983, 2929, 1762, 1443, 1137, 876, 851, 711. $[\alpha]_D^{20}$ −27 (0.5; $CHCl_3$).

5.6.5. (1*R*,3a*R*,5*R*,7a*R*)-5-Bromo-1-((*R*)-1,5-di-methylhexyl)-3a,7a-dimethyloctahydroinden-4-one (16)

At 0 °C, to a stirred solution of **15** (910 mg, 2.62 mmol) in THF (40 mL) was added a mixture of *N*-bromosuccinimide (580 mg, 3.16 mmol) and sodium acetate (23.0 mg, 0.26 mmol), dissolved in THF (20 mL) and water (20 mL). The reaction mixture was allowed to warm up to room temperature and was stirred for 12 h. After evaporating THF under reduced pressure, a saturated aqueous solution of sodium bicarbonate (50 mL) was added. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with water (50 mL), dried over sodium sulphate, and evaporated under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 85:15) to afford ketone **16** as a colourless oil (850 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.84 (dd, 1H, H-5, J = 1.7 Hz, J = 4.7 Hz), 2.56–2.46 (m, 1H, H-6), 2.40–2.31 (m, 1H, H-7), 2.29–2.13 (m, 1H, H-3), 1.96–1.89 (m, 1H, H-2), 1.83–1.70 (m, 2H, H-1′, H-3), 1.46–1.41 (m, 1H, H-5′), 1.37–1.10 (m, 9H), 1.04 (s, 3H, CH_3-3a), 0.94–0.89 (m, 1H, H-2′), 0.84 (d, 3H, CH_3-1′, J = 6.2 Hz,), 0.82 (s, 3H, CH_3-7a), 0.78 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.76 (d, 3H, H-6′, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 207.8 (CO), 59.8 (3a-C), 46.8 (5-CH), 46.5 (7a-C), 45.8 (1-CH), 37.9 (6-CH_2), 34.3 (3-CH_2), 33.3 (7-CH_2), 30.1 (1′-CH), 28.4 (4′-CH_2), 26.5 (2′-CH_2), 25.4 (5′-CH), 23.9 (2-CH_2), 23.2 (3′-CH_2), 22.8 (CH_3-3a), 21.4 (6′-CH_3), 21.1 (CH_3-5′), 17.2 (CH_3-7a), 16.4 (CH_3-1′). HRMS Found 356.1714 (Calcd 356.1715). IR (NaCl, film, cm^{-1}): 2955, 2868, 1718, 1466, 1432, 1382, 1201, 868, 667. $[\alpha]_D^{20}$ −26 (0.5; $CHCl_3$).

5.6.6. General procedure A (nucleophilic substitution at bromoketone 16)

To a stirred solution of bromoketone **16** (150 mg, 0.42 mmol) in DMF (2 mL), the required amine (5–20 equiv) was added under nitrogen atmosphere. The solution was stirred under reflux for 12 h and then a saturated aqueous solution of sodium bicarbonate (20 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The residue was subjected to SCC as specified below to afford pure compounds **17a–e** as colourless oils.

5.6.6.1. (1*R*,3a*R*,5*S*,7a*R*)-5-Dimethylamino-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-one (17a).

Ketone **16** (150 mg, 0.42 mmol) and *N*,*N*-dimethylamine (2 M solution in THF, 4.20 mL, 8.41 mmol) in DMF (2 mL) were treated as described in procedure A. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 10:0.5:0.1) to afford **17a** (68 mg, 50%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.32 (dd, 1H, H-5, J = 6.1 Hz, J = 12.3 Hz), 2.55–2.43 (m, 1H, H-6), 2.38 (bs, 6H, $N(CH_3)_2$), 2.08–1.92 (m, 2H, H-3, H-7), 1.92–1.67 (m, 3H, H-1′, H-2, H-6), 1.53–1.43 (m, 1H, H-5′), 1.40–1.16 (m, 5H, H-1, H-2, H-3, H-3′), 1.16–1.01 (m, 4H, with underneath s, 3H, CH_3-3a at 1.09 ppm), 0.99–0.92 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 5.8 Hz), 0.85 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.84–0.80 (m, 3H, H-6′, with underneath s, 3H, CH_3-7a at 0.83 ppm). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.5 (CO), 67.6 (3a-C), 61.1 (5-CH), 49.6 (7a-C), 46.5 (1-CH), 41.6 (2C, $N(CH_3)_2$), 39.4 (6-CH_2), 35.9 (3-CH_2), 35.0 (7-CH_2), 30.5 (1′-CH), 29.1 (4′-CH_2), 28.0 (2′-CH_2), 25.3 (5′-CH), 24.2 (2-CH_2), 24.1 (3′-CH_2), 22.8 (6′-CH_3), 22.6 (CH_3-5′), 19.9 (CH_3-3a), 18.8 (CH_3-7a), 17.7 (CH_3-1′). HRMS Found 321.3060 (Calcd 321.3032). IR (NaCl, film, cm^{-1}): 2987, 2870, 1709, 1466, 1103, 705. $[\alpha]_D^{20}$ −18 (0.5; $CHCl_3$).

5.6.6.2. (1*R*,3a*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-(4-methylpiperazine-1-yl)-octahydroinden-4-one (17b).

Ketone **16** (150 mg, 0.42 mmol) and 1-methylpiperazine (0.33 mL, 2.94 mmol) in DMF (2 mL) were treated as described in procedure A. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 7:3:0.3) to afford **17b** (114 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.31 (dd, 1H, H-5, J = 6.2 Hz, J = 12.3 Hz,), 2.83–2.51 (m, 8H), 2.47–2.41 (m, 1H, H-6), 2.39 (s, 3H, N-CH_3), 2.07–1.95 (m, 2H, H-3, H-7), 1.85–1.64 (m,

3H, H-1′, H-2, H-6) 1.53–146 (m, 1H, H-5′), 1.39–1.16 (m, 6H), 1.15–0.97 (m, 3H, H-3′, H-4′), 1.05 (s, 3H, CH_3-3a) 0.95–0.89 (m, 1H, H-2′), 0.88 (d, 3H, CH_3-1′, J = 6.1 Hz), 0.84 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.83 (d, 3H, H-6′, J = 5.8 Hz), 0.80 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.1 (CO), 67.7 (N-CH_3), 65.9 (3a-C), 61.0 (2C, 3″-CH_2, 5″-CH_2), 55.1 (2C, 2″-CH_2, 6″-CH_2), 49.9 (5-CH_2), 46.5 (7a-C), 45.7 (1-CH), 39.4 (6-CH_2), 35.8 (3-CH_2), 35.1 (7-CH_2), 29.3 (1′-CH), 28.0 (4′-CH_2), 25.4 (2′-CH_2), 24.3 (5′-CH), 23.6 (2-CH_2), 22.8 (3′-CH_2), 22.6 (CH_3-3a), 19.9 (6′-CH_3), 18.8 (CH_3-5′), 17.8 (CH_3-7a), 15.3 (CH_3-1′). HRMS Found 376.3437 (Calcd 376.3454). IR (NaCl, film, cm^{-1}): 3302, 2955, 2794, 2360, 1712, 1635, 1456, 1383, 1286, 767. $[\alpha]_D^{20}$ −23 (0.5; $CHCl_3$).

5.6.6.3. (1*R*,3a*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-[(pyridin-3-ylmethyl)-amino]-octahydroinden-4-one (17c).

Ketone **16** (150 mg, 0.42 mmol) and 3-(aminomethyl)pyridine (0.31 mL, 2.94 mmol) in DMF (2 mL) were treated as described in procedure A. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 7:3:0.1) to afford **17c** (112 mg, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (s, 1H, H-2‴), 8.49 (d, 1H, H-6‴, J = 3.8 Hz), 7.76 (d, 1H, H-4‴, J = 7.8 Hz), 7.25 (dd, 1H, H-5‴, J = 3.8 Hz, J = 7.8 Hz), 3.84 (d, 1H, H-1″, J = 13.3 Hz), 3.76 (d, 1H, H-1″, J = 13.3 Hz), 3.49–3.36 (m, 1H, H-5), 2.47–2.42 (m, 1H, H-6), 2.19–2.05 (m, 1H, H-7), 1.92 (m, 1H, H-3), 1.82–1.60 (m, 3H, H-1′, H-2, H-6), 1.47 (m, 1H, H-5′), 1.38–1.04 (m, 9H), 1.02 (s, 3H, CH_3-3a), 0.95–0.90 (m, 1H, H-2′), 0.87 (d, 3H, CH_3-1′, J = 6.0 Hz), 0.80 (s, 3H, CH_3-7a), 0.76 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.74 (d, 3H, H-6′, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 214.2 (CO), 149.7 (6‴-CH), 148.6 (2‴-CH), 136.1(4‴-CH), 135.5 (3‴-CH), 123.5 (5‴-CH), 61.3 (1″-CH_2), 60.4 (3a-C), 50.0 (5-CH), 49.3 (7a-C), 46.5 (1-CH), 39.4 (6-CH_2), 35.9 (3-CH_2), 35.0 (7-CH_2), 30.2 (1′-CH), 30.1 (2′-CH_2), 29.2 (4′-CH_2), 28.0 (5′-CH), 25.3 (2-CH_2), 24.3 (3′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 19.8 (CH_3-3a), 18.8 (CH_3-7a), 17.8 (CH_3-1′). HRMS Found 384.6111 (Calcd 384.6103). IR (NaCl, film, cm^{-1}): 3444, 3012, 2958, 2901, 1704, 1469, 1424, 1382, 1026, 713. $[\alpha]_D^{20}$ −22 (0.5; $CHCl_3$).

5.6.6.4. (1*R*,3a*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-(2,6-dimethylmorpholine-4-yl)-3a,7a-dimethyloctahydroinden-4-one (17d).

Ketone **16** (150 mg, 0.42 mmol) and 2,6-dimethylmorpholine (0.36 mL, 2.94 mmol) in DMF (2 mL) were treated as described in procedure A. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **17d** (98 mg, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.91–3.79 (m, 2H, H-2″, H-6″), 3.32 (dd, 1H, H-5, J = 6.1 Hz, J = 12.3 Hz,), 2.82–2.69 (m, 2H, H-6, H-7), 2.49–2.38 (m 1H, H-2), 2.20–1.93 (m, 3H, H-3, H-3″, H-5″), 1.85–1.67 (m, 3H, H-3″, H-5″, H-6), 1.55–1.40 (m, 1H, H-1′), 1.39–1.16 (m, 5H, H-2′, H-3, H-3′, H-7), 1.14–1.03 (m, 10H, H-2, H-2′, H-4′, CH_3-2″, CH_3-6″, with underneath s, 3H, CH_3-3a at 1.09 ppm), 0.91–0.87 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.91 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.91–0.85 (m, 3H, H-6′, with underneath s, 3H, CH_3-7a at 0.87 ppm). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.2 (CO), 71.6 (2C, 2″-CH, 6″-CH), 67.6 (3a-C), 61.1 (5-CH), 55.0 (7a-C), 49.9 (1-CH), 46.5 (6-CH_2), 39.4 (3-CH_2), 35.9 (2C, 3″-CH_2, 5″-CH_2), 35.1 (7-CH_2), 30.5 (1′-CH), 29.2 (4′-CH_2), 28.0 (2′-CH_2), 25.4 (5′-CH), 24.3 (2-CH_2), 23.8 (3′-CH_2), 22.8 (6′-CH_3), 22.6 (CH_3-5′), 19.9 (CH_3-3a), 19.2 (CH_3-6″), 19.1 (CH_3-2″), 18.8 (CH_3-7a), 17.7 (CH_3-1′). HRMS Found 391.3436 (Calcd 391.3450). IR (NaCl, film, cm^{-1}): 2990, 2874, 1722, 1466, 1219, 1001, 723. $[\alpha]_D^{20}$ −31 (0.5; $CHCl_3$).

