Structure Activity Relationships of New Inhibitors of Mammalian 2,3-Oxidosqualene Cyclase Designed from Isoquinoline Derivatives

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We have designed more potent inhibitors from the previously reported LF 05-0038, a 6-isoquinolinol based inhibitor of 2,3-oxidosqualene cyclase (IC_{50}: 1.1 μM). Replacement of the 3-OH group by various 3-substituted amino groups, and modification of the alkyl chain borne by the endocyclic nitrogen led to inhibitors with IC_{50} in the range of 0.15 to 1 μM. In a second step, opening of the bicyclic ring system afforded the corresponding aminoalkylpiperidines which were slightly more potent. Finally, introduction of suitable aromatic containing moieties on the piperidine nitrogen yielded very potent inhibitors such as 20x (IC_{50}=18 nM) easy to synthesize and achiral. The recent availability of the crystal structure of squalene-hopene cyclase allowed us to construct a three-dimensional (3D) model of the related 2,3-oxidosqualene cyclase (OSC) which was tentatively used to describe the possible mode of binding of our compounds and which can be useful for designing new inhibitors.

Key words 2,3-oxidosqualene cyclase inhibitor; 6-isoquinolineamine; aminoalkylpiperidine; squalene-hopene cyclase; 3D model

Inhibition of 2,3-oxidosqualene cyclase (OSC; EC 5.4.99.7) is an interesting target for the design of new hypocholesterolemic drugs useful for the prevention of cardiovascular diseases.[1)] OSC catalyzes the conversion of (*S*)-2,3-oxidosqualene to lanosterol which is probably one of the most complex enzymatic reaction described so far. A huge number of studies have been devoted to the elucidation of its mechanism of action for more than four decades.[2)] Although either kinetic or structural approaches have been recently described,[3)] none of them is really able to give a full picture of the cyclisation/rearrangement process. In this perspective, crystallographic study of this enzyme could be very helpful but has still to be performed. However, the crystal structure of a closely-related enzyme: squalene-hopene cyclase, has been recently determined.[4)] Moreover, the photolabeling of this enzyme[5a,b)] with [^{3}H]Ro48-8071, a molecule known as a potent inhibitor of both lanosterol synthase and squalene-hopene cyclase, has also shed some light on this issue. Finally an important review[5c)] on the mechanistic aspects of the synthesis of polycyclic triterpene gives a general picture on the role of the enzyme in protecting the intermediate carbocations against addition of water allowing the polycyclisation to proceed. We recently described inhibitors of OSC[6)] based on the 6-isoquinolinol structure. This template which is supposed to mimic a postulated *pro*-C8 carbocation intermediate **I** (Fig. 1) along the cyclisation-rearrangement pathway to lanosterol, was initially developed by Rahier and coworkers.[7)] Our study focused on the investigation of the structural requirements of 6-isoquinolinol-based inhibitors for OSC inhibition. Unfortunately, the obtained inhibitors remained synthetically poorly accessible due to the presence of several chiral centers. Nevertheless, we have determined some important features that can be used for the design of more readily accessible molecules. In this publication, we present our efforts based on previous results, to obtain new potent and easily accessible inhibitors of OSC.

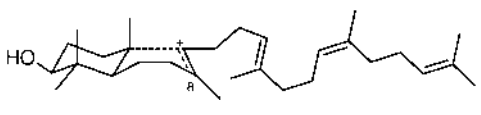

Fig. 1. Postulated *pro*-C8 Carbocation Intermediate **I**

Chemistry

The synthetic route to the key intermediates leading to the compounds listed in Tables 1 and 2 is shown in Chart 1. Reductive amination of the carbonyl compounds **1a**—**c**[6)] with NH_4OAc and $NaBH_3CN$[8)] in CH_3OH provided amino derivatives which were acylated using TFAA in THF. Chromatographic separation of the isomers afforded β and α isomers **2a**—**c** and **3a**, **b** in a 85/15 ratio. Assignments of the stereochemistry of **2a**—**c** and **3a**, **b** were made by ^{1}H-NMR analysis using the chemical shift of the proton borne by C-6.[9)] Deprotection of the trifluoroacetyl group was carried out with K_2CO_3 in refluxing aqueous CH_3OH (Method A).

Deprotection of the N-Boc group of **2c** (Chart 2) was achieved in a conventional way with 3 N HCl in CH_3OH to afford **6** which was alkylated with *n*-bromododecane in CH_3CN (Method B). Compound **7** was deprotected using method A to obtain **8a**. Preparation of **8d** was achieved using CH_3I as alkylating agent with NaH in *N*,*N*-dimethylformamide (DMF) followed by hydrolysis of the trifluoroacetyl moiety. The synthetic route to **8b**, **c**, **e**—**h** is shown in Chart 3. The intermediates **4a** and **5b** were converted to **9a** and **10b** by reductive alkylation with HCHO and $NaBH_3CN$ (Method C).[10)] Removal of the protective groups of **9a** and **10b** was achieved by either hydrogenolysis for **9a** or the Olah's method[11)] for **10b** to afford **11** and **12**, respectively. Alkylation of **12** with *n*-bromododecane in CH_3CN (Method B) afforded **8b**. The isoquinolines **8c**, **e**—**h** were obtained by either alkylation using 1-bromo-6,6-dimethyl-2-hepten-4-yne or a reductive alkylation when aldehydes or ketones were commercially available (Method D), or by a two-step procedure involving the formation of an amide followed by reduction with Red-Al (Method E). The preparation of piperidineethanamine derivatives (Tables 3, 5) is illustrated in Charts 4—6. Aldol condensation between 4-piperidone **13** and ethyl isobutyrate in the presence of lithium diisopropylamide (LDA) led to 4-hydroxy-piperidine[12)] **14** which was subsequently dehydrated with $SOCl_2$ in $CHCl_3$ to give **15** (Chart

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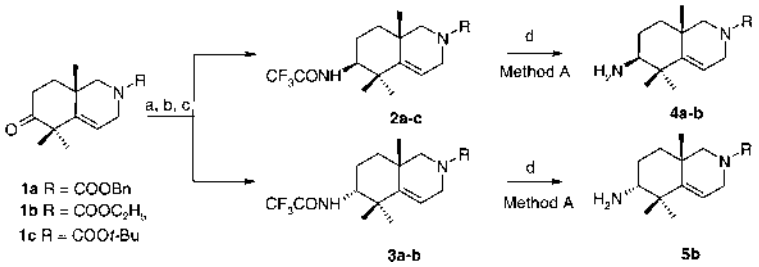
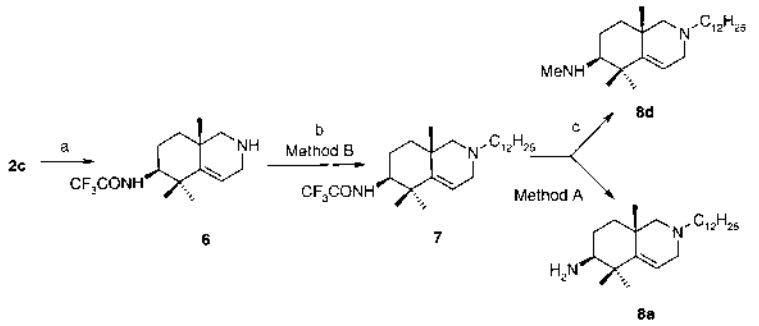


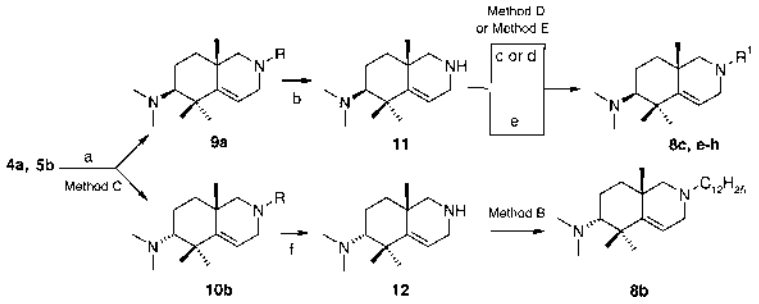
Reagents: (a) NH_4OAc, $NaBH_3CN$, MeOH; (b) TFAA, Et_3N, THF; (c) chromatographic separation; (d) K_2CO_3, MeOH, H_2O, reflux.

Chart 1



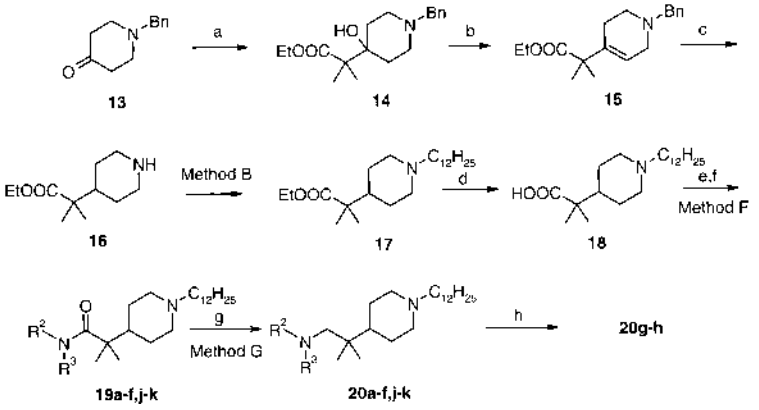
Reagents: (a) 3 N HCl, MeOH; (b) *n*-$C_{12}H_{25}Br$, K_2CO_3, CH_3CN; (c) NaH, CH_3I, DMF then K_2CO_3, MeOH, H_2O, reflux.