5.6.6.5. (1*R*,3a*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-(2,3-dimethylphenylamino)-3a,7a-dimethyloctahydroinden-4-one (17e).

Ketone **16** (150 mg, 0.42 mmol) and 2,3-dimethylaniline (0.68 mL, 5.58 mmol) in DMF (2 mL) were treated as described in procedure A. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.3) to afford **17e** (137 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.00 (t, 1H, H-5″, J = 7.8 Hz), 6.59 (d, 1H, H-6″, J = 7.4 Hz), 6.42 (d, 1H, H-4″, J = 8.0 Hz), 4.17 (dd, 1H, H-5-H, J = 6.5 Hz, J = 12.3 Hz), 2.59–2.41 (m, 2H, H-6, H-7), 2.28 (s, 3H, CH_3-2″), 2.14 (s, 3H, CH_3-3″), 2.04–1.78 (m, 3H, H-1′, H-2, H-3), 1.73–1.56 (m, 1H, H-3), 1.57–1.43 (m, 2H, H-1, H-5′), 1.43–1.17 (m, 5H, H-2, H-2′, H-3′, H-6, H-7), 1.16–1.07 (m, 6H, CH_3-3a, H-3′, H-4′), 1.02–0.95 (m, 1H, H-2′), 0.94–0.88 (m, 3H, CH_3-1′, with underneath s, 3H, CH_3-7a at 0.87 ppm), 0.87 (d, 3H, CH_3-5′, J = 5.8 Hz,), 0.85 (d, 3H, H-6′, J = 5.8 Hz,). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 212.2 (CO), 144.9 (1″-C), 137.1 (2″-C), 126.1 (6″-CH), 121.1 (3″-C), 119.5 (4″-CH), 107.9 (5″-CH), 60.4 (3a-C), 58.1 (5-CH), 50.4 (7a-C), 46.6 (1-CH), 39.4 (6-CH_2), 35.9 (3-CH_2), 35.1 (1-CH), 30.4 (7-CH_2), 29.8 (4′-CH_2), 29.3 (2′-CH_2), 28.0 (5′-CH), 25.4 (2-CH_2), 24.4 (3′-CH_2), 22.9 (CH_3-3″), 22.6 (CH_3-2″), 20.8 (6′-CH_3), 20.1 (CH_3-5′), 18.9 (CH_3-3a), 17.9 (CH_3-7a), 12.6 (CH_3-1′). HRMS Found 397.3373 (Calcd 397.3345). IR (NaCl, film, cm^{-1}): 3412, 3003, 2987, 2866, 1780, 1723, 1489, 1372, 997, 789, 742. $[\alpha]_D^{20}$ −42 (0.5; $CHCl_3$).

5.6.7. General procedure B (reduction of ketones 17a–e)

To a stirred solution of the required ketone **17a–e** in anhydrous THF, lithium aluminium hydride (3–5 equiv) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, then quenched with a saturated aqueous solution of sodium bicarbonate (3 mL) and diluted with water (20 mL). The biphasic mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to SCC as specified below to afford amino alcohols **18a–e** as colourless oils.

5.6.7.1. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-Dimethylamino-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (18a).

Ketone **17a** (150 mg, 0.47 mmol) and lithium aluminium hydride (60.0 mg, 1.54 mmol) in anhydrous THF (2 mL) were treated as described in procedure B. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 8:2:0.3) to afford **18a** (140 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.49 (d, 1H, H-4, J = 1.9 Hz), 2.37–2.27 (m, 1H, H-1′), 2.25 (s, 6H, N(CH_3)2), 2.03–1.76 (m, 4H, H-3, H-5, H-6, H-7), 1.65–1.38 (m, 4H, H-1, H-2, H-3, H-5′), 1.37–1.18 (m, 5H, H-2, H-2′, H-3′, H-6, H-7), 1.14–1.06 (m, 3H, H-3′, H-4′), 1.04–0.95 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.5 Hz), 0.87–0.82 (m, 6H, CH_3-5′, H-6′), 0.82 (s, 3H, CH_3-3a), 0.71 (s, 3H, CH_3-3a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.9 (4-CH), 64.5 (5-CH), 48.3 (3a-C), 46.8 (1-CH), 43.8 (7a-C), 42.3 (2C, N(CH_3)$_2$), 39.2 (6-CH_2), 36.1 (3-CH_2), 35.3 (1′-CH), 34.5 (7-CH_2), 31.3 (4′-CH_2), 28.8 (2′-CH_2), 27.6 (5′-CH), 23.8 (2-CH_2), 22.5 (6′-CH_3), 22.2 (CH_3-5′), 20.9 (3′-CH_2), 20.1 (CH_3-3a), 19.4 (CH_3-7a), 18.6 (CH_3-1′). HRMS Found 323.3201 (Calcd 323.3188). IR (NaCl, film, cm^{-1}): 3412, 3017, 2870, 1452, 1353, 1237, 1002, 773. $[\alpha]_D^{20}$ +11 (0.5; $CHCl_3$).

5.6.7.2. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-(4-methylpiperazine-1-yl)-octahydroinden-4-ol (18b).

Ketone **17b** (140 mg, 0.37 mmol) and lithium aluminium hydride (72.0 mg, 1.86 mmol) in anhydrous THF (2 mL) were treated as described in procedure B. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 5:5:0.4) to afford **18b** (124 mg, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.49 (d, 1H, H-4, J = 1.6 Hz), 2.41 (m, 8H, H-2″, H-3″, H-5″, H-6″), 2.35–2.28 (m, 1H, H-5′), 2.26 (s, 3H, NCH_3), 2.22–2.17 (m, 1H, H-5), 1.99–1.77 (m, 3H, H-3, H-6, H-7), 1.63–1.53 (m, 1H, H-2), 1.53–1.39 (m, 2H, H-3, H-5′), 1.38–1.16 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.15–1.06 (m, 3H, H-3′, H-4′), 1.02–0.95 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.86 (d, 3H, CH_3-5′,

J = 6.1 Hz,), 0.84 (d, 3H, H-6′, J = 6.1 Hz), 0.82 (s, 3H, CH_3-3a), 0.72 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.6 (4-CH), 62.9 (5-CH), 55.6 (2C, 3″-CH_2, 5″-CH_2), 49.3 (2C, 2″-CH_2, 6″-CH_2), 48.4 (3a-C), 47.1 (1-CH), 45.8 (NCH_3), 44.2 (7a-C), 39.4 (6-CH_2), 36.3 (3-CH_2), 35.6 (1′-CH), 34.8 (2′-CH_2), 31.4 (5-CH_2), 29.1 (7-CH_2), 27.8 (5′-CH), 24.2 (2-CH_2), 22.7 (6′-CH_3), 22.4 (CH_3-5′), 21.1 (CH_3-3a), 19.6 (2C, CH_3-7a, 3′-CH_2), 18.8 (CH_3-1′). HRMS Found 378.3596 (Calcd 378.3610). IR (NaCl, film, cm^{-1}): 3398, 3001, 2987, 2856, 1501, 1372, 997. $[\alpha]_D^{20}$ +17 (0.5; $CHCl_3$).

5.6.7.3. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-[(pyridine-3-ylmethyl)-amino]-octahydroinden-4-ol (18c). Ketone **17c** (132 mg, 0.34 mmol) and lithium aluminium hydride (39.0 mg, 1.02 mmol) in anhydrous THF (2 mL) were treated as described in procedure B. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 8:2:0.3) to afford **18c** (125 mg, 96%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (s, 1H, H-2‴), 8.51 (d, 1H, H-6‴, J = 3.3 Hz), 7.66 (d, 1H, H-4‴, J = 7.8 Hz), 7.30–7.23 (m, 1H, H-5‴), 3.83 (d, 1H, H-1″, J = 13.3 Hz), 3.74 (d, 1H, H-1″, J = 13.3 Hz), 3.46 (d, 1H, 4-4, J = 2.6 Hz), 2.80–2.65 (m, 1H, H-5), 2.39–2.28 (m, 1H, H-1′), 2.01–1.90 (m, 1H, H-6), 1.88–1.78 (m, 2H, H-3, H-7), 1.78–1.65 (m, 1H, H-2), 1.58–1.43 (m, 2H, H-3, H-5′), 1.36–1.20 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.17–1.08 (m, 3H, H-3′, H-4′), 1.05–0.97 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.86 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.86–0.83 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.84 ppm), 0.73 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.5 (2‴-CH), 148.6 (6‴-CH), 135.8 (4‴-CH), 135.4 (3‴-C), 123.4 (5‴-CH), 75.7 (4-CH), 56.8 (5-CH), 48.5 (1″-CH_2), 47.9 (1-CH), 47.2 (3a-C), 44.9 (7a-C), 39.5 (6-CH_2), 36.4 (3-CH_2), 35.5 (1′-CH), 34.8 (7-CH_2), 31.3 (4′-CH_2), 29.1 (2′-CH_2), 27.9 (5′-CH), 24.2 (2-CH_2), 23.0 (3′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 19.9 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 386.3289 (Calcd 386.3297). IR (NaCl, film, cm^{-1}): 3411, 3007, 2963, 2887, 1499, 1713, 1312, 997, 739, 699. $[\alpha]_D^{20}$ +37 (0.5; $CHCl_3$).