Chart 2



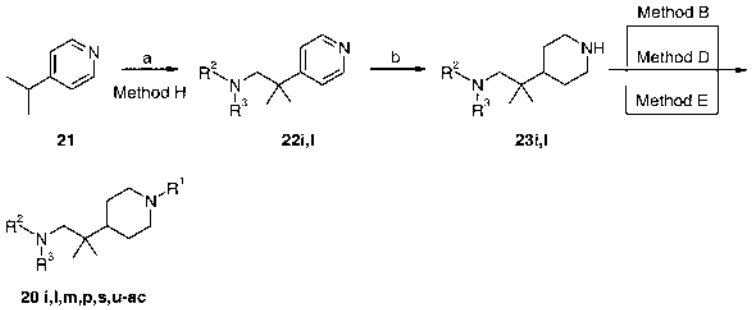
Reagents: (a) HCHO, $NaBH_3CN$, MeOH; (b) H_2, Pd/C, AcOH; (c) R^2COR^3, $NaBH_3CN$, MeOH; (d) R^4COOH, CDI, THF then Red-Al®, toluene; (e) R^1Br, K_2CO_3, CH_3CN; (f) Me_3SiCl, NaI, CH_3CN.

Chart 3



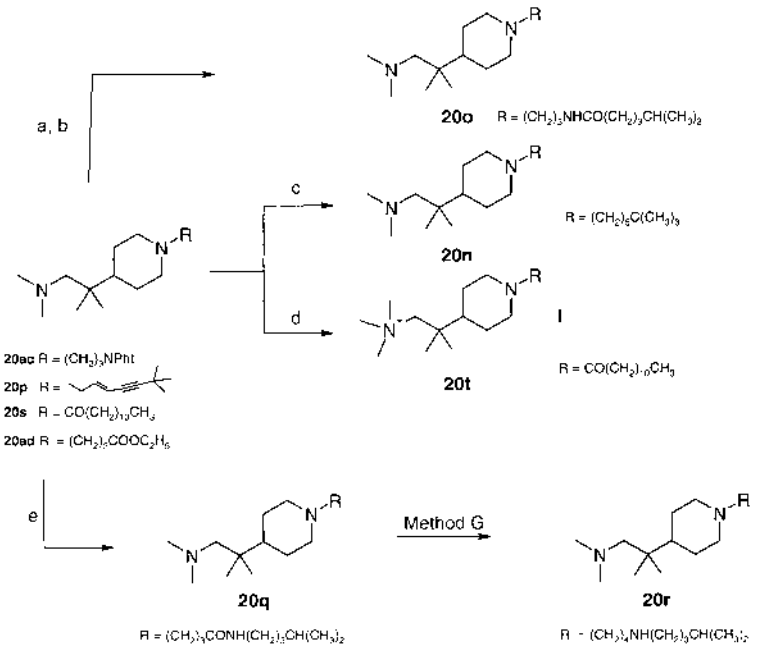
Reagents: (a) LDA, $(CH_3)_2CHCOOEt$, THF, −50 °C; (b) $SOCl_2$, $CHCl_3$, cat DMF; (c) 80 atm H_2, Pd/C, MeOH, 70 °C; (d) NaOH, EtOH, H_2O then 5 N HCl; (e) $SOCl_2$; (f) R^2R^3NH; (g) Red-Al®, toluene, reflux; (h) Ac_2O, Et_3N, CH_2Cl_2.

Chart 4



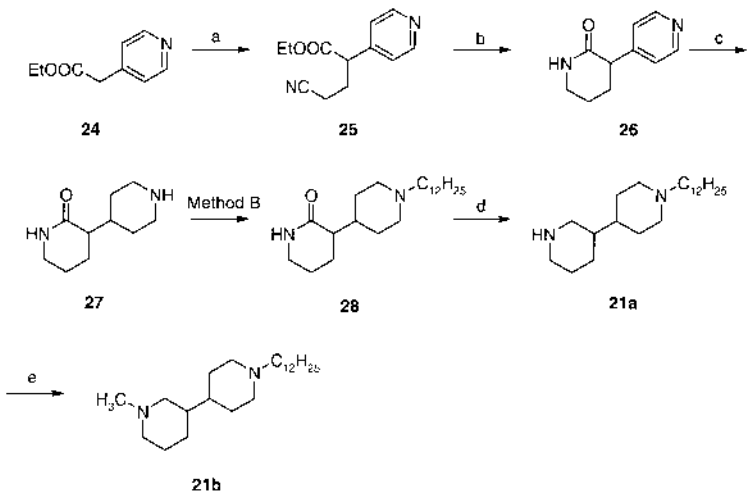
Reagents: (a) R^2R^3NH, HCHO, AcOH; (b) PtO_2, AcOH, H_2 45 psi, 60 °C.

Chart 5



Reagents: (a) $N_2H_4 \cdot H_2O$, EtOH; (b) $Me_2CH(CH_2)_3COCl$, Et_3N, CH_2Cl_2; (c) H_2, Pd/C, MeOH; (d) CH_3I, Et_2O; (e) $Me_2CH(CH_2)_3NH_2$, toluene, reflux.

Chart 6



Reagents: (a) acrylonitrile, Triton B, *tert*-BuOH; (b) Raney Ni, EtOH, NH_3, 50 °C, H_2 50 psi; (c) H_2, PtO_2, AcOH then NaOH; (d) $LiAlH_4$, THF; (e) HCOOH, HCHO.

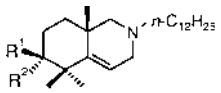
Chart 7

4). Hydrogenation of the double bond and hydrogenolysis of the benzyl group of **15** proceeded in one step with 5% Pd/C as catalyst under 80 atm H_2 pressure to afford **16**. Alkylation of **16** gave **17** which was hydrolyzed with NaOH to afford **18**. Reaction of acid **18** with $SOCl_2$ followed by condensation of the resulting acid chloride with various amines, afforded amide derivatives **19a**—**f**, **j**, **k** (Method F) which were reduced with Red-Al (Method G). An alternative original three-step synthesis has been developed for the preparation of **20i**, **l**, **m**, **p**, **s**, **u**—**ab** (Chart 5) which involved a Mannich reaction (Method H)[13a,b] between commercially available 4-isopropylpyridine, formaldehyde and secondary amines in the first step. Hydrogenation of the pyridine ring with PtO_2 as catalyst in the second step was followed by alkylation of the resulting piperidine derivatives using methods B, D or E. The preparation of compounds **20n**, **o**, **q**, **r**, **t** was performed following the pathways described in Chart 6. Hydrazinolysis of **20ac** and subsequent acylation of the resulting amine with 5-methyl hexanoyl chloride in CH_2Cl_2 in the presence of Et_3N gave **20o**. Compound **20n** was prepared by hydrogenation of the unsaturated bonds of **20p** with Pd/C as catalyst. Quaternary ammonium salt **20t** was obtained by reacting **20s** with CH_3I in ether. Refluxing **20ad** with 4-methyl pentaneamine in toluene gave **20q** which was reduced following Method G. Preparation of bipiperidine derivatives (Table 4) is shown in Chart 7. Michael addition of acrylonitrile with **24** afforded **25**.[14] Hydrogenation of **25** and simultaneous cyclization of the resulting amino ester was performed in a Parr apparatus with Raney nickel as catalyst and afforded **26** in good yield. Catalytic hydrogenation of the pyridine ring of **26** with PtO_2 in AcOH followed by alkylation of the resulting compound **27** yielded **28**. Reduction of the piperidone **28** with $LiAlH_4$ led to **21a**. This compound was finally methylated following Eschweiler–Clarke[15a—c] procedure to provide **21b**.

Results and Discussion

OSC inhibition was measured using rat liver microsomes and synthetic (*R*,*S*)-2,3-oxidosqualene. The inhibition potencies were expressed as IC_{50} values. The 6-isoquinolinol derivative LF 05-0038 (see Table 1)[6] was designed as a mimic of the postulated *pro*-C8 carbocation intermediate **I** along the cyclisation-rearrangement pathway, *i.e.* the second intermediate step of the 2,3-oxidosqualene cyclization (Fig. 1). The hydroxyl group of 6-isoquinolinol was the equivalent of the hydroxyl group of the A ring system in the intermediate **I**. On the other hand, the positive charge borne by the protonated nitrogen was supposed to mimic the C-8 carbocation of **I**. Most of the results obtained with various analogues were consistent with this hypothesis.[6] In this study we turned our attention to several features of the 6-isoquinolinol derivatives with the aim of finding synthetically more accessible inhibitors with more drug-like structures. We first investigated

Table 1. 1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-6-isoquinolineamine Derivatives



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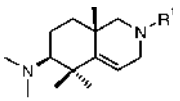
Compd.	R^1	R^2	mp, °C	Yield, % (Method)	Formula[a]	OSC inh IC_{50} μM
LF05-0038[d]	OH	H				1.1
8a	NH_2	H	170	75 (A)	$C_{24}H_{46}N_2 \cdot C_4H_4O_4$[b]	85
8b	H	NMe_2	139	34 (D)	$C_{26}H_{50}N_2 \cdot 2C_2H_2O_4$[c]	5.7
8c	NMe_2	H	193	80 (C)	$C_{26}H_{50}N_2 \cdot 3C_4H_4O_4$[b]	0.44
8d	NHMe	H	130	47 (A)	$C_{25}H_{48}N_2 \cdot C_2H_2O_4$[c]	25

a) Analytical results are within ±0.4% of theoretical values unless otherwise noted. *b*) Fumarate. *c*) Oxalate. *d*) Reference 6.