5.6.7.4. (1*R*,3a*R*,4*RS*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-(2,6-dimethylmorpholine-4-yl)-3a,7a-di-methyl-octahydroinden-4-ol (epimeric mixture) (18d). Ketone **17d** (140 mg, 0.36 mmol) and lithium aluminium hydride (42.0 mg, 1.08 mmol) in anhydrous THF (2 mL) were treated as described in procedure B. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine7:3:0.3) to afford **18d** (138 mg, 98%). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.71–3.45 (m, 3H, H-2″, H-4, H-6″), 2.93 (dd, 1.4H, H-3″, H-5″, J = 6.7 Hz, J = 11.4 Hz), 2.85 (dd, 1.4H, H-3″, H-5″, J = 6.3 Hz, J = 11.1 Hz), 2.60 (dd, 0.6H, H-3″, H-5″, J = 6.6 Hz, J = 11.4 Hz), 2.44 (dd, 0.6H, H-3″, H-5″, J = 6.2 Hz, J = 11.5 Hz), 2.39–2.25 (m, 1H, H-1′), 2.18–2.10 (m, 0.7H, H-5), 2.04–1.75 (m, 4.3H, H-3, H-5, H-6, H-7), 1.64–1.11 (m, 17H), 1.05–0.94 (m, 1H, H-2′) 0.92 (d, 0.9H, CH_3-1′, J = 5.9 Hz), 0.91 (d, 2.1H, CH_3-1′, J = 5.9 Hz), 0.87–0.81 (m, 9H, CH_3-3a, CH_3-5′, H-6′), 0.73 (s, 0.9H, CH_3-7a), 0.71 (s, 2.1H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.6 (4-CH), 72.4 (2″-CH), 72.4 (6″-CH), 72.3 (2″-CH), 72.0 (6″-CH), 69.0 (4-CH), 65.3 (5-CH), 63.1 (5-CH), 58.3 (3a-C), 56.4 (3a-C), 55.2 (1-CH), 50.8 (1-CH), 50.7 (7a-C), 48.5 (7a-C), 47.3 (6-CH_2), 46.7 (6-CH_2), 46.2 (3-CH_2), 44.4 (3-CH_2), 39.6 (2′-CH_2), 39.5 (2′-CH_2), 36.5 (2C, 3″-CH_2, 5″-CH_2), 36.3 (2C, 3″-CH_2, 5″-CH_2), 36.1 (1′-CH), 35.8 (1′-CH), 34.9 (4′-CH_2), 33.2 (4′-CH_2), 31.5 (7-CH_2), 31.3 (7-CH_2), 29.3 (5′-CH), 28.0 (5′-CH), 27.9 (2-CH_2), 26.9 (2-CH_2), 24.4 (3′-CH_2), 24.3 (3′-CH_2), 22.9 (CH_3-3a), 22.8 (CH_3-3a), 22.6 (2C, CH_3-2″, CH_3-6″), 21.2 (2C, CH_3-2″, CH_3-6″), 19.7 (6′-CH_3), 19.3 (6′-CH_3), 19.2 (CH_3-5′), 19.0 (CH_3-5′), 18.9 (CH_3-7a), 18.9 (CH_3-7a), 18.5 (CH_3-1′), 17.4 (CH_3-1′). HRMS Found 393.3603 (Calcd 393.3606). IR (NaCl, film, cm^{-1}): 3423, 3392, 3032, 2987, 2897, 1541, 1372, 1132, 997.

5.6.7.5. (1*R*,3a*R*,4*RS*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-(2,3-dimethylphenylamino)-3a,7a-dimethyl-octahydroinden-4-ol (epimeric mixture) (18e). Ketone **17e** (170 mg, 0.42 mmol) and lithium aluminium hydride (52.0 mg, 1.28 mmol) in anhydrous THF (2 mL) were treated as described in procedure B. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 6:4:0.3) to afford **18e** (163 mg, 97%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.05–6.97 (m, 1H, H-5″), 6.67 (d, 0.85H, H-6″, J = 8.2 Hz), 6.64 (d, 0.85H, H-4″, J = 7.5 Hz), 6.58 (d, 0.15H, H-4″, J = 7.5 Hz), 6.51 (d, 0.15H, H-6″, J = 8.2 Hz), 3.60 (d, 0.15H, H-4, J = 10.3 Hz), 3.54–3.45 (m, 1H, H-4, H-5), 3.29 (ddd, 0.85H, H-5, J = 4.2 Hz, J = 7.4 Hz, J = 10.6 Hz), 2.28 (s, 2.55H, CH_3-2″), 2.27 (s, 0.45H, CH_3-2″), 2.08 (s, 2.55H, CH_3-3″), 2.06 (s, 0.45H, CH_3-3″), 2.03–1.89 (m, 4H, H-1′, H-6, H-7), 1.87–1.72 (m, 2H, H-3, H-2), 1.61–1.47 (m, 1H, H-5), 1.45–1.27 (m, 7H), 1.23–1.06 (m, 3H, H-3′, H-4′), 1.07–1.00 (m, 1H, H-2′), 0.99 (s, 0.45H, CH_3-3a), 0.97 (s, 2.55H, CH_3-3a), 0.96–0.90 (m, 3H, CH_3-1′), 0.89–0.81 (m, 6H, CH_3-5′, H-6′), 0.80 (s, 2.55H, CH_3-7a), 0.77 (s, 0.45H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.7 (1″-C), 145.0 (1″-C), 137.0 (2″-C), 136.9 (2″-C), 126.2 (6″-CH), 126.1 (6″-CH), 121.9 (3″-C), 120.9 (3″-C), 120.4 (4″-CH), 119.5 (4″-CH), 110.3 (5″-CH), 108.9 (5″-CH), 77.3 (4-CH), 75.3 (4-CH), 56.4 (5-CH), 53.1 (5-CH), 51.3 (3a-C), 49.6 (3a-C), 47.6 (1-CH), 47.0 (1-CH), 46.4 (7a-C), 45.1 (7a-C), 39.6 (6-CH_2), 39.5 (6-CH_2), 36.6 (3-CH_2), 36.5 (3-CH_2), 36.0 (1′-CH), 35.8 (1′-CH), 35.0 (7-CH_2), 32.8 (7-CH_2), 32.0 (4′-CH_2), 31.1 (4′-CH_2), 29.1 (5′-CH), 28.0 (5′-CH), 27.9 (2′-CH_2), 27.5 (2′-CH_2), 26.8 (2-CH_2), 26.7 (2-CH_2), 24.4 (3′-CH_2), 24.3 (3′-CH_2), 22.9 (CH_3-2″), 22.8 (CH_3-2″), 22.6 (CH_3-3″), 21.5 (CH_3-3″), 20.9 (CH_3-3a), 20.6 (CH_3-3a), 20.0 (6′-CH_3), 19.1 (6′-CH_3), 18.9 (CH_3-5′), 18.7 (CH_3-5′), 15.7 (CH_3-7a), 14.0 (CH_3-7a), 12.9 (1′-CH_3), 12.7 (1′-CH_3). HRMS Found 399.3483 (Calcd 393.3501). IR (NaCl, film, cm^{-1}): 3412, 3307, 3010, 2962, 1723, 1412, 1272, 983, 791, 733.

5.6.8. (1*R*,3a*R*,4*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (19)

To a stirred solution of the ketone **12** (500 mg, 1.82 mmol) in anhydrous THF (30 mL), lithium aluminium hydride (215 mg, 5.40 mmol) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h, then quenched by dropwise addition of a saturated aqueous solution of sodium bicarbonate (15 mL) and diluted with water (30 mL). The biphasic mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with water (100 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 9:1) to afford alcohol **19** (505 mg, 99%) as a white solid. Mp 151 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 3.51 (dd, 1H, H-4, J = 3.3 Hz, J = 5.4 Hz), 2.11–1.99 (m, 1H, H-5), 1.89–1.78 (m, 1H, H-6), 1.74–1.60 (m, 4H, H-2, H-3, H-5, H-7), 1.59–1.53 (m, 1H, H-1′), 1.51–1.45 (m, 1H, H-5′), 1.45–1.31 (m, 6H, H-1, H-2, H-3, H-3′, H-6, H-7), 1.24–1.05 (m, 4H, H-2′, H-3′, H-4′), 1.04–0.95 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.88 (s, 3H, CH_3-3a), 0.86 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.85 (d, 3H, H-6′, J = 6.2 Hz), 0.79 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 77.1 (4-CH), 50.1 (3a-C), 49.0 (5-CH_2), 45.6 (7a-C), 39.6 (1-CH), 36.1 (3-CH_2), 35.5 (1′-CH), 35.3 (6-CH_2), 33.0 (7-CH_2), 30.4 (4′-CH_2), 28.4 (2′-CH_2), 28.0 (5′-CH), 24.3 (2-CH_2), 22.9 (3′-CH_2), 22.6 (6′-CH_3), 21.9 (CH_3-5′), 19.9 (CH_3-3a), 19.6 (CH_3-7a), 17.3 (CH_3-1′). Anal. Cald: C, 81.36; H, 12.92. Found: C, 81.13; H, 12.93. IR (NaCl, film, cm^{-1}): 3448, 2954, 2870, 1467, 1304, 735. $[\alpha]_D^{20}$ +9 (0.5; $CHCl_3$).

5.6.9. (1*R*,3*R*,3a*R*,7a*S*)-3-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-2,3,3a,6,7,7a-hexahydro-1H-indene (20)

To a stirred solution of **19** (500 mg, 1.79 mmol) in anhydrous pyridine (4 mL), phosphorous oxychloride (0.50 mL, 5.40 mmol)

was added dropwise in a careful manner. The resulting mixture was stirred at room temperature for 30 min. After cooling down to −10 °C the excess of phosphorous oxychloride was quenched slowly by dropwise addition of a saturated aqueous solution of sodium bicarbonate (10 mL). The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (50 mL), water (50 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 95:5) to afford **20** (369 mg, 78%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.43 (d, 1H, H-4, J = 3.7 Hz), 5.27 (ddd, 1H, H-5, J = 3.6 Hz, J = 6.4 Hz, J = 7.2 Hz), 2.07–1.98 (m, 1H, H-6), 1.95–1.90 (m, 1H, H-6), 1.89–1.82 (m, 1H, H-7), 1.78–1.70 (m, 2H, H-1′, H-3), 1.59–1.47 (m, 2H, H-5′, H-7), 1.29–1.23 (m, 4H, H-1, H-2, H-3), 1.18–1.10 (m, 5H, H-2′, H-3′, H-4′), 1.03–0.98 (m, 1H, H-2′), 0.95 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.88 (s, 3H, CH_3-3a), 0.86 (d, 3H, CH_3-5′, J = 6.5 Hz), 0.85 (d, 3H, H-6′, J = 6.5 Hz), 0.75 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.0 (4-CH), 121.6 (5-CH), 45.6 (3a-C), 44.5 (6-CH_2), 42.5 (7a-C), 40.8 (1-CH), 38.1 (7-CH_2), 34.8 (3-CH_2), 34.1 (1′-CH), 27.8 (4′-CH_2), 26.6 (2′-CH_2), 25.1 (5′-CH), 22.8 (2-CH_2), 22.1 (3′-CH_2), 21.4 (CH_3-3a), 21.1 (CH_3-5′), 21.0 (6′-CH_3), 17.0 (CH_3-7a), 16.6 (CH_3-1′). HRMS Found 262.4815 (Calcd 262.4830). IR (NaCl, film, cm^{-1}): 2980, 2873, 1465, 1381, 851, 720. $[\alpha]_D^{20}$ −46 (0.5; $CHCl_3$).

5.6.10. (1a*R*,3a*R*,4*R*,6a*R*,6b*S*)-3a,6a-Dimethyl-4-((*R*)-1,5-dimethylhexyl)-octahydro-1a*H*-indeno[5,4-*b*]-oxirene (21)

Sodium bicarbonate (82.0 mg, 0.98 mmol) and 3-chloroperbenzoic acid (300 mg, 0.84 mmol) were suspended in dichloromethane (5 mL) at 5 °C, and a solution of **20** (200 mg, 0.76 mmol) in dichloromethane (2 mL) was added to the suspension under nitrogen atmosphere. The resulting mixture was allowed to warm up to ambient temperature and was stirred for 2 h. The excess of 3-chloroperbenzoic acid was quenched with an aqueous 5% solution of sodium thiosulphate (4 mL). The reaction mixture was diluted with water and extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with water (50 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 97:3) to afford **21** (198 mg, 93%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.22–3.18 (m, 1H, H-5), 2.70 (d, 1H, H-4, J = 3.8 Hz), 1.90–1.82 (m, 2H, H-6, H-7), 1.81–1.72 (m, 1H, H-3), 1.70–1.61 (m, 2H, H-1′, H-3), 1.59–1.44 (m, 2H, H-6, H-2), 1.41–1.20 (m, 6H, H-1, H-2, H-2′, H-3, H-3′, H-7), 1.18–1.04 (m, 3H, H-3′, H-4′), 1.02–0.97 (m, 1H, H-2′), 0.97 (s, 3H, CH_3-3a), 0.93 (d, 3H, CH_3-1′, J = 6.7 Hz), 0.86 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.85 (d, 3H, H-6′, J = 5.8 Hz), 0.65 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 62.6 (4-CH), 54.3 (5-CH), 46.7 (1-CH), 43.7 (3a-C), 43.2 (7a-C), 39.5 (6-CH_2), 36.6 (3-CH_2), 35.9 (7-CH_2), 34.1 (1′-CH), 28.0 (5′-CH), 26.2 (4′-CH_2), 25.2 (2′-CH_2), 24.5 (2-CH_2), 22.8 (6′-CH_3), 22.6 (CH_3-5′), 21.4 (3′-CH_2), 19.6 (CH_3-3a), 18.7 (CH_3-7a), 18.0 (CH_3-1′). Anal. Calcd: C, 81.95; H, 12.31. Found: C, 81.99; H, 12.34. IR (NaCl, film, cm^{-1}): 2943, 2870, 2830, 1412, 1381, 851, 723. $[\alpha]_D^{20}$ +31 (0.5; $CHCl_3$).