Table 2. *N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-6-isoquinolineamine Derivatives



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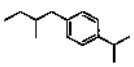
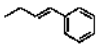
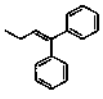
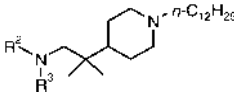
Compd.	R^1	mp, °C	Yield, % (Method)	Formula[a]	OSC inh IC_{50} μM
8c	n-$C_{12}H_{25}$	193	74 (D)	$C_{26}H_{50}N_2 \cdot 3C_4H_4O_4$[b]	0.44
8e		142	41 (D)	$C_{27}H_{44}N_2 \cdot C_4H_4O_4$[b]	0.23
8f		oil	26 (B)	$C_{23}H_{38}N_2$	0.26
8g		210	59 (E)	$C_{23}H_{34}N_2 \cdot 2C_7H_8O_3S$[c]	0.15
8h		150	95 (E)	$C_{29}H_{38}N_2 \cdot 2C_2H_2O_4$[d]	0.32

a) Analytical results are within ±0.4% of theoretical values unless otherwise noted. *b*) Fumarate. *c*) Tosylate. *d*) Oxalate.

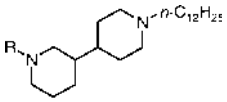
Table 3. β,β-Dimethyl-1-dodecyl-4-piperidineethanamine Derivatives



Compd.	R^2	R^3	mp, °C	Yield, % (Method)	Formula[a]	OSC inh IC_{50} μM
20a	H	H	100	64 (G)	$C_{21}H_{44}N_2 \cdot C_4H_4O_4$[b]	7.1
20b	Me	H	139	79 (G)	$C_{22}H_{46}N_2 \cdot 2C_7H_8O_3S$[d]	0.34
20c	Et	H	160	100 (G)	$C_{23}H_{48}N_2 \cdot 2C_4H_4O_4$[b]	0.66
20d	Pr	H	186	95 (G)	$C_{24}H_{50}N_2 \cdot C_4H_4O_4$[b]	>50
20e	*i*-Pr	H	114	80 (G)	$C_{24}H_{50}N_2 \cdot 2C_7H_8O_3S$[d]	55
20f	Bn	H	174	95 (G)	$C_{28}H_{50}N_2 \cdot 2C_4H_4O_4$[b]	>50
20g	Ac	Me	102	97	$C_{24}H_{48}N_2O \cdot C_7H_8O_3S$[d]	18.9
20h	Ac	H	113	86	$C_{23}H_{46}N_2O \cdot C_4H_4O_4$[b]	14.3
20i	Me	Me	132	100 (B)	$C_{23}H_{48}N_2 \cdot 2C_4H_4O_4$[b]	0.12
20j	Et	Et	108	85 (G)	$C_{25}H_{52}N_2 \cdot 2C_4H_4O_4$[b]	13.7
20k	Me	Bn	124	82 (G)	$C_{29}H_{52}N_2 \cdot C_4H_4O_4$[b]	>50
20l	$(CH_2)_5$		129	70 (D)	$C_{26}H_{52}N_2 \cdot 2C_4H_4O_4$[c]	35

a) Analytical results are within ±0.4% of theoretical values unless otherwise noted. *b*) Fumarate. *c*) Maleate. *d*) Tosylate.

Table 4. 3-[4-(1-Dodecylpiperidinyl)]piperidine Derivatives



Compd.	R	mp, °C	Yield, %	Formula[a]	OSC inh IC_{50} μM
21a	H	176	97	$C_{22}H_{44}N_2 \cdot 2C_7H_8O_3S$[b]	>50
21b	Me	160	95	$C_{23}H_{46}N_2 \cdot 2C_7H_8O_3S$[b]	42

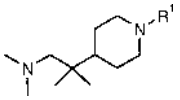
a) Analytical results are within ±0.4% of theoretical values unless otherwise noted. *b*) Tosylate.

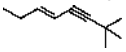
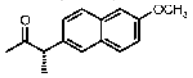
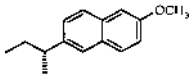
the importance of the hydroxyl group. Indeed, the cyclization process mediated by the enzyme is triggered by the protonation of the epoxide and the proton donor is very likely the Asp456.[5c,20] We thus introduced several types of amine in place of the hydroxyl group in order to increase the affinity for the active site by the putative resulting ionic interaction with the Asp456. A similar approach was fruitful in the case of squalene based inhibitors.[1b] Table 1 shows that the primary amine **8a** is much less active than the parent hydroxylated analogue. However, the corresponding dimethylated tertiary amine **8c**[18] is about two orders of magnitude more potent than the primary amine **8a** and about two-fold more potent than the corresponding hydroxylated compound. As previously observed for the corresponding α-hydroxylated analogue,[6] the α-isomer **8b** is about ten-fold less active than the β-isomer **8c**. The monomethyl derivative **8d** is fifty-fold less active than the dimethyl derivative **8c**. These results are consistent with the formation of an ionic interaction with the Asp456 although the part played by the methyl groups is still unclear. Table 2 presents a few derivatives in which the saturated dodecyl chain was replaced by various unsaturated substituents intended to better mimic the terpenic chain of the natural substrate. The chains supposed to mimic the squalenoid moiety encountered in terbinafine[25] and naftifine,[26] led to more potent compounds **8f** and **8g**. In order to simplify the core of these inhibitors, we opened the ring, mimicking the A ring system of the *pro*-C8 carbocation intermediate **I**,[17] and removed the angular methyl group leading to the achiral 4-piperidineethanamine derivatives.[19] We have indeed shown in a previous study,[6] that the angular methyl group was not necessary for the activity. The flexibility brought by the ring opening seems to be favorable to the activity as shown by the resulting primary amine **20a** found to be about ten-fold more potent than the corresponding bicyclic analogue **8a**. We then investigated in details the influence of the substituents borne by the terminal nitrogen atom. Among the secondary amines, the smaller the substituent was, the better the activity: the IC_{50} was 0.34 μM for **20b**, 0.66 μM for **20c** and >50 μM for **20d**—**f**. The same trend was observed with tertiary amines, where the best activity, similarly to the bicyclic series, was observed for the dimethyl derivative **20i** (IC_{50}=0.12 μM). Finally, we synthesized the amides **20g** and **20h**.

The decrease of activity observed between **20h** and **20c** seems to be consistent with the existence of an ionic interaction. The last structural change made on this part of the molecule was the insertion of the nitrogen atom in a ring, resulting into two 3-(piperidinyl)-piperidine derivatives **21a** and **21b** (Table 4). This new constraint proved to be detrimental to the activity: **21a**, which can be viewed as a rigid analogue of the active compound **20c**, was found inactive (*i.e.* IC_{50}> 50 μM) whereas the corresponding methylated analogue **21b** proved to be a weak inhibitor. A similar structure activity relationship has been published for azasqualene based inhibitors of pea seedlings and rat liver OSC.[24]

Having optimized the core structure *i.e.* a β,β-dimethyl-4-piperidineethanamine, we then studied different replacements of the saturated dodecyl chain (Table 5). In our previous work, we found that the optimal carbon chain length corresponded to a 10 to 12 carbon unit substituent. In the present study we confirmed that a very short chain (a methyl group) led to an inactive compound **20m**. The branched chain of terbinafine led to an active compound **20p**. Its complete reduction afforded **20n** showing the same activity. In contrast, introduction of polar functions such as amides or amines in the chain afforded weak inhibitors: **20o** and **20r**, except **20q** which is rather active. As previously observed[6,16] in related series, the conversion of the tertiary amine of **20i** into a tertiary amide afforded an almost equipotent derivative **20s**. In contrast, the quaternarisation of the amine of this derivative