5.6.11. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-5-Azido-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (22)

In a sealable microwave tube, epoxide **21** (100 mg, 0.36 mmol) was dissolved in a mixture of DMF (2 mL) and water (0.5 mL). Sodium azide (233 mg, 3.64 mmol) was added and the tube was closed under nitrogen atmosphere. The reaction mixture was stirred under microwave irradiation (150 W, 4 psi) at 130 °C for 2 h. After cooling a saturated aqueous solution of sodium bicarbonate (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (30 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (petroleum ether/ethyl acetate 9:1) to afford **22** (86 mg, 81%) as a white resin. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.40 (d, 1H, H-4, J = 10.4 Hz), 3.33 (ddd, 1H, H-5, J = 4.5 Hz, J = 7.6 Hz, J = 10.9 Hz), 1.92–1.78 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.71–1.59 (m, 1H, H-3), 1.56–1.47 (m, 1H, H-5′), 1.44–1.20 (m, 6H, H-1, H-2, H-3′, H-6, H-7), 1.16–1.07 (m, 3H, H-2′, H-4′), 1.03–0.95 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.89–0.84 (m, 3H, CH_3-5′, with underneath s, 3H, CH_3-3a at 0.86 ppm), 0.85 (d, 3H, H-6′, J = 6.4 Hz), 0.76 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 74.7 (4-CH), 64.3 (5-CH), 51.6 (3a-Ca), 46.9 (7a-C), 46.2 (1-CH), 39.5 (6-CH_2), 36.5 (3-CH_2), 36.0 (1-CH), 32.7 (7-CH_2), 30.4 (4′-CH_2), 28.1 (5′-CH), 26.6 (2′-CH_2), 25.5 (2-CH_2), 24.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 18.9 (CH_3-3a), 18.5 (CH_3-7a), 13.8 (CH_3-1′). Anal. Cald: C, 70.98; H, 10.97; N, 13.07. Found: C, 71.33; H, 11.06; N, 13.05. IR (NaCl, film, cm^{-1}): 3473, 2985, 2872, 2100, 1468, 1382, 1023, 735. $[\alpha]_D^{20}$ −17 (0.5; $CHCl_3$).

5.6.12. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-5-Amino-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (23)

To a stirred solution of azide **22** (100 mg, 0.31 mmol) in anhydrous THF (5 mL), lithium aluminium hydride (40.0 mg, 1.04 mmol) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, then quenched with a saturated aqueous solution of sodium bicarbonate (3 mL) and diluted with water (20 mL). The biphasic mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (dichloromethane/methanol/triethylamine 9:1:0.2) to afford amino alcohol **23** (91 mg, 99%) as a white resin. Mp 104 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.26 (d, 1H, H-4, J = 10.3 Hz), 2.72–2.58 (m, 2H, H-1′, H-5), 2.52 (bs, 3H, NH_2, OH), 1.99–1.83 (m, 3H, H-3, H-6, H-7), 1.79–1.73 (m, 1H, H-2), 1.70–1.62 (m, 1H, H-3), 1.52–1.42 (m, 2H, H-5′, H-6), 1.38–1.27 (m, 5H, H-1, H-2′, H-2, H-3′, H-7), 1.18–1.05 (m, 3H, H-3′, H-4′), 1.00–0.93 (m, 1H, H-2′), 0.91 (d, J = 6.5 Hz, 3H, CH_3-1′), 0.86 (d, J = 6.6 Hz, 3H, CH_3-5′), 0.85–0.79 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.82 ppm), 0.75 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 76.5 (4-CH), 52.7 (5-CH), 51.1 (3a-C), 47.2 (1-CH), 46.3 (7a-C), 39.6 (6-CH_2), 36.5 (3-CH_2), 36.0 (7-CH_2), 32.8 (1′-CH), 31.0 (4′-CH_2), 29.9 (2′-CH_2), 28.1 (5′-CH), 26.7 (2-CH_2), 24.3 (3′-CH_2), 22.9 (6′-CH_3), 22.7 (CH_3-5′), 19.0 (CH_3-3a), 18.8 (CH_3-7a), 14.1 (CH_3-1′). HRMS Found 295.2860 (Calcd 295.2875). IR (NaCl, film, cm^{-1}): 3473, 2985, 2872, 2100, 1468, 1382, 1023, 735. $[\alpha]_D^{20}$ −10 (0.5; $CHCl_3$).

5.6.13. (1*R*,3a*R*,5*S*,7a*R*)-5-Azido-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-one (24)

To a stirred solution of bromoketone **16** (150 mg, 0.42 mmol) in DMF (3 mL), sodium azide (33 mg, 0.50 mmol) was added under nitrogen atmosphere. The solution was stirred at 0 °C for 2 h. Then a saturated aqueous solution of sodium bicarbonate (20 mL) was added. The resulting mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The residue was subjected to SCC (petroleum ether/ethyl acetate 98:2) to afford **24** (117 mg, 87%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.11 (dd, 1H, H-5, J = 6.8 Hz, J = 12.4 Hz), 2.56–2.48 (m, 1H, H-6), 2.12–2.05 (m, 1H, H-7), 2.03–1.96 (m, 1H, H-3), 1.92–1.73 (m, 3H, H-1′, H-2, H-3), 1.53–1.42 (m, 1H, H-5′), 1.41–1.20 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.13–1.05 (m, 6H, CH_3-3a, H-3′, H-4′), 1.00–0.92 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.89–0.84 (m, 3H, CH_3-5′, with underneath s, 3H, CH_3-7a at 0.88 ppm), 0.84 (d, 3H, H-6′,

J = 6.2 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.2 (CO), 63.1 (5-CH), 60.9 (3a-C), 49.7 (7a-C), 46.6 (1-CH), 39.4 (6-CH_2), 35.8 (3-CH_2), 35.0 (1′-CH), 29.6 (7-CH_2), 29.1 (4′-CH_2), 28.0 (2C, 2′-CH_2, 5′-CH), 25.3 (2-CH_2), 24.2 (3′-CH_2), 22.8 (6′-CH_3), 22.6 (CH_3-5′), 19.5 (CH_3-3a), 18.7 (CH_3-7a), 17.7 (CH_3-1′). IR (NaCl, film, cm^{-1}): 2954, 2870, 2103, 1717, 1467, 1266, 952. $[\alpha]_D^{20}$ −13 (0.5; $CHCl_3$).

5.6.14. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-Amino-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (25)

To a stirred solution of the azidoketone **24** (100 mg, 0.31 mmol) in anhydrous THF, lithium aluminium hydride (40 mg, 1.04 mmol) was added at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min, then quenched with a saturated aqueous solution of sodium bicarbonate (3 mL) and diluted with water (20 mL). The biphasic mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate and evaporated to dryness under reduced pressure. The crude product was subjected to SCC (dichloromethane/methanol/triethylamine 9:1:0.2) to afford amino alcohol **25** (91 mg, 99%) as a white resin. Mp 117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.21 (d, 1H, H-4, J = 2.7 Hz), 2.90 (ddd, 1H, H-5, J = 2.7 Hz, J = 4.2 Hz, J = 12.1 Hz), 2.49 (bs, 2H, NH_2), 2.27–2.18 (m, 1H, H-1′), 1.90–1.81 (m, 1H, H-6), 1.80–1.69 (m, 2H, H-3, H-7), 1.68–1.56 (m, 1H, H-2), 1.49–1.34 (m, 2H, H-5′, H-6), 1.32–1.17 (m, 6H, H-1, H-2, H-2′, H-3, H-3′, H-7), 1.11–0.98 (m, 3H, H-3′, H-4′), 0.97–0.89 (m, 1H, H-2′), 0.85 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.80 (d, 3H, CH_3-5′, J = 6.4 Hz), 0.79–0.71 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.75 ppm), 0.66 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 79.3 (4-CH), 50.4 (5-CH), 49.2 (3a-C), 47.3 (1-CH), 44.7 (7a-C), 39.6 (6-CH_2), 36.5 (3-CH_2), 35.7 (1′-CH), 34.8 (7-CH_2), 31.6 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.7 (2-CH_2), 24.4 (3′-CH_2), 22.9 (6′-CH_3), 22.7 (CH_3-5′), 21.5 (CH_3-3a), 20.0 (CH_3-7a), 19.2 (CH_3-1′). HRMS Found 295.2875 (Calcd 295.2875). IR (NaCl, film, cm^{-1}): 3473, 2985, 2872, 2100, 1468, 1382, 1023, 735. $[\alpha]_D^{20}$ +13 (0.5; $CHCl_3$).

5.6.15. General procedure C (reductive alkylation of amino alcohols)

To a stirred solution of the respective amino alcohol **23** or **25** (0.30–0.40 mmol) and the required aldehyde (1.05–2.00 equiv) in methanol, acetic acid (1.10 equiv) and sodium cyanoborohydride (3 equiv) were added at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 40 °C for 12 h, then quenched with a saturated aqueous solution of sodium bicarbonate (3 mL) and diluted with water (10 mL). The mixture was extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were washed with water (30 mL), dried over sodium sulphate, and evaporated to dryness under reduced pressure. The crude product was subjected to SCC as specified below to afford compounds **26a**–**g**, **27a**–**g**, **28a**–**c**, **29a**–**c** and **30**.

5.6.15.1. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-5-Benzylamino-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (26a).