Table 5. β,β-Dimethyl-*N*,*N*-dimethyl-4-piperidineethanamine Derivatives



Compd.	R^1	mp, °C	Yield, % (Method)	Formula[a)]	OSC inh IC_{50} μM
20m	Me	160	100 (B)	$C_{12}H_{26}N_2 \cdot 2C_4H_4O_4$[c)]	>50
20i	*n*-$C_{12}H_{25}$	132	100 (B)	$C_{23}H_{48}N_2 \cdot 2C_4H_4O_4$[c)]	0.12
20n	$(CH_2)_5C(CH_3)_3$	138	100	$C_{20}H_{42}N_2 \cdot 2C_4H_4O_4$[c)]	0.28
20o	$(CH_2)_3NHCO(CH_2)_3CH(CH_3)_2$	87	32	$C_{21}H_{43}N_3O \cdot 2C_2H_2O_4$[d)]	1.9
20p		192	56 (B)	$C_{20}H_{36}N_2 \cdot 2C_2H_2O_4$[e)]	0.23
20q	$(CH_2)_3CONH(CH_2)_3CH(CH_3)_2$	140	71	$C_{21}H_{43}N_3O \cdot 2C_4H_4O_4$[c)]	0.7
20r	$(CH_2)_4NH(CH_2)_3CH(CH_3)_2$	142	83 (G)	$C_{21}H_{45}N_3 \cdot 3C_4H_4O_4$[c)]	18
20s	$CO(CH_2)_{10}CH_3$	138	66	$C_{23}H_{46}N_2O \cdot C_2H_2O_4$[d)]	0.26
20t	$CO(CH_2)_{10}CH_3$[b)]	208	100	$C_{24}H_{49}IN_2O$	1.7
20u	$COCH{=}CHC_6H_5$	169	52	$C_{20}H_{30}N_2O \cdot C_4H_4O_4$[c)]	0.76
20v	$CH_2CH{=}CHC_6H_5$	150	95 (G)	$C_{20}H_{32}N_2 \cdot 2C_4H_4O_4$[c)]	0.73
20w	$COC(CH_3)_2OC_6H_4$-4Cl	194	60	$C_{21}H_{33}ClN_2O_2 \cdot C_4H_4O_4$[c)]	0.33
20x	$CH_2C(CH_3)_2OC_6H_4$-4Cl	110	83 (G)	$C_{21}H_{35}ClN_2O \cdot 2C_4H_4O_4$[c)]	0.018
20y		169	58	$C_{25}H_{36}N_2O_2 \cdot C_2H_2O_4$[d)]	41
20z		166	100 (G)	$C_{25}H_{38}N_2O \cdot 2C_4H_4O_4$[c)]	0.82
20aa	$COCH(CH_3)C_6H_4$-4*i*Bu	172	74	$C_{24}H_{40}N_2O \cdot C_4H_4O_4$[c)]	2.7
20ab	$CH_2CH(CH_3)C_6H_4$-4*i*Bu	145	88 (G)	$C_{24}H_{42}N_2 \cdot 2C_4H_4O_4$[c)]	0.42

a) Analytical results are within ±0.4% of theoretical values unless otherwise noted. *b*) Quaternary methylammonium iodide. *c*) Fumarate. *d*) Oxalate. *e*) Maleate.

led to **20t** which was six-fold less active. Different compounds bearing aromatic containing substituents were then synthesized as amides and their corresponding amines. In general, the amines proved to be more active than the amides. For example, **20ab** is six-fold more active than **20aa**. This trend culminates with compounds **20w** and **20x**, this one being the most potent inhibitor of this series with an IC_{50} of 0.018 μM.

The publication of the crystal structure of squalene-hopene cyclase led us to construct a 3D model of the rat OSC starting from the sequence alignment suggested by Wendt *et al.*[4)] The conformation of the inserted loops was then deduced from similar sequences encountered in proteins structures of the Protein Data Bank according to a well-validated homology modeling methodology.[21)] The amino-acids close to the site which triggers the cyclisation, *i.e.* around the Asp456 (or the corresponding Asp376 of the squalene-hopene cyclase), are well conserved among the two enzymes, except Asp377 which is only present in squalene-hopene cyclase.[4,5c)] This suggests a high similarity of the active sites of the two enzymes at least in this region. Consequently, although our model should be confirmed by further studies, it could be tentatively used *a posteriori* to explain some of the features of the structure activity relationships observed in our series of inhibitors. The crystal structure of the squalene-hopene cyclase co-crystallized with a competitive inhibitor: *N*,*N*′-dimethyldodecylamine-*N*-oxide shows that the nitrogen atom of this inhibitor is close to the Asp376. It was previously shown[6,16)] that the 6-isoquinolinol-based inhibitors of OSC behave as competitive inhibitors. In the hypothesis that the closely-related amino analogues behave similarly, their binding to the active site should position the exocyclic protonated nitrogen nearby the Asp456 which corresponds to Asp376 in hopene-squalene cyclase. The docking of the two inhibitors **8c** and **20x** was made starting from this assumption (Figs. 2, 3). The cavity surrounding the Asp456 can easily accommodate one or two methyl groups but not bulkier groups without destroying the possible salt bridge. In the case of compound **8c**, the two methyl groups come in close contact to the aromatic ring of Trp388 (Figs. 2, 3). However a dramatic decrease of potency was observed in the piperidine series and with compounds bearing moieties bulkier than the dimethylamino group such as **20d**, **20e**, **20f**, **20j**, **20k**, **20l**, **21a** and **21b**. However, this model does not explain the very bad activities of the primary amine **8a** and the secondary amine **8d**. It should not be forgotten that this enzyme is membrane bound and that the inhibitor, similarly to the substrate,[4)] should diffuse to the active site through the phospholipid bilayer. The amount of the inhibitor available at the active site is thus depending on the partitioning of the inhibitor between the aqueous phase and the membrane, and a direct analysis of the structure activity relationships is consequently difficult. Fig. 4 shows a possible mode of binding of the best inhibitor **20x** in the active site of the enzyme. It is worthnoting that the flexibility brought by the opening of the bicycle induces a better positioning of the dimethylamino group of this derivative towards the Asp456 and Trp388, optimizing ionic interaction and Van der Waals contacts (the distance between the nitrogen of **20x** and the closest oxygen of Asp486 is 2.84 Å *versus* 3.23 Å for **8c**). A H-bond between the hydrogen of the cyclic ammonium and the oxygen of Tyr99 is made possible with this compound (the distance between the corresponding atoms in the case of **8c** is 3.99 Å compared to 2.54 Å with **20x**). Finally, the 4-chlorophenoxy moiety is lo-

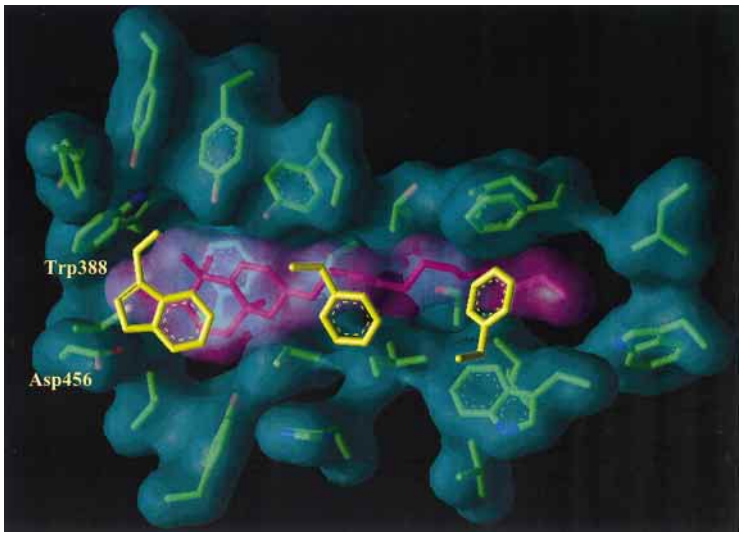


Fig. 2. Compound **8c** Docked in the 3D Model of the Active Site of Rat OSC

The solvent accessible surface of the residues is visualized except for Trp582, Phe697 and Phe522 (in yellow) to make the inhibitor (in magenta) more perceptible. This picture shows the interactions between the two methyl groups and the exocyclic ammonium moiety of the inhibitor respectively with Trp388 and Asp456.

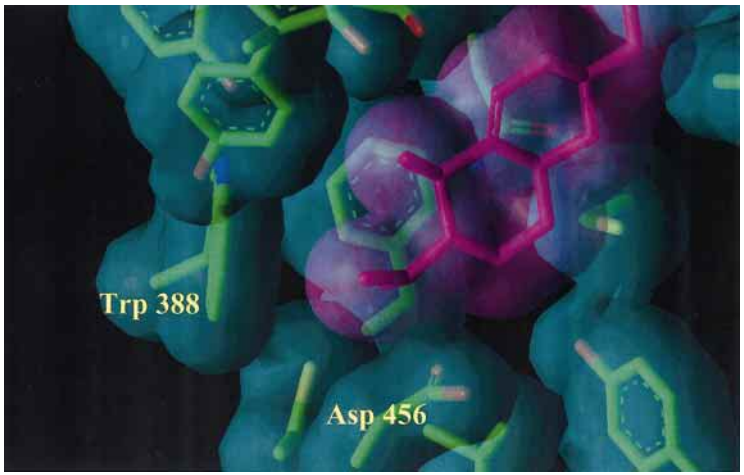


Fig. 3. A Closer View of the Interactions between the Two Methyl Groups and the Exocyclic Ammonium Moiety of the Inhibitor **8c** (in Magenta) Respectively with Trp388 and Asp456 of the Enzyme

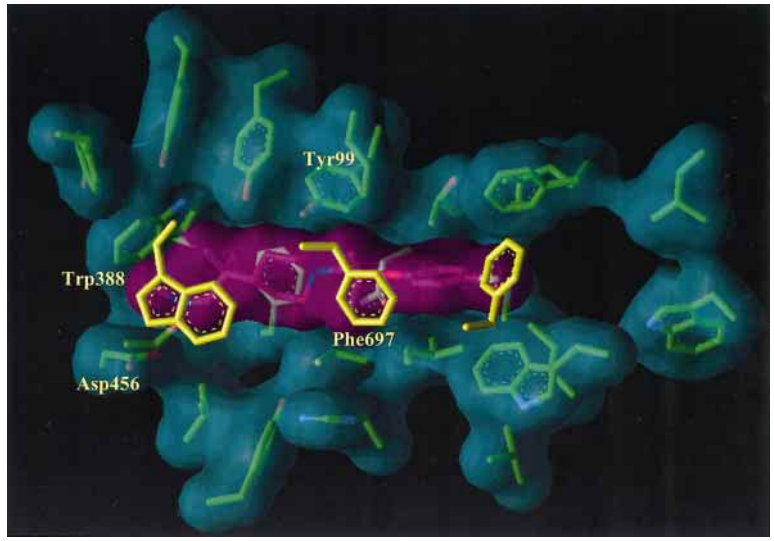


Fig. 4. Compound **20x** Docked in the 3D Model of the Active Site of Rat OSC

The solvent accessible surface of the residues is visualized except for Trp582, Phe697 and Phe522 (in yellow) to make the inhibitor **20x** (in magenta) more perceptible. This view shows: the interactions between the two methyl groups and the exocyclic ammonium moiety of the inhibitor respectively with Trp388 and Asp456, the cyclic ammonium possibly H-bound to the oxygen atom of Tyr99, a T-shape interaction between the phenoxy group of **20x** and Phe697, and the highly hydrophobic environment of the chlorine atom of the inhibitor.

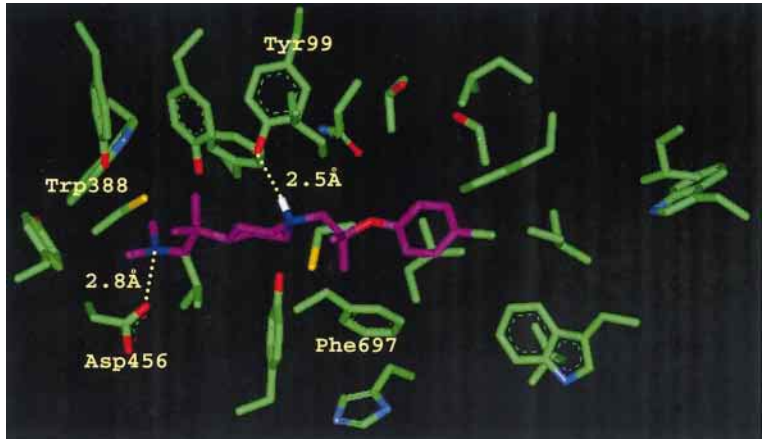


Fig. 5. Compound **20x** Docked in the 3D Model of the Active Site of Rat OSC

This view shows: the possible interactions of the dimethylamino moiety of **20x** between the two methyl groups with the Trp388 and the exocyclic ammonium with the Asp456, the cyclic ammonium H-bound to the oxygen atom of Tyr99, a T-shape interaction between the phenoxy group of **20x** and Phe697, and the highly hydrophobic environment of the chlorine atom of the inhibitor.

cated in a cavity suitably adapted and highly hydrophobic where the Phe697 develops a clear T-shape interaction with the phenyl of **20x** and where the chlorine atom is surrounded with aliphatic and aromatic residues (Fig. 5). All these features may explain the high potency of this inhibitor. A closer look at these docking models could help the design of more potent inhibitors, for instance, replacing the chlorine atom of **20x** by a hydrophobic group such a phenyl which could bring a supplementary interaction surface. It can be noticed that halogenated aryl substituents have been successfully introduced in Roche and Karl Thomae OSC inhibitors.[1c,d] In conclusion, based on a good OSC inhibitor (LF 05-0038) obtained in a previous study, we designed structurally simpler molecules and found a rather potent inhibitor: **20x**. Contrary to LF 05-0038, this molecule, which is achiral and readily accessible, deserves further biological tests, in particular *in vivo* studies. Furthermore, the recent availability of the crystal structure of hopene-squalene cyclase led us to construct a 3D model of OSC that could help designing new inhibitors of this enzyme.

Experimental

Melting points were determined on a Büchi melting point apparatus and were uncorrected. IR spectra were measured on a Perkin-Elmer 782 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker AC300 spectrometer using tetramethylsilane as internal standard. MS spectra were measured with a Nermag Model R30-10 spectrometer. Structural assignments for all new compounds are consistent with their spectra. Elemental analyses were performed on a Perkin-Elmer 240C apparatus.

(6*β*,8a*β*)-3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-6-trifluoroacetylamino-2(1*H*)-isoquinolinecarboxylic Acid Phenylmethyl Ester (2a) and (6*α*,8a*β*)-3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-6-trifluoroacetylamino-2(1*H*)-isoquinolinecarboxylic Acid Phenylmethyl Ester (3a) To a solution of **1a** (65 g, 20 mmol) in 700 ml of methanol was added ammonium acetate (153 g, 2 mol), the pH of the resulting solution was adjusted at 7.3 with AcOH then $NaBH_3CN$ (20 g, 30 mmol) was added portionwise. The mixture was stirred for 2 d at room temperature then concentrated. The residue was extracted with EtOAc, washed with water, dried ($MgSO_4$) and evaporated to afford 3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-6-amino-2(1*H*)-isoquinolinecarboxylic acid phenylmethyl ester (52 g, 82%) as an oil. To a solution of this product (50 g, 0.15 mol) and Et_3N (25.5 ml) in 200 ml of THF was added dropwise TFAA (25.8 ml, 0.18 mol) in 50 ml of THF keeping the temperature at 0 °C then the mixture was stirred overnight at room temperature. After evaporation, the residue was dissolved in ether, washed with 1 N HCl, with water, dried ($MgSO_4$) and evaporated. Purification of the oily residue by silica-gel column chromatography (isopropyl ether–methylcyclohexane, 9/1) gave **2a** (37.1 g, 59%) as a solid: mp 138 °C and **3a** (6.5 g, 12%) as an oil: n_D^{36}=1.5145. **2a**: ^{1}H-NMR ($CDCl_3$) *δ*: 1.07—1.09 (6H, br s, CH_3), 1.16 (1.5H, s, CH_3), 1.20 (1.5H, s, CH_3), 1.28—1.39 (1H, m, H-8$_a$), 1.53—1.64 (1H, m, H-8$_b$), 1.71—1.85 (2H, m, H-7$_a$, H-7$_b$), 2.56 (0.5H, d, *J*=12.5 Hz, H-1$_a$), 2.62 (0.5H, d, *J*=12.7 Hz, H-1$_a$), 3.67—3.91 (3H, m, H-3$_a$, H-1$_b$, H-6*α*), 4.25—4.38 (1H, m, H-3$_b$), 5.16 (2H, s, $\underline{CH_2}$–Ph), 5.55 (1H, d, *J*=21.9 Hz, H-4), 6.19 (1H, d, *J*=9.4 Hz, $CF_3CON\underline{H}$), 7.30—7.38 (5H, m, Ph). *Anal.* Calcd for $C_{22}H_{27}F_3N_2O_3$: C, 62.25; H, 6.41; N, 6.60. Found: C, 62.17; H, 6.39; N, 6.54. **3a**: ^{1}H-NMR (250 MHz, $CDCl_3$) *δ*: 1.08 (3H, s, CH_3), 1.22—1.27 (7H, m, CH_3, H-8$_a$), 1.43—1.54 (1H, m, H-8$_b$), 1.70—1.81 (1H, m, H-7$_a$), 2.09—2.27 (1H, m, H-7$_b$), 2.54—2.65 (1H, m, H-1$_a$), 3.73—4.03 (3H, m, H-3$_a$, H-1$_a$, H-6*β*), 4.28—4.41 (1H, m, H-3$_b$), 5.17 (2H, s, $\underline{CH_2}$–Ph), 5.49—5.56 (1H, m, H-4), 6.00 (1H, d, *J*=7.5 Hz, $CF_3CON\underline{H}$), 7.31—7.38 (5H, m, Ph).

The following compounds were prepared in a similar manner from **1b** and **1c**.

(6*β*,8a*β*)-3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-6-trifluoroacetylamino-2(1*H*)isoquinolinecarboxylic Acid Ethyl Ester (2b) mp 70—80 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.08 (3H, s), 1.10 (3H, s), 1.18 (1.5H, s), 1.19 (1.5H, s), 1.27 (3H, t, *J*=5.08 Hz), 1.37 (1H, m), 1.55 (1H, m), 1.80 (2H, m), 2.56 (1H, m), 3.76 (3H, m), 4.17 (2H, q, *J*=5.08 Hz), 4.32 (1H, m), 5.55 (1H, m), 6.13 (1H, d, *J*=9.5 Hz).

(6*α*,8a*β*)-3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-6-trifluoroacetylamino-2(1*H*)-isoquinolinecarboxylic Acid Ethyl Ester (3b) n_D^{32}=1.4845; ^{1}H-NMR ($CDCl_3$) *δ*: 1.08 (3H, s), 1.24 (11H, m), 1.27 (3H, t, *J*=5.08 Hz), 1.47 (1H, m), 1.75 (1H, m), 2.21 (1H, m), 2.56 (1H, m), 3.77 (1H, m), 3.95 (1H, m), 4.17 (2H, q, *J*=5.08 Hz), 4.34 (1H, m), 5.50—5.55 (1H, m), 6.01 (1H, d, *J*=7.16 Hz).