Amino alcohol **23** (100 mg, 0.34 mmol) and benzaldehyde (39.0 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **26a** (76 mg, 58%) as a white solid. Mp 145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.29 (m, 4H, H-2‴, H-3‴, H- 5‴, H-6‴), 7.24 (dd, 1H, H-4‴, J = 2.9 Hz, J = 5.9 Hz), 3.94 (d, 1H, H-1″, J = 12.8 Hz), 3.67 (d, 1H, H-1″, J = 12.8 Hz), 3.30 (d, 1H, H-4, J = 10.4 Hz), 2.48–2.42 (m, 1H, H-5), 2.07–1.73 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.55–1.46 (m, 1H, H-5′), 1.40–1.27 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.16–1.06 (m, 3H, H-3′, H-4), 1.02–0.95 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.86 (d, 3H, CH_3-5′, J = 6.4 Hz), 0.88–0.81 (m, 3H, 6′-C, with underneath s, 3H, CH_3-3a at 0.84 ppm), 0.75 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.6 (1‴-C), 128.5 (2C, 2‴-CH, 6‴-CH), 128.2 (2C, 3‴-CH, 5‴-CH), 127.1 (4‴-CH), 74.9 (4-CH), 58.8 (5-CH), 51.0 (3a-C), 50.9 (7a-C), 46.9 (1″-CH_2), 46.3 (1-CH), 39.6 (6-CH_2), 36.6 (3-CH_2), 36.0 (7-CH_2), 33.0 (1′-CH), 31.1 (4-CH_2), 28.1 (2′-CH_2), 26.8 (5′-CH), 26.3 (2-CH_2), 24.3 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 19.0 (CH_3-3a), 18.7 (CH_3-7a), 14.07 (CH_3-1′). HRMS Found 385.3380 (Calcd 385.3345). IR (NaCl, film, cm^{-1}): 3465, 3056, 2970, 2875, 1468, 1382, 1023, 750, 689. $[\alpha]_D^{20}$ −13 (0.5; $CHCl_3$).

5.6.15.2. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-[(5-iodofuran-2-ylmethyl)-amino]-3a,7a-dimethyloctahydroinden-4-ol (26b).

Amino alcohol **23** (100 mg, 0.34 mmol) and 5-iodo-2-furaldehyde (80.0 mg, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 8:2:0.2) to afford **26b** (146 mg, 86%) as a white solid. Mp 162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.45 (d, 1H, H-4‴, J = 3.2 Hz), 6.11 (d, 1H, H-3‴, J = 3.2 Hz), 3.91 (d, 1H, H-1″, J = 14.4 Hz), 3.72 (d, 1H, H-1″, J = 14.4 Hz), 3.29 (d, 1H, H-4, J = 10.3 Hz), 2.41 (ddd, 1H, H-5, J = 3.7 Hz, J = 7.2 Hz, J = 10.8 Hz), 1.97–1.72 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.61–1.45 (m, 1H, H-5′), 1.42–1.24 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.17–1.06 (m, 3H, H-3′, H-4′), 1.02–0.96 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87 (d, 3H, CH_3-1′, J = 5.8 Hz), 0.86–0.83 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.83 ppm), 0.75 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.1 (5‴-C), 120.9 (4‴-CH), 109.8 (3‴-CH), 86.2 (2‴-C), 75.0 (4-CH), 58.7 (5-CH), 51.0 (3a-C), 46.9 (1-CH), 46.2 (7a-C), 43.9 (1″-CH_2), 39.6 (6-CH_2), 36.6 (3-CH_2), 36.0 (1′-CH), 32.9 (7-CH_2), 31.0 (4′-CH_2), 28.1 (5′-CH), 26.8 (2′-CH_2), 26.3 (2-CH_2), 24.3 (3′-CH_2), 23.0 (6′-CH_3), 22.7 (CH_3-5′), 19.0 (CH_3-3a), 18.8 (CH_3-7a), 14.1 (CH_3-1′). HRMS Found 501.2151 (Calcd 501.2104). IR (NaCl, film, cm^{-1}): 3412, 3012, 2973, 1478, 1313, 1201, 1058, 839, 793. $[\alpha]_D^{20}$ −29 (0.5; $CHCl_3$).

5.6.15.3. (1*R*,4*S*,5*S*,7a*R*)-5-(3-Chlorobenzylamino)-1-((*R*)-1,5-dimethylhexyl)-7a-methyloctahydroinden-4-ol (26c).

Amino alcohol **23** (100 mg, 0.34 mmol) and 3-chlorobenzaldehyde (50 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **26c** (113 mg, 79%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (s, 1H, H-2‴), 7.25–7.18 (m, 3H, H-4‴, H-5‴, H-6‴), 3.92 (d, 1H, H-1″, J = 13.1 Hz), 3.65 (d, 1H, H-1″, J = 13.1 Hz), 3.31 (d, 1H, H-4, J = 10.3 Hz), 2.99 (s, 1H, NH), 2.44 (ddd, 1H, H-5, J = 5.2 Hz, J = 7.2 Hz, J = 10.3 Hz), 2.02–1.73 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.60–1.44 (m, 1H, H-5′), 1.44–1.24 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.19–1.04 (m, 3H, H-3′, H-4′), 1.01–0.96 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87–0.82 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.83 ppm), 0.76 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.8 (1‴-C), 134.4 (3‴-C), 128.3 (2‴-CH), 129.8, 127.3, 126.3 (3C, 4‴-CH, 5‴-CH, 6‴-CH), 74.9 (4-CH), 58.9 (5-CH), 50.9 (1″-CH_2), 50.6 (3a-C), 46.9 (7a-C), 46.3 (1-CH), 39.6 (6-CH_2), 36.6 (3-CH_2), 36.0 (1′-CH), 33.0 (7-CH_2), 31.1 (4′-CH_2), 28.1 (5′-CH), 26.8 (2′-CH_2), 26.4 (2-CH_2), 24.3 (3′-CH_2), 23.0 (6′-CH_3), 22.7 (CH_3-5′), 19.0 (CH_3-3a), 18.7 (CH_3-7a), 14.1 (CH_3-1′). HRMS Found 419.2947 (Calcd 419.2955). IR (NaCl, film, cm^{-1}): 3493, 3011, 2996, 2891, 1499, 1312, 1031, 852, 778. $[\alpha]_D^{20}$ −11 (0.5; $CHCl_3$).

5.6.15.4. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-[(furan-3-ylmethyl)-amino]-3a,7a-dimethyl-octahydroinden-4-ol (26d).

Amino alcohol **23** (100 mg, 0.34 mmol) and furan-3-carboxaldehyde (29 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to

afford **26d** (86 mg, 67%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, 2H, H-4‴, H-5‴, J = 8.7 Hz), 6.39 (s, 1H, H-2‴), 3.82 (d, 1H, H-1″, J = 13.3 Hz), 3.54 (d, 1H, H-1″, J = 13.3 Hz), 3.30 (d, 1H, H-4, J = 10.4 Hz), 2.43 (ddd, 1H, H-5, J = 4.3 Hz, J = 7.2 Hz, J = 10.5 Hz), 2.04–1.77 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.61–1.46 (m, 1H, H-5′), 1.40–1.26 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.11 (s, 3H, H-3′, H-4′), 1.03–0.94 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.87 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.86–0.81 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.83 ppm), 0.76 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.2 (2‴-CH), 139.7 (5‴-CH), 124.1 (3‴-C), 110.4 (4‴-CH), 74.7 (4-CH), 58.5 (5-CH), 50.8 (1″-CH_2), 46.8 (3a-C), 46.2 (7a-C), 41.4 (1-CH), 39.5 (6-CH_2), 36.5 (3-CH_2), 35.9 (7-CH_2), 32.9 (1′-CH), 31.0 (4′-CH_2), 28.0 (2′-CH_2), 26.7 (5′-CH), 26.0 (2-CH_2), 24.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 18.9 (CH_3-3a), 18.6 (CH_3-7a), 13.9 (CH_3-1′). HRMS Found 375.3125 (Calcd 375.3137). IR (NaCl, film, cm^{-1}): 3501, 3066, 2981, 2870, 1472, 1378, 750, 689. $[\alpha]_D^{20}$ −18 (0.5; $CHCl_3$).

5.6.15.5. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-(pent-4-enylamino)-octahydro-inden-4-ol (26e).

Amino alcohol **23** (100 mg, 0.34 mmol) and pent-4-enal (36.0 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **26e** (69 mg, 56%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (ddt, 1H, H-4″, J = 6.7 Hz, J = 10.1 Hz, J = 16.9 Hz), 5.01 (dd, 1H, H-5″, J = 1.8 Hz, J = 17.1 Hz), 4.95 (dd, 1H, H-5″, J = 1.8 Hz, J = 17.1 Hz), 3.23 (d, 1H, H-4, J = 10.4 Hz), 2.79 (dt, 1H, H-1″, J = 7.1 Hz, J = 9.3 Hz), 2.44 (dt, 1H, H-1″, J = 7.1 Hz, J = 9.3 Hz), 2.32 (ddd, 1H, H-5, J = 4.5 Hz, J = 7.4 Hz, J = 10.7 Hz), 2.13–2.04 (m, 2H, H-3″), 1.98–1.73 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.62–1.44 (m, 3H, H-2″, H-5′), 1.37–1.21 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.16–1.04 (m, 3H, H-3′, H-4′), 1.02–0.95 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 5.4 Hz), 0.86 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.85 (s, 3H, CH_3-3a), 0.84 (d, 3H, H-6′, J = 6.0 Hz), 0.74 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.5 (4″-CH), 114.7 (5″-CH_2), 74.7 (4-CH), 59.1 (5-CH), 50.7 (3a-C), 46.8 (7a-C), 46.2 (2C, 1-CH, 1″-CH_2), 39.5 (6-CH_2), 36.5 (3-CH_2), 35.9 (7-CH_2), 32.9 (3″-CH_2), 31.6 (1′-CH_2), 31.1 (2″-CH_2), 29.8 (4′-CH_2), 28.0 (2′-CH_2), 26.7 (5′-CH), 26.2 (2-CH_2), 24.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 18.9 (CH_3-3a), 18.7 (CH_3-7a), 14.0 (CH_3-1′). HRMS Found 363.3493 (Calcd 363.3501). IR (NaCl, film, cm^{-1}): 3448, 3038, 2980, 2870, 1452, 1353, 841, 750, 689. $[\alpha]_D^{20}$ −9 (0.5; $CHCl_3$).

5.6.15.6. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-5-(2,4-Dichlorobenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (26f).

Amino alcohol **23** (100 mg, 0.34 mmol) and 2,4-dichlorobenzaldehyde (62.0 mg, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **26f** (112 mg, 73%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (s, 1H, H-3‴), 7.27 (d, 1H, H-6‴, J = 8.2 Hz), 7.20 (d, 1H, H-5‴, J = 8.2 Hz), 3.83 (d, 1H, H-1″, J = 13.8 Hz), 3.77 (d, 1H, H-1″, J = 13.8 Hz), 3.46 (d, 1H, H-4, J = 10.6 Hz), 2.80–2.52 (m, 1H, H-5), 2.30–2.21 (m, 1H, H-1′), 2.00–1.76 (m, 3H, H-3, H-6, H-7), 1.77–1.60 (m, 1H, H-2), 1.57–1.40 (m, 2H, H-3, H-5′), 1.37–1.19 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.17–1.03 (m, 3H, H-3′, H-4′), 1.02–0.95 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.85 (d, CH_3-1′, J = 6.4 Hz, 3H), 0.84 (d, 3H, H-6′, J = 6.4 Hz), 0.83 (s, CH_3-3a), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.1 (1‴-C), 134.5 (2‴-C), 133.6 (4‴-C), 131.1 (6‴-CH), 129.5 (3‴-CH), 127.2 (5‴-CH), 75.6 (4-CH), 56.4 (5-CH), 48.5 (3a-C), 47.4 (1″-CH_2), 47.2 (1-CH), 45.0 (7a-C), 39.6 (6-CH_2), 36.5 (3-CH_2), 35.6 (1′-CH), 34.8 (7-CH_2), 31.4 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.2 (2-CH_2), 23.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.0 (CH_3-7a), 19.1 (CH_3-1′). HRMS Found 453.2591 (Calcd 453.2565). IR (NaCl, film, cm^{-1}): 3446, 3009, 2991, 2792, 1488, 1291, 1093, 1002, 856, 801. $[\alpha]_D^{20}$ −26 (0.5; $CHCl_3$).

5.6.15.7. (1*R*,3a*R*,4*S*,5*S*,7a*R*)-5-(2,3-Dichlorobenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (26g).

Amino alcohol **23** (100 mg, 0.34 mmol) and 2,3-dichlorobenzaldehyde (62 mg, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **26g** (132 mg, 85%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (d, 1H, H-4‴, J = 8.0 Hz), 7.32 (d, 1H, H-6‴, J = 7.7 Hz), 7.17 (t, 1H, H-5‴, J = 7.8 Hz), 4.04 (d, 1H, H-1″, J = 13.8 Hz), 3.79 (d, 1H, H-1″, J = 13.8 Hz), 3.30 (d, 1H, H-4, J = 10.3 Hz), 2.99–2.91 (m, 1H, H-5), 2.47–2.39 (m, 1H, NH), 2.02–1.74 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.58–1.43 (m, 1H, H-5′), 1.43–1.23 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.16–1.07 (m, 3H, H-3′, H-4′), 1.00–0.95 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.86 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.86–0.83 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.83 ppm), 0.75 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.6 (1‴-C), 133.3 (2‴-C), 132.0 (3‴-C), 129.2 (5‴-CH), 128.0 (4‴-CH), 127.4 (6‴-CH), 75.0 (4-CH), 59.1 (5-CH), 50.9 (3a-C), 49.5 (1″-CH_2), 46.9 (7a-C), 46.4 (1-CH), 39.6 (6-CH_2), 36.6 (3-CH_2), 36.0 (1′-CH), 33.0 (7-CH_2), 31.1 (4′-CH_2), 28.1 (5′-CH), 26.8 (2′-CH_2), 26.5 (2-CH_2), 24.3 (3′-CH_2), 23.0 (6′-CH_3), 22.7 (CH_3-5′), 19.0 (CH_3-3a), 18.7 (CH_3-7a), 14.1 (CH_3-1′). HRMS Found 453.2583 (Calcd 453.2565). IR (NaCl, film, cm^{-1}): 3442, 3032, 2995, 2912, 1500, 1311, 1023, 792. $[\alpha]_D^{20}$ −29 (0.5; $CHCl_3$).

5.6.15.8. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-Benzylamino-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyoctahydroinden-4-ol (27a).

Amino alcohol **25** (100 mg, 0.34 mmol) and benzaldehyde (21 μL, 0.36 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **27a** (111 mg, 85%) as a white solid. Mp 148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46–7.13 (m, 5H, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 3.81 (d, 1H, 1″-H, J = 12.9 Hz), 3.67 (d, J = 12.9 Hz, 1H, 1″-H), 3.46 (d, J = 2.3 Hz, 1H, H-4), 2.82–2.62 (m, 1H, H-5), 2.39–2.31 (m, 1H, H-1′), 2.02–1.77 (m, 3H, H-3, H-6, H-7), 1.76–1.61 (m, 1H, H-2), 1.56–1.40 (m, 2H, H-3, H-5′), 1.37–1.20 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.17–1.07 (m, 3H, H-3′, H-4′), 1.05–0.96 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.5 Hz), 0.84 (s, 3H, CH_3-3a), 0.83 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.82 (d, 3H, H-6′, J = 5.8 Hz), 0.72 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.3 (1‴-C), 128.5 (2‴-CH, 6‴-CH), 128.2 (3‴-CH, 5‴-CH), 127.1 (4‴-CH), 75.6 (4-CH), 56.7 (5-CH), 50.6 (1″-CH_2), 48.4 (3a-C), 47.2 (1-CH), 45.0 (7a-CH), 39.6 (7-CH_2), 36.5 (3-CH_2), 35.6 (1′-CH), 34.9 (7-CH_2), 31.4 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.2 (2-CH_2), 23.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.0 (CH_3-7a), 19.10 (CH_3-1′). HRMS Found 385.3333 (Calcd 385.3345). IR (NaCl, film, cm^{-1}): 3467, 3026, 2997, 2853, 1452, 1298, 1023, 750, 689. $[\alpha]_D^{20}$ +28 (0.5; $CHCl_3$).

5.6.15.9. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-[(5-iodofuran-2-ylmethyl)-amino]-3a,7a-dimethyloctahydroinden-4-ol (27b).

Amino alcohol **25** (90 mg, 0.31 mmol) and 5-iodo-2-furaldehyde (74 mg, 0.34 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **27b** (115 mg, 75%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.44 (d, 1H, H-4‴, J = 3.1 Hz), 6.08 (d, 1H, H-3‴, J = 3.1 Hz), 3.78 (d, J = 14.8 Hz, 1H, H-1″), 3.71 (d, J = 14.8 Hz, 1H, H-1″), 3.38 (d, 1H, H-4, J = 2.2 Hz), 2.69–2.62 (m, 1H, H-5), 2.35–2.27 (m, 1H, H-1′), 2.00–1.88 (m, 1H, H-6), 1.87–1.74 (m, 2H, H-3, H-7), 1.72–1.46 (m, 3H, H-2, H-3, H-5′), 1.37–1.21 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.18–1.05 (m, 3H, H-3′, H-4′),

1.04–0.95 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.5 Hz), 0.87 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.84 (d, 3H, H-6′, J = 6.0 Hz), 0.83 (s, 3H, CH_3-3a), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3 (5‴-C), 120.7 (4‴-CH), 110.1 (3‴-CH), 86.3 (2‴-C), 75.4 (4-CH), 55.6 (5-CH), 48.4 (3a-C), 47.1 (1-CH), 44.9 (7a-C), 42.4 (1′-CH_2), 39.5 (7-CH_2), 36.4 (6-CH_2), 35.5 (1′-CH), 34.7 (3-CH_2), 31.3 (4′-CH_2), 29.1 (2′-CH_2), 27.9 (5′-CH), 24.1 (2-CH_2), 22.8 (2C, 3′-CH_2, 6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 19.8 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 501.2151 (Calcd 501.2104). IR (NaCl, film, cm^{-1}): 3400, 3008, 2996, 1532, 1413, 1121, 1013, 839, 801, 793. $[\alpha]_D^{20}$ +23 (0.5; $CHCl_3$).

5.6.15.10. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(3-Chlorobenzylamino)-1-((*R*)-1,5-di-methylhexyl)-7a-methyloctahydroinden-4-ol (27c). Amino alcohol **25** (100 mg, 0.34 mmol) and 3-chlorobenzaldehyde (50 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **27c** (113 mg, 79%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (s, 1H, H-2‴), 7.25–7.18 (m, 3H, H-4‴, H-5‴, H-6‴), 3.92 (d, 1H, H-1″, J = 13.1 Hz), 3.65 (d, 1H, H-1″, J = 13.1 Hz), 3.31 (d, 1H, H-4, J = 2.3 Hz), 2.99 (s, 1H, NH), 2.44 (ddd, 1H, H-5, J = 5.2 Hz, J = 7.2 Hz, J = 10.3 Hz), 2.02–1.73 (m, 5H, H-1′, H-2, H-3, H-6, H-7), 1.60–1.44 (m, 1H, H-5′), 1.44–1.24 (m, 7H, H-1, H-2, H-2′, H-3, H-3′, H-6, H-7), 1.19–1.04 (m, 3H, H-3′, H-4′), 1.01–0.96 (m, 1H, H-2′), 0.92 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87 (d, 3H, CH_3-5′, J = 6.6 Hz), 0.87–0.82 (m, 3H,H-6′, with underneath s, 3H, CH_3-3a at 0.83 ppm), 0.76 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.8 (1‴-C), 134.4 (3‴-CH), 128.3 (2‴-CH), 129.8, 127.3, 126.3 (3C, 4‴-C, 5‴-CH, 6‴-CH), 74.9 (4-CH), 58.9 (5-CH), 50.9 (1″-CH_2), 50.6 (3a-C), 46.9 (7a-C), 46.3 (1-CH), 39.6 (6-CH_2), 36.6 (3-CH_2), 36.0 (1′-CH), 33.0 (7-CH_2), 31.1 (4′-CH_2), 28.1 (5′-CH), 26.8 (2′-CH_2), 26.4 (2-CH_2), 24.3 (3′-CH_2), 23.0 (6′-CH_3), 22.7 (CH_3-5′), 19.0 (CH_3-3a), 18.7 (CH_3-7a), 14.1 (CH_3-1′). HRMS Found 419.2947 (Calcd 419.2955). IR (NaCl, film, cm^{-1}): 3493, 3011, 2996, 2891, 1499, 1312, 1031, 852, 778. $[\alpha]_D^{20}$ +27 (0.5; $CHCl_3$).

5.6.15.11. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-[(furan-3-ylmethyl)-amino]-3a,7a-dimethyloctahydroinden-4-ol (27d). Amino alcohol **25** (100 mg, 0.34 mmol) and furan-3-carboxaldehyde (29 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 7:3:0.2) to afford **27d** (107 mg, 84%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (s, 1H, H-2‴), 7.32 (d, 1H, H-5‴, J = 4.2 Hz), 6.35 (d, 1H, H-4‴, J = 4.2 Hz), 3.63 (d, 1H, H-1″, J = 13.5 Hz), 3.57 (d, 1H, H-1″, J = 13.5 Hz), 3.41 (d, 1H, H-4, J = 2.4 Hz), 2.70 (ddd, 1H, H-5, J = 2.4 Hz, J = 7.6 Hz, J = 11.7 Hz), 2.37–2.30 (m, 1H, H-1′), 2.00–1.89 (m, 1H, H-6), 1.89–1.77 (m, 2H, H-3, H-7), 1.75–1.60 (m, 1H, H-2), 1.56–1.40 (m, 2H, H-3, H-5′), 1.36–1.20 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.17–1.05 (m, 3H, H-3′, H-4′), 1.04–0.94 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.5 Hz), 0.86 (s, 3H, CH_3-3a), 0.84 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.83 (d, 3H, H-6′, J = 5.8 Hz), 0.76 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3 (2‴-CH), 139.7 (5‴-CH), 124.0 (3‴-C), 110.4 (4‴-CH), 75.6 (4-CH), 56.6 (5-CH), 48.4 (3a-C), 47.2 (1-CH), 45.0 (7a-C), 40.9 (6-CH_2), 39.6 (1″-CH_2), 36.5 (3-CH_2), 35.6 (1′-CH), 34.9 (7-CH_2), 31.4 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.2 (2-CH_2), 23.1 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.0 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 375.3125 (Calcd 375.3137). IR (NaCl, film, cm^{-1}): 3501, 3022, 2980, 2895, 1472, 882, 750, 689. $[\alpha]_D^{20}$ +26 (0.5; $CHCl_3$).