(6*β*,8a*β*)-3,5,6,7,8,8a-Hexahydro-5,5,8a-trimethyl-6-trifluoroacetylamino-2(1*H*)-isoquinolinecarboxylic Acid 2-Methyl-2-propyl Ester (2c) mp 156 °C; ^{1}H-NMR ($CDCl_3$) *δ*: 1.08 (3H, s), 1.12 (3H, s), 1.18 (3H, s), 1.34—1.61 (11H, m), 1.73—1.87 (2H, m), 2.48—2.59 (1H, m), 3.64—3.76 (1H, m), 3.79—3.84 (1H, m), 5.52—5.58 (1H, m), 6.13 (1H, d, *J*=9.5 Hz).

(6*β*,8a*β*)-6-Amino-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-2(1*H*)-isoquinolinecarboxylic Acid Phenylmethyl Ester (4a) Method A A mixture of **2a** (35 g, 80 mmol), of K_2CO_3 (115 g, 0.8 mol) in 500 ml of CH_3OH and 100 ml of H_2O was refluxed for 8 h. Upon cooling at room temperature, the mixture was evaporated and the residue was partitioned between EtOAc and water. The organic solution was washed with water, dried ($MgSO_4$) and concentrated to give 27 g (100%) of **4a**. ^{1}H-NMR ($CDCl_3$) *δ*: 0.99 (3H, s), 1.17—1.28 (8H, m), 1.46—1.67 (3H, m), 2.17 (2H, br s), 2.45—2.61 (1H, m), 3.65—3.86 (2H, m), 4.24—4.36 (1H, m), 5.16 (2H, s), 5.50 (1H, m), 7.30—7.38 (5H, m).

The following compounds were prepared in a similar manner from **2b**, **c** and **3a**, **b**.

(6*β*,8a*β*)-6-Amino-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-2(1*H*)-isoquinolinecarboxylic Acid Ethyl Ester (4b) ^{1}H-NMR ($CDCl_3$) *δ*: 0.99 (3H, s), 1.13—2.04 (16H, complex m), 2.39—2.60 (2H, m), 3.82—3.84 (1H, m), 4.12—4.20 (2H, m), 4.25—4.35 (1H, m), 5.50 (1H, d).

(6*α*,8a*β*)-6-Amino-3,5,6,7,8,8a-hexahydro-5,5,8a-trimethyl-2(1*H*)-isoquinolinecarboxylic Acid Ethyl Ester (5b) ^{1}H-NMR ($CDCl_3$) *δ*: 1.10 (3H, s), 1.15—1.84 (14H, complex m), 2.58—2.68 (1H, m), 2.75 (1H, br), 3.67—3.84 (2H, m), 4.12—4.34 (3H, m), 5.39—5.44 (1H, m).

(6*β*,8a*β*)-*N*-Trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-6-isoquinolineamine (6) A solution of **2c** (3.27 g, 8.37 mmol) in methanol (30 ml) and 3 N HCl (4.2 ml) was refluxed for 6 h. After cooling, the solution was evaporated, the resulting residue was poured into ice-cold 1 N NaOH (15 ml) and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated to afford **6** as a white solid (2.1 g, 87.5%): mp 160 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.08 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.22—1.34 (4H, m, CH_3, H-8$_a$), 1.46—1.53 (1H, m, H-8$_b$), 1.63 (1H, br s, N$\underline{H}$), 1.70—1.86 (2H, m, H-7), 2.48 (1H, d, *J*=12.2 Hz, H-1$_a$), 2.87 (1H, d, *J*=12.1 Hz, H1$_b$), 3.36 (1H, dd, *J*=3.8, 18 Hz, H-3$_a$), 3.45 (1H, dd, *J*=2.4, 18.0 Hz, H-3$_b$), 3.74—3.82 (1H, m, 6*α*-H), 5.59 (1H, t, *J*=3.8 Hz, H-4), 6.13 (1H, br d, CF_3CONH). This solid was converted into its tosylate: mp >260 °C. *Anal.* Calcd for $C_{14}H_{21}F_3N_2O\cdot C_7H_8O_3S$: C, 53.73; H, 6.39; N, 5.97. Found: C, 53.73; H, 6.28; N, 5.93.

(6*β*,8a*β*)-*N*-Trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine (7) Method B A suspension of **6** (2.38 g, 8.2 mmol), K_2CO_3 (2.37 g, 16.4 mmol) and of 1-bromododecane (2.25 g, 9.03 mmol) in 50 ml of acetonitrile was refluxed for 8 h. After cooling, the mixture was poured into brine and extracted with EtOAc. The combined organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The oily residue was separated on a silica gel column eluting with a solvent mixture of hexane–EtOAc (9/1) to afford **7** as a solid (3.2 g, 85%): mp 80 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 0.89 (3H, t, *J*=6.46 Hz), 1.07 (3H, s), 1.09 (3H, s), 1.28—1.34 (23H, m), 1.45—1.51 (2H, m), 1.68—1.87 (3H, m), 2.21—2.39 (2H, m), 2.46 (1H, d, *J*=11.3 Hz), 2.65 (1H, dd, *J*=2.09, 16.7 Hz), 3.30 (1H, dd, *J*=3.96, 16.7 Hz), 3.71—3.80 (1H, m), 5.55 (1H, dd, *J*=2.4, 4 Hz), 6.11 (1H, br d).

(6*β*,8a*β*)-*N*-Methyl-1,2,3,5,6,7,8,8a-octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine (8d) A solution of **7** (3.5 g , 11 mmol) in 20 ml of DMF was carefully added to a suspension of NaH (0.43 g, 60% dispersion in mineral oil). After completion of the addition, the mixture was heated at 40 °C for 1 h. The mixture was cooled, iodomethane (0.8 ml, 13 mmol) was then added and the reaction mixture was stirred at room temperature for 48 h. The mixture was poured into water and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give (6*β*,8a*β*)-*N*-methyl-*N*-trifluoroacetyl-1,2,3,5,6,7,8,8a-octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine as a solid (2.6 g, 72%): mp 60 °C. 2.5 g (5 mmol) of the previous compound was refluxed for 48 h in 200 ml of methanol, 50 ml of water and K_2CO_3 (14.6 g, 0.1 mol). After cooling, the reaction mixture was evaporated. The residue was partitioned between water and methylene chloride. The organic phase was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography with CH_2Cl_2–CH_3OH–NH_4OH (98.5/1/0.5) as eluent to give **8d** as an oil (1.5 g, 79%). ^{1}H-NMR ($CDCl_3$) *δ*: 0.88 (3H, t, *J*=6.42 Hz), 0.94 (3H, s), 1.00 (3H, s), 1.13 (3H, s), 1.25 (24H, complex m), 1.42—1.56

(1H, m), 1.74—1.96 (2H, m), 2.19—2.45 (6H, m), 2.59—2.85 (1H, dd, *J*=2.11, 16.3 Hz), 3.25—3.32 (1H, dd, *J*=4.28, 16.3 Hz), 5.47—5.49 (1H, m). This oil was converted into its oxalate: mp 134 °C. *Anal.* Calcd for $C_{25}H_{48}N_2 \cdot C_2H_2O_4$: C, 65.72; H, 10.04; N, 5.47. Found: C, 65.38; H, 9.79; N, 5.49.

(6*β*,8a*β*)-1,2,3,5,6,7,8,8a-Octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine (8a) Following Method A the title compound was prepared from **7** as an oil. ^{1}H-NMR ($CDCl_3$) *δ*: 0.88 (3H, t, *J*=6.46 Hz), 1.00 (3H, s), 1.10 (3H, s), 1.16—1.71 (29H, m), 1.77 (1H, d, *J*=10.6 Hz), 2.19—2.45 (4H, m), 2.62 (1H, dd, *J*=2.15, 16.4 Hz), 3.29 (1H, dd, *J*=3.52, 16.40 Hz), 5.48 (1H, dd, *J*=2.19, 4.43 Hz). This oil was converted into its fumarate (1.25 g, 75%): mp 170—173 °C. *Anal.* Calcd for $C_{24}H_{46}N_2 \cdot C_4H_4O_4$: C, 74.23; H, 11.50; N, 6.66. Found: C, 74.24; H, 11.61; N, 6.54.

(6*β*,8a*β*)-3,5,6,7,8,8a-Hexahydro-6-dimethylamino-5,5,8a-trimethyl-2(1*H*)-isoquinolinecarboxylic Acid Phenylmethyl Ester (9a). Method C To a solution of **4a** (27 g, 80 mmol) in 500 ml of acetonitrile were added 74 ml of formaldehyde (37% solution in water). The pH of the resulting mixture was adjusted to 7.5 by addition of acetic acid. $NaBH_3CN$ (15.5 g, 0.25 mol) was added portionwise, then the reaction mixture was stirred at room temperature for 12 h and evaporated. The residue was taken up with 1 N NaOH and extracted with EtOAc. The organic layers were washed with water, dried ($MgSO_4$) and concentrated. Purification of the residue with chromatography (eluent CH_2Cl_2–CH_3OH–NH_4OH, 8.5/1/0.5) gave **9a** (23.5 g, 80%) as an oil. ^{1}H-NMR ($CDCl_3$) *δ*: 1.02 (3H, s), 1.07—1.25 (8H, m), 1.54—1.73 (4H, m), 1.96—2.02 (1H, m), 2.29 (6H, s), 2.46—2.59 (1H, m), 3.62—3.84 (2H, m), 4.20—4.36 (1H, m), 5.16 (2H, s), 5.40—5.48 (1H, s), 7.32—7.35 (5H, m).