5.6.15.12. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-(pent-4-enylamino)-octahydroinden-4-ol (27e). Amino alcohol **25** (100 mg, 0.34 mmol) and pent-4-enal (36.0 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **27e** (97 mg, 79%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (ddt, 1H, H-4″, J = 6.7 Hz, J = 10.2 Hz, J = 16.9 Hz), 5.05–4.92 (m, 2H, H-5″), 3.35 (d, 1H, H-4, J = 2.4 Hz), 2.65–2.57 (m, 3H, H-5, H-1″), 2.37–2.28 (m, 1H, H-1′), 2.15–2.02 (m, 2H, H-3″), 1.98–1.90 (m, 1H, H-6), 1.88–1.76 (m, 2H, H-3, H-7), 1.70–1.39 (m, 5H, H-2, H-2″, H-3, H-5′), 1.37–1.22 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.15–1.04 (m, 3H, H-3′, H-4′), 1.03–0.96 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.82 (s, 3H, CH_3-3a), 0.81 (d, 3H, CH_3-5′, J = 6.2 Hz), 0.79 (d, 3H, H-6′, J = 6.2 Hz), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.4 (4″-CH), 114.8 (5″-CH_2), 75.8 (4-CH), 57.2 (5-CH), 48.3 (3a-C), 47.2 (1-CH), 45.9 (1″-CH_2), 45.0 (7a-C), 39.6 (6-CH_2), 36.5 (3-CH_2), 35.6 (1′-CH), 34.8 (7-CH_2), 31.5 (3″-CH_2), 31.4 (2″-CH_2), 29.7 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.3 (2-CH_2), 23.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.0 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 363.3489 (Calcd 363.3501). IR (NaCl, film, cm^{-1}): 3399, 2995, 2867, 1511, 1291, 841, 753. $[\alpha]_D^{20}$ +11 (0.5; $CHCl_3$).

5.6.15.13. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(2,4-Dichlorobenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (27f). Amino alcohol **25** (90 mg, 0.31 mmol) and 2,4-dichlorobenzaldehyde (56.0 mg, 0.32 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **27f** (123 mg, 89%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (s, 1H, H-3‴), 7.27 (d, 1H, H-5‴, J = 10.0 Hz), 7.20 (d, 1H, H-6‴, J = 10.0 Hz), 3.83 (d, 1H, H-1″, J = 13.8 Hz), 3.77 (d, 1H, H-1″, J = 13.8 Hz), 3.46 (d, 1H, H-4, J = 2.5 Hz), 2.71–2.60 (m, 1H, H-5), 2.35–2.24 (m, 1H, H-1′), 2.01–1.77 (m, 3H, H-3, H-6, H-7), 1.73–1.66 (m, 1H, H-2), 1.53–1.40 (m, 2H, H-3, H-5′), 1.36–1.20 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.15–0.98 (m, 3H, H-3′, H-4′), 1.04–0.93 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.85 (d, 3H, CH_3-5′, J = 6.4 Hz), 0.84 (d, 3H, H-6′, J = 6.4 Hz), 0.83 (s, 3H, CH_3-3a), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 136.1 (1‴-C), 134.4 (2‴-C), 133.4 (4‴-C), 131.0 (5‴-CH), 129.4 (3‴-CH), 127.1 (6‴-CH), 75.5 (4-CH), 56.3 (5-CH), 48.4 (3a-C), 47.4 (1″-CH_2), 47.1 (1-CH), 44.9 (7-CH_2), 39.5 (6-CH_2), 36.4 (3-CH_2), 35.5 (1′-CH), 34.8 (7-CH_2), 31.3 (4′-CH_2), 29.1 (2′-CH_2), 27.9 (5′-CH), 24.2 (2-CH_2), 23.1 (3′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 19.9 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 453.2596 (Calcd 453.2565). IR (NaCl, film, cm^{-1}): 3431, 3012, 3007, 2996, 2890, 1432, 1311, 1121, 1093, 854, 820. $[\alpha]_D^{20}$ +34 (0.5; $CHCl_3$).

5.6.15.14. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(2,3-Dichlorobenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (27g). Amino alcohol **25** (90 mg, 0.31 mmol) and 2,3-dichlorobenzaldehyde (56.0 mg, 0.32 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **27g** (107 mg, 77%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, 1H, H-4‴, J = 7.9 Hz), 7.25 (d, 1H, H-6‴, J = 7.8 Hz), 7.16 (t, 1H, H-5‴, J = 7.8 Hz), 3.89 (d, 1H, H-1″, J = 13.8 Hz), 3.83 (d, 1H, H-1″, J = 13.8 Hz), 3.47 (d, 1H, H-4, J = 2.5 Hz), 2.72–2.61 (m, 1H, H-5), 2.36–2.30 (m, 1H, H-1′), 1.96–1.79 (m, 3H, H-3, H-6, H-7), 1.73–1.62 (m, 1H, H-2), 1.54–1.42 (m, 2H, H-3, H-5′), 1.36–1.19 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.14–1.06 (m, 3H, H-3′, H-4′), 1.04–0.97 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.85 (d, 3H, CH_3-5′, J = 5.4 Hz), 0.84–0.80 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.81 ppm), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.8 (1‴-C), 133.3 (2‴-C), 132.0 (3‴-C), 129.2 (4‴-CH), 128.2 (6‴-CH), 127.2 (5‴-CH), 75.5 (4-CH), 56.24 (5-CH), 48.6 (1″-CH_2), 48.4 (3a-C), 47.1 (1-CH), 44.9 (7a-C), 39.5 (6-CH_2), 36.4 (3-CH_2), 35.5 (1′-CH), 34.8

(7-CH_2), 31.3 (4′-CH_2), 29.1 (2′-CH_2), 27.9 (5′-CH), 24.1 (2-CH_2), 23.1 (3′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 19.9 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 453.2583 (Calcd 453.2565). IR (NaCl, film, cm^{-1}): 3442, 3032, 3002, 2983, 2871, 1413, 1332, 1231, 1023, 773. $[\alpha]_D^{20}$ +36 (0.5; $CHCl_3$).

5.6.15.15. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-(4-methoxybenzylamino)-3a,7a-dimethyloctahydroinden-4-ol (28a). Amino alcohol **25** (100 mg, 0.34 mmol) and 4-methoxybenzaldehyde (44 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **28a** (104 mg, 73%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, 2H, H-2‴, H-6‴, J = 8.6 Hz), 6.85 (d, 2H, H-3‴, H-5‴, J = 8.6 Hz), 3.79 (s, 3H, OCH_3), 3.74 (d, 1H, H-1″, J = 12.7 Hz), 3.60 (d, 1H, H-1″, J = 12.7 Hz), 3.44 (d, 1H, 4-H, J = 2.7 Hz), 2.78–2.65 (m, 1H, H-5), 2.42–2.31 (m, 1H, H-1′), 2.04–1.90 (m, 1H, H-6), 1.90–1.77 (m, 2H, H-3, H-7), 1.73–1.59 (m, 1H, H-2), 1.55–1.40 (m, 2H, H-3, H-5′), 1.38–1.17 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.15–1.05 (m, 3H, H-3′, H-4′), 1.03–0.96 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.86 (d, 3H, CH_3-5′, J = 5.8), 0.84 (d, 3H, H-6′, J = 5.8 Hz), 0.84 (s, 3H, CH_3-3a), 0.72 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.9 (1‴-C), 130.7 (4‴-C), 127.5 (2C, 2‴-CH, 6‴-CH), 112.1 (2C, 3‴-CH, 5‴-CH), 73.8 (4-CH), 54.8 (5-CH), 53.5 (OCH_3), 48.2 (1″-CH_2), 46.6 (3a-C), 45.4 (1-CH), 43.2 (7a-C), 37.8 (6-CH_2), 34.7 (3-CH_2), 33.8 (1′-CH), 33.1 (7-CH_2), 29.6 (4′-CH_2), 27.4 (2′-CH_2), 26.2 (5′-CH), 22.4 (2-CH_2), 21.4 (3′-CH_2), 21.1 (6′-CH_3), 20.8 (CH_3-5′), 19.5 (CH_3-3a), 18.2 (CH_3-7a), 17.29 (CH_3-1′). HRMS Found 415.3455 (Calcd 415.3450). IR (NaCl, film, cm^{-1}): 3491, 3031, 2956, 2870, 1414, 1342, 1085, 802. $[\alpha]_D^{20}$ +41 (0.5; $CHCl_3$).

5.6.15.16. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(2,4-Dimethoxybenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (28b). Amino alcohol **25** (100 mg, 0.34 mmol) and 2,4-dimethoxybenzaldehyde (62 mg, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.2) to afford **28b** (86 mg, 57%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (d, 1H, H-6‴, J = 8.2 Hz), 6.44 (s, 1H, H-3‴), 6.41 (d, 1H, H-5‴, J = 8.2 Hz), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.71 (d, 1H, H-1″, J = 13.1 Hz), 3.59 (d, 1H, H-1″, J = 13.1 Hz), 3.47 (d, 1H, H-4, J = 2.7 Hz), 2.66–2.60 (m, 1H, H-5), 2.38–2.29 (m, 1H, H-1′), 1.99–1.83 (m, 2H, H-3, H-6), 1.81–1.74 (m, 1H, H-7), 1.70–1.59 (m, 1H, H-2), 1.57–1.39 (m, 2H, H-3, H-5′), 1.38–1.22 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.19–1.06 (m, 3H, H-3′, H-4′), 1.05–0.97 (m, 1H, H-2′), 0.89 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.85 (d, 3H, CH_3-1′, J = 6.2 Hz), 0.84 (d, 3H, H-6′, J = 6.2 Hz), 0.82 (s, 3H, CH_3-3a), 0.70 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.0 (2‴-C), 158.6 (4‴-C), 130.3 (6‴-CH), 120.8 (1‴-C), 103.6 (5‴-CH), 98.5 (3‴-CH), 75.2 (4-CH), 55.6 (5-CH), 55.3 (OCH_3), 55.2 (OCH_3), 48.2 (3a-C), 47.0 (1-CH), 45.0 (7a-C), 44.9 (1″-CH_2), 39.5 (6-CH_2), 36.4 (3-CH_2), 35.5 (1′-CH), 34.8 (7-CH_2), 31.4 (4′-CH_2), 29.0 (2′-CH_2), 27.9 (5′-CH), 24.1 (2-CH_2), 23.2 (3′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 19.9 (CH_3-7a), 18.9 (CH_3-1′). HRMS Found 445.3546 (Calcd 445.3556). IR (NaCl, film, cm^{-1}): 3472, 3022, 2931, 2853, 1413, 1321, 1266, 1085, 873, 802. $[\alpha]_D^{20}$ +53 (0.5; $CHCl_3$).

5.6.15.17. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-5-ethylamino-3a,7a-dimethyloctahydroinden-4-ol (28c). Amino alcohol **25** (100 mg, 0.34 mmol) and acetaldehyde (20 μL, 0.35 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 7:3:0.2) to afford **28c** (83 mg, 75%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.35 (d, 1H, H-4, J = 2.8 Hz), 2.68–2.52 (m, 3H, H-1″, H-5), 2.35–2.27 (m, 1H, H-1′), 1.99–1.90 (m, 1H, H-6), 1.87–1.76 (m, 2H, H-3, H-7), 1.68–1.59 (m, 1H, H-2), 1.49–1.36 (m, 2H, H-3, H-5′), 1.34–1.21 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.14–1.04 (m, 6H, H-2″, H-3′, H-4′), 1.01–0.93 (m, 1H, H-2′), 0.90 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.85 (d, 3H, CH_3-1′, J = 6.3 Hz), 0.84–0.79 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.81 ppm), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR (CDCl3, 125 MHz): δ 76.0 (4-CH), 57.1 (5-CH), 48.4 (3a-C), 47.1 (1-CH), 45.0 (7a-C), 40.7 (1″-CH_2), 39.6 (6-CH_2), 36.5 (3-CH_2), 35.6 (1′-CH), 34.8 (7-CH_2), 31.5 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.2 (2-CH_2), 23.2 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.0 (CH_3-7a), 19.0 (CH_3-1′), 15.7 (2″-CH_3). HRMS Found 323.3158 (Calcd 323.3188). IR (NaCl, film, cm^{-1}): 3399, 2995, 2867, 1511, 1291, 841, 753. $[\alpha]_D^{20}$ +16 (0.5; $CHCl_3$).