(6*α*,8a*β*)-3,5,6,7,8,8a-Hexahydro-6-dimethylamino-5,5,8a-trimethyl-2(1*H*)-isoquinolinecarboxylic Acid Ethyl Ester (10b) The titled compound was prepared using the same procedure as described above, starting from **5b** (1.2 g, 4.5 mmol) in 60% yield as an oil (0.82 g). ^{1}H-NMR ($CDCl_3$) *δ*: 1.15—1.20 (9H, m), 1.26 (3H, t, *J*=6.74 Hz), 1.38—1.47 (2H, m), 1.78—1.88 (2H, m), 2.30 (6H, s), 2.43 (1H, t, *J*=4.45 Hz), 2.53—2.63 (1H, m), 3.64—3.81 (2H, m), 4.12—4.26 (3H, m), 5.44 (1H, br d).

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-6-isoquinolineamine (11) A mixture of **9a** (21.5 g, 60 mmol) and 3.5 g of 5% Pd/C in 250 ml of acetic acid was stirred at room temperature under 1 atm of H_2. The catalyst was filtered and the solvent was removed. The residue was taken up with 1 N NaOH and extracted with ether. The organic solution was washed with water, dried over $MgSO_4$ and concentrated to give **11** (12.6 g, 95%) as a solid: mp 92 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.04 (3H, s, CH_3), 1.08—1.22 (4H, m, H-8$_a$ CH_3), 1.48 (3H, s, CH_3), 1.49—1.54 (1H, m, H-8$_b$), 1.63—1.73 (3H, m, H-7, N<u>H</u>), 1.96—2.01 (1H, s, H-6*α*), 2.29 (6H, s, N(<u>CH</u>$_3$)$_2$), 2.43 (1H, d, *J*=12.2 Hz, H-1$_a$), 2.60 (1H, d, *J*=12.2 Hz, H-1$_a$), 3.31 (1H, dd, *J*=17.8, 3.74 Hz, H-3$_a$), 3.41 (1H, dd, *J*=17.7, 2.39 Hz, H-3$_b$), 5.48 (1H, m, H-4).

(6*α*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-5,5,8a-trimethyl-6-isoquinolineamine (12) Trimethylsilyl chloride (4 ml) were carefully added at room temperature to a solution of **10b** (0.8 g, 2.7 mmol) and NaI (5.2 g, 34 mmol) in 15 ml of acetonitrile. The resulting mixture was refluxed for 24 h. After cooling the solvent was removed under reduced pressure and the residue was taken up with 1 N HCl, then washed with ether. The aqueous phase was made basic with 1 N NaOH and extracted with ether. The ethereal phase was washed with water, dried over $MgSO_4$ and the solvent was removed under reduced pressure to provide **12** as a crude solid (0.5 g, 77%): mp 103 °C. ^{1}H-NMR ($CDCl_3$) *δ*: 1.15 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.22—1.49 (5H, m, CH_3, H-8), 1.70 (1H, s, N<u>H</u>), 1.78—1.88 (2H, m, H-7), 2.32 (6H, s, N(<u>CH</u>$_3$)$_2$), 2.41 (1H, m, H-6*β*), 2.49 (1H, d, *J*=12.2 Hz, H-1$_a$), 2.60 (1H, d, *J*=12.2 Hz, H-1$_b$), 3.36 (1H, dd, *J*=17.8, 4.15 Hz, H-3$_a$), 3.45 (1H, dd, *J*=17.9, 2.55 Hz, H-3$_b$), 5.46 (1H, m, H-4).

(6*α*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine (8b) The title compound was prepared following Method B starting from **12** (0.42 g, 1.89 mmol), *n*-bromododecane (0.5 g, 2 mmol) and K_2CO_3 in CH_3CN to afford **8b** (37%) as an oil which was converted into its oxalate: mp 139 °C. ^{1}H-NMR (DMSO-d_6) *δ*: 0.85 (3H, t, *J*=6.4 Hz), 1.21 (3H, s), 1.25 (21H, m), 1.35 (3H, s), 1.47 (4H, m), 2.0 (1H, m), 2.68 (6H, s), 2.73 (3H, m), 2.91 (1H, d, *J*=11.0 Hz), 3.19 (2H, m), 3.84 (1H, dd, *J*=17.6, 3.5 Hz), 5.52 (1H, br s), 6.9 (4H, br s). *Anal.* Calcd for $C_{26}H_{50}N_2 \cdot 2C_4H_4O_4$: C, 63.13; H, 9.54; N, 4.91. Found: C, 62.81; H, 9.50; N, 5.09.

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-dodecyl-5,5,8a-trimethyl-6-isoquinolineamine (8c). Method D The pH of a solution of **11** (2.3 g, 10.3 mmol) and dodecanal (2.3 g, 12.5 mmol) in 60 ml of methanol was adjusted to 7 by addition of AcOH, $NaBH_3CN$ (0.82 g, 13.0 mmol) was then carefully added. The resulting solution was stirred overnight. After evaporation, the residue was poured into ice-cooled dilute NaOH and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) evaporated and purified by silica gel column chromatography (toluene, iso-PrOH 98/2) to give **8c** (3.25 g, 74%) as a solid. This solid was converted into its fumarate salt: mp 193 °C. ^{1}H-NMR (CD_3OD) *δ*: 0.89 (3H, t, *J*=6.5 Hz), 1.29 (20H, m), 1.39 (6H, s), 1.48 (3H, s), 1.80 (2H, m), 2.08 (1H, m), 2.20 (1H, m), 2.78 (1H, d, *J*=11.8 Hz), 2.89 (6H, s), 3.10 (3H, m), 3.27 (1H, d, *J*=11.8 Hz), 3.59 (1H, dd, *J*=16.9, 2.0 Hz), 3.90 (1H, dd, *J*=16.9, 3.5 Hz), 5.75 (1H, t, *J*=2.4 Hz), 6.73 (6H, s). *Anal.* Calcd for $C_{26}H_{50}N_2 \cdot 3C_4H_4O_4$: C, 61.76; H, 8.46; N, 3.79. Found: C, 61.87; H, 8.54; N, 3.41.

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-[-1-[2-methyl-3-[4-isopropylphenyl]-propyl]-5,5,8a-trimethyl-6-isoquinolineamine (8e) This compound was prepared using Method D starting from **11** (3 g, 13.5 mmol), 3-[4-isopropyl phenyl)]-2-methyl propanal (2.8 g, 14.7 mmol), $NaBH_3CN$ (1.28 g, 20.3 mmol), Na_2SO_4 (2 g, 13.5 mmol) in CH_3OH (100 ml) as an oil in a 41% yield (2.2 g). This oil was converted into its fumarate: mp 142 °C. ^{1}H-NMR (CD_3OD) *δ*: 0.84 (3H, d, *J*=6.6 Hz), 1.22 (6H, d, *J*=6.9 Hz), 1.26 (3H, s), 1.34 (3H, s), 1.40 (2H, m), 1.43 (3H, s), 1.70 (1H, m), 1.99 (3H, m), 2.23 (4H, m), 2.63 (1H, d, *J*=10.8 Hz), 2.68 (1H, dd, *J*=18.4, 2.1 Hz), 2.84 (2H, m), 2.86 (6H, s), 3.0 (1H, dd, *J*=12.6, 3.4 Hz), 5.67 (1H, dd, *J*=4.1, 2.4 Hz), 6.67 (2H, s), 7.09 (4H, m). ^{13}C-NMR (CD_3OD) *δ*: 18.1, 18.5, 24.5, 24.7, 26.5, 27.5, 33.8, 34.9, 36.5, 37.5, 41.4, 41.7, 43.9, 55.7, 65.4, 67.9, 76.3, 121.3, 127.1, 130.2, 138.3, 139.3, 147.3, 147.5, 171.8. *Anal.* Calcd for $C_{27}H_{44}N_2 \cdot C_4H_4O_4$: C, 72.62; H, 9.44; N, 5.46. Found: C, 72.73; H, 9.28; N, 5.41.

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-(6,6-dimethyl-2-hepten-4-yn-1-yl)-5,5,8a-trimethyl-6-isoquinolineamine (8f) The titled compound was prepared starting from **11** (3.5 g, 15.8 mmol), 1-bromo-6,6-dimethyl-2-hepten-4-yne (3.8 g, 18.8 mmol) and K_2CO_3 in CH_3CN to afford **8f** (1.4 g, 26%) as an oil (E/Z 65/35). ^{1}H-NMR ($CDCl_3$) *δ*: 1.05 (3H, s), 1.10 (1H, m), 1.14 (1.95H, s), 1.15 (1.05H, s), 1.25 (9H, s), 1.27 (1.05H, s), 1.28 (1.95H, s), 1.51 (1H, m), 1.60—1.85 (3H, m), 1.95 (1H, m), 2.29 (6H, s), 2.43 (1H, m), 2.65 (0.65H, dd, *J*=10.3, 2.1 Hz), 2.75 (0.35H, dd, *J*=10.5, 2.2 Hz), 2.88 (0.65H, dd, *J*=14.0, 7.0 Hz), 3.08 (0.65H, dd, *J*=12.5, 5.8 Hz), 3.25 (1.7H, m), 5.45 (1H, m), 5.62 (1H, m), 5.92 (0.35H, m), 6.04 (0.65H, m). *Anal.* Calcd for $C_{23}H_{38}N_2$: C, 80.64; H, 11.18; N, 8.18. Found: C, 80.35; H, 10.86; N, 8.00.