5.6.15.18. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(*N*-Benzyl-*N*-methylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (29a). Amino alcohol **27a** (112 mg, 0.29 mmol) and a 34% aqueous solution of formaldehyde (50 μL, 0.58 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **29a** (97 mg, 83%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.21 (m, 5H, H-2‴, H-3‴, H-4, H-5‴, H-6‴), 3.75 (d, 1H, H-1″, J = 13.3 Hz), 3.63 (d, 1H, H-4, J = 2.8 Hz), 3.40 (d, 1H, H-1″, J = 13.3 Hz), 2.42–2.33 (m, 2H, H-1′, H-5), 2.15 (s, 3H, NCH_3), 2.04–1.83 (m, 3H, H-3, H-6, H-7), 1.75–1.64 (m, 1H, H-2), 1.63–1.41 (m, 2H, H-3, H-5′), 1.40–1.18 (m, 6H, H-1, H-2, H-2′, H-3′, H-6, H-7), 1.18–1.07 (m, 3H, H-3′, H-4′), 1.06–0.98 (m, 1H, H-2′), 0.93 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87 (s, 3H, CH_3-3a), 0.85 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.83 (d, 3H, H-6′, J = 6.0 Hz), 0.74 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.34 (1‴-C), 128.8 (2C, 2‴-CH, 6‴-CH), 128.2 (2C, 3‴-CH, 5‴-CH), 126.8 (4‴-CH), 75.5 (4-CH), 63.0 (5-CH), 58.1 (1″-CH_2), 48.6 (3a-C), 47.2 (1-CH), 44.3 (7a-C), 39.4 (6-CH_2), 38.2 (NCH_3), 36.4 (3-CH_2), 35.6 (1′-CH), 34.8 (7-CH_2), 31.7 (4′-CH_2), 29.2 (2′-CH_2), 27.9 (5′-CH), 24.2 (2′-CH_2), 22.8 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 20.4 (3′-CH_2), 19.7 (CH_3-7a), 18.8 (CH_3-1′). HRMS Found 399.3523 (Calcd 399.3501). IR (NaCl, film, cm^{-1}): 3431, 3019, 2932, 2854, 1501, 1345, 1023, 743, 691. $[\alpha]_D^{20}$ +19 (0.5; $CHCl_3$).

5.6.15.19. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(*N*,*N*-Dibenzylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (29b). Amino alcohol **27a** (150 mg, 0.39 mmol) and benzaldehyde (67 μL, 0.58 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **29b** (156 mg, 84%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.17 (m, 10H, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 3.81 (d, 2H, H-1″, J = 14.5 Hz), 3.76 (d, 2H, H-1″, J = 14.5 Hz), 3.65 (d, 1H, H-4, J = 2.8 Hz), 2.94–2.70 (m, 1H, H-5), 2.38–2.29 (m, 1H, H-1′), 2.01–1.90 (m, 1H, H-6), 1.90–1.80 (m, 2H, H-3, H-7), 1.77–1.63 (m, 1H, H-2), 1.59–1.41 (m, 3H, H-2, H-3, H-5′), 1.40–1.25 (m, 4H, H-1, H-2′, H-3′, 7-H), 1.24–1.17 (m, 1H, H-6), 1.21–1.05 (m, 3H, H-3′, H-4′), 1.04–0.96 (m, 1H, H-2′), 0.88 (d, 3H, CH_3-1′, J = 6.1 Hz), 0.87 (d, 3H, CH_3-5′, J = 5.8 Hz), 0.87 (d, 3H, H-6′, J = 5.8 Hz), 0.83 (s, 3H, CH_3-3a), 0.72 (s, 3H, CH_3-7a). ^{13}C NMR (CDCl3, 125 MHz): δ 139.8 (2C, 1‴-C), 128.7 (4C, 2‴-C, 6‴-C), 128.3 (4C, 3‴-C, 5‴-C), 126.8 (2C, 4‴-C), 76.6 (4-CH), 61.0 (5-CH), 53.9 (2C, 1″-CH_2), 49.0 (3a-C), 47.3 (1-CH), 44.6 (7a-C), 39.5 (6-CH_2), 36.4 (3-CH_2), 35.6 (1′-CH), 34.9 (7-CH_2), 32.2 (4′-CH_2), 29.2 (2′-CH_2), 28.0 (5′-CH), 24.2 (2-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.4 (CH_3-3a), 20.7 (3′-CH_2), 19.8 (CH_3-7a), 19.0 (CH_3-1′). HRMS Found 475.3718 (Calcd 475.3814). IR (NaCl, film, cm^{-1}): 3467, 3025, 2932, 2857, 1452, 1304, 1298, 1023, 749, 684. $[\alpha]_D^{20}$ +47 (0.5; $CHCl_3$).

5.6.15.20. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-5-(*N*-Benzyl-*N*-pent-4-enylamino)-1-((*R*)-1,5-dimethylhexyl)-3a,7a-dimethyloctahydroinden-4-ol (29c). Amino alcohol **27a** (150 mg, 0.39 mmol) and pent-4-enal (59 μL, 0.58 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **29c** (146 mg, 82%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.17 (m, 5H, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 5.72 (ddt, 1H, H-4⁗, J = 6.6 Hz, J = 10.2 Hz, J = 16.9 Hz), 5.02–4.73 (m, 2H, H-5⁗), 3.78 (d, 1H, H-1″, J = 14.1 Hz), 3.66 (d, 1H, H-1″, J = 14.1 Hz), 3.55 (d, 1H, H-4, J = 2.5 Hz), 2.72–2.62 (m, 1H, H-5), 2.61–2.49 (m, 2H, H-1‴), 2.39–2.30 (m, 1H, H-1′), 2.01–1.93 (m, 1H, H-6), 1.92–1.83 (m, 4H, H-3, H-3⁗, H-7), 1.74–1.65 (m, 1H, H-2), 1.60–1.40 (m, 5H, H-1, H-2⁗, H-3, H-5′), 1.39–1.18 (m, 5H, H-2, H-2′, H-3′, H-6, H-7), 1.19–1.05 (m, 3H, H-3′, H-4′), 1.04–0.96 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 6.6 Hz), 0.87 (d, 3H, CH_3-5′, J = 5.9 Hz), 0.86–0.83 (m, 3H, H-6′, with underneath s, 3H, CH_3-3a at 0.84 ppm), 0.73 (s, 3H, CH_3-7a). ^{13}C NMR (CDCl3, 125 MHz): δ 139.9 (1‴-C), 138.2 (4⁗-CH), 128.4 (2C, 2‴-CH, 6‴-CH), 128.1 (2C, 3‴-CH, 5‴-CH), 126.7 (4‴-CH), 114.5 (5⁗-CH_2), 75.8 (4-CH), 60.6 (5-CH), 53.4 (1″-CH_2), 48.6 (3a-C), 48.1 (1⁗-CH_2), 47.1 (1-CH), 44.3 (7a-C), 39.4 (6-CH_2), 36.3 (3-CH_2), 35.6 (1′-CH), 34.8 (7-CH_2), 31.8 (4′-CH_2), 31.3 (3⁗-CH_2), 29.1 (2′-CH_2), 27.8 (5′-CH), 24.1 (2-CH_2), 24.0 (2⁗-CH_2), 22.7 (6′-CH_3), 22.5 (CH_3-5′), 21.2 (CH_3-3a), 20.4 (3′-CH_2), 19.6 (CH_3-7a), 18.8 (CH_3-1′). HRMS Found 453.3988 (Calcd 453.3970). IR (NaCl, film, cm^{-1}): 3442, 3012, 2949, 2867, 1412, 1319, 1023, 992, 917, 749. $[\alpha]_D^{20}$ +39 (0.5; $CHCl_3$).

5.6.15.21. (1*R*,3a*R*,4*R*,5*S*,7a*R*)-1-((*R*)-1,5-Dimethylhexyl)-3a,7a-dimethyl-5-(N-methyl-N-pent-4-enylamino)-octahydroinden-4-ol (30). Amino alcohol **27e** (150 mg, 0.41 mmol) and a 34% aqueous solution of formaldehyde (71 μL, 0.58 mmol) in methanol (3 mL) were treated as described in procedure C. The crude product was subjected to SCC (petroleum ether/ethyl acetate/triethylamine 9:1:0.1) to afford **30** (137 mg, 87%) as colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (ddt, 1H, H-4⁗, J = 6.6 Hz, J = 10.2 Hz, J = 16.8 Hz), 5.11–4.87 (m, 2H, H-5⁗), 3.44 (d, 1H, H-4, J = 2.4 Hz), 2.67–2.47 (m, 1H, H-1⁗), 2.46–2.28 (m, 2H, H-1⁗, H-5), 2.26–2.19 (m, 1H, H-1′, with underneath s, 3H, NCH_3 at 2.23 ppm), 2.11–1.75 (m, 5H, H-3, H-3⁗, H-6, H-7), 1.66–1.40 (m, 6H, H-1, H-2, H-2⁗, H-3, H-5′), 1.38–1.17 (m, 5H, H-2, H-2′, H-3′, H-6, H-7), 1.16–1.06 (m, 3H, H-3′, H-4′), 1.04–0.94 (m, 1H, H-2′), 0.91 (d, 3H, CH_3-1′, J = 5.9 Hz), 0.86 (s, 3H, CH_3-3a), 0.84 (d, 3H, CH_3-5′, J = 6.0 Hz), 0.82 (d, 3H, H-6′, J = 6.0 Hz), 0.71 (s, 3H, CH_3-7a). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.6 (4⁗-CH), 114.7 (5⁗-CH_2), 75.5 (4-CH), 62.7 (5-CH), 53.0 (1⁗-CH_2), 48.5 (3a-C), 47.2 (1-CH), 44.3 (7a-C), 39.6 (NCH_3), 38.4 (6-CH_2), 36.5 (3-CH_2), 35.8 (1′-CH), 34.9 (7-CH_2), 31.8 (4′-CH_2), 31.5 (3⁗-CH_2), 29.3 (2′-CH_2), 28.0 (5′-CH), 25.8 (2-CH_2), 24.3 (3′-CH_2), 22.9 (6′-CH_3), 22.6 (CH_3-5′), 21.3 (CH_3-3a), 20.5 (2⁗-CH_2), 19.8 (CH_3-7a), 18.9 (CH_3-1′). HRMS Found 377.3659 (Calcd 377.3658). IR (NaCl, film, cm^{-1}): 3401, 2951, 2867, 1497, 1346, 1201, 1037, 991, 916, 841, 753. $[\alpha]_D^{20}$ +12 (0.5; $CHCl_3$).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.01.041. These data include MOL files and InChiKeys of the most important compounds described in this article.

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