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-(3-phenyl-2-propen-1-yl)-5,5,8a-trimethyl-6-isoquinolineamine (8g). Method E 1,1′-Carbonyldiimidazole (2.6 g, 16 mmol) was added portionwise to a solution of *trans*-cinnamic acid (2.4 g, 16 mmol) in 50 ml of THF and the reaction mixture was stirred at room temperature for 0.5 h then heated at 50 °C for 1 h. After cooling at 5 °C, a solution of **11** (3 g, 13.5 mmol) in 40 ml of THF was added dropwise. The reaction mixture was stirred overnight, diluted with water then extracted with ether. The organic phase was washed with water, dried ($MgSO_4$) and concentrated to leave an oil which was purified by chromatography on silica gel eluting with a mixture of CH_2Cl_2–CH_3OH–NH_4OH (9/0.9/0.1) to afford (6*β*,8a*β*)-*N*,*N*-dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-(3-phenyl-2-propenoyl)-5,5,8a-trimethyl-6-isoquinolineamine (2.76 g, 59%). This material (1.5 g, 4.26 mmol) was dissolved in 30 ml of toluene and a 70% solution of Red-Al in toluene (2.5 ml, 8.6 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2.5 h then cooled to 0 °C. A solution (50 ml) of 5 N NaOH was carefully added and the resulting mixture was allowed to warm to room temperature with stirring for 0.5 h. Ether was then added and the mixture was washed with water, dried then concentrated to dryness to give **8g** (1.4 g, 100%) as a pale-yellow oil. This oil was converted to a tosylate: mp 210 °C. ^{1}H-NMR (DMSO-d_6) *δ*: 1.14 (3H, s), 1.25 (1H, m), 1.29 (3H, s), 1.38 (3H, s), 1.75 (1H, d, *J*=13.1 Hz), 2.05 (2H, m), 2.28 (6H, s), 2.76 (4H, m), 2.87 (3H, m), 2.99 (1H, t, *J*=7.3 Hz), 3.32 (1H, d, *J*=12.1 Hz), 3.67 (1H, m), 3.82 (1H, m), 4.0 (2H, m), 5.66 (1H, s), 6.38 (1H, dt, *J*=15.8, 7.1 Hz), 6.85 (1H, d, *J*=15.8 Hz), 7.12 (4H, d, *J*=7.9 Hz), 7.35 (3H, m), 7.47 (6H, m), 8.45 (1H, br s), 9.19 (1H, br s). ^{13}C-NMR (DMSO-d_6) *δ*: 16.3, 20.7, 23.4, 24.6, 25.5, 32.7, 33.7, 34.5, 46.1, 50.3, 57.8, 61.3, 73.0, 115.1, 117.3, 125.4, 126.8, 128.0, 128.7, 135.2, 137.7, 139.0, 145.3, 146.2. *Anal.* Calcd for $C_{23}H_{34}N_2 \cdot 2C_7H_8O_3S$: C, 64.10; H, 7.23; N, 3.86. Found: C, 63.92; H, 7.22; N, 4.05.

(6*β*,8a*β*)-*N*,*N*-Dimethyl-1,2,3,5,6,7,8,8a-octahydro-2-(3,3-diphenyl-2-propen-1-yl)-5,5,8a-trimethyl-6-isoquinolineamine (8h) The title compound was prepared following Method E starting from **11** (3 g, 13.5 mmol), 3-phenyl-2-propenoic acid (3.6 g, 16 mmol) and carbonyl diimidazole (2.6 g,

16 mmol) in THF (50 ml) to afford the corresponding amide. This was reduced with RedAl (7 ml, 24 mmol) to give **8h** (5.1 g, 95%) which was converted into its oxalate: mp 150 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, s), 1.17 (1H, m), 1.26 (3H, s), 1.34 (3H, s), 1.60 (1H, d, J=13.0 Hz), 2.01 (3H, m), 2.6—2.9 (9H, m), 3.28 (2H, m), 3.50 (1H, dd, J=16.8, 3.7 Hz), 5.56 (1H, s), 6.21 (1H, t, J=6.7 Hz), 7.19 (4H, m), 7.39 (6H, m). *Anal.* Calcd for $C_{29}H_{38}N_2 \cdot 2C_2H_2O_4$: C, 64.31; H, 7.26; N, 4.54. Found: C, 64.62; H, 6.93; N, 4.56.

4-Hydroxy-α,α-dimethyl-1-phenylmethyl-4-piperidineacetic Acid Ethyl Ester (14) A solution of diisopropylamine (152.8 ml, 1.09 mol) in dry THF (100 ml) was stirred at −50 °C under an atmosphere of N_2 and a 2.5 M solution of nBuLi in hexane (400 ml, 1 mol) was added dropwise. The mixture was stirred at −50 °C for 45 min, then 2-methylpropanoic acid ethyl ester (121.8 ml, 0.91 mol) in THF (100 ml) was added dropwise and stirring was maintained during 1 h. A solution of 1-phenylmethyl-4-piperidone **13** (120.5 ml, 0.68 mol) in THF (100 ml) was added dropwise at −50 °C, then the reaction mixture was warmed to room temperature overnight. Saturated aqueous NH_4Cl (400 ml) was added, and the resulting mixture was then extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to leave an oil which was distilled under reduced pressure to afforded **14** (172.3 g, 83%) as an orange oil: bp 150—156 °C/0.45 mmHg. IR (neat): 3500, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, s), 1.27 (3H, t, J=7.1 Hz), 1.43 (2H, m), 1.78 (2H, dt, J=4.39, 12.9 Hz), 2.37 (2H, dt, J=2.39, 12.99 Hz), 2.69 (2H, m), 3.48 (1H, s), 3.52 (2H, s), 4.16 (2H, q, J=7.1 Hz), 7.22—7.33 (5H, m). *Anal.* Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.43; H, 8.81; N, 4.96.

1,2,3,6-Tetrahydro-α,α-dimethyl-1-phenylmethyl-4-pyridineacetic Acid Ethyl Ester Hydrochloride (15) To a stirred solution of **14** (50 g, 0.164 mol) in $CHCl_3$ (200 ml) and DMF (0.52 ml) was added $SOCl_2$ (24 ml, 0.33 mol) dropwise. The reaction mixture was stirred under reflux for 8 h, then the solution was evaporated *in vacuo.* The resulting residue was alkalined with 10 N NaOH (20 ml) and extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo.* Hydrochloride salt was prepared in iso-PrOH solution by adding HCl gas to afford **15** as a white powder, which was recrystallized from iso-PrOH (38.9 g, 74%): mp 208 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=7.1 Hz), 1.24 (6H, s), 2.17 (2H, m), 3.02—3.57 (4H, complex m), 4.05 (2H, q, J=7.1 Hz), 4.27 (2H, m), 5.54 (1H, m), 7.44 (3H, m), 7.58 (2H, m), 10.90 (1H, br s). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 1.10 (3H, t, J=7.1 Hz), 1.19 (6H, s), 2.21 (2H, m), 3.14 (2H, m), 3.50 (2H, m), 4.00 (2H, q, J=7.1 Hz), 4.17 (2H, s), 5.50 (1H, m), 7.42 (5H, s). *Anal.* Calcd for $C_{18}H_{25}NO_2 \cdot HCl$: C, 66.76; H, 8.09; N, 4.32. Found: C, 66.89; H, 8.10; N, 4.36.

α,α-Dimethyl-4-piperidineacetic Acid Ethyl Ester (16) A solution of **15** (54.6 g, 0.169 mol) in CH_3OH (800 ml) was hydrogenated over 5% Pd/C (3 g) at 70 °C under 80 atm H_2 pressure. After completion of the reaction, the mixture was filtered, and the filtrate evaporated *in vacuo.* The solid residue was quenched with 10 N NaOH, then extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give **16** as a yellow oil (28.6 g, 85%). IR (neat) 3150, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, s), 1.25 (5H, m), 1.52 (3H, m), 1.69 (1H, m), 2.58 (2H, dt, J=2.5, 12.2 Hz), 3.11 (2H, m), 4.12 (2H, q, J=7.1 Hz). A sample of the free base was converted into its hydrochloride salt. mp: 190 °C (iso-PrOH). *Anal.* Calcd for $C_{11}H_{21}NO_2 \cdot HCl$: C, 56.04; H, 9.41; N, 5.94. Found: C, 56.44; H, 9.62; N, 5.96.

α,α-Dimethyl-1-dodecyl-4-piperidineacetic Acid Ethyl Ester (17) The title compound was obtained following Method B starting from **16** (9.85 g, 0.05 mol), K_2CO_3 (17.3 g, 0.125 mol) and 1-bromododecane (14.9 ml, 0.062 mol) in CH_3CN (50 ml). The crude compound was chromatographed on SiO_2 with hexane–EtOAc (9/1) as eluent to give **17** as an orange oil (6.7 g, 78%). IR (neat) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.4 Hz), 1.11 (6H, s), 1.22—1.60 (28H, m), 1.85 (2H, dt, J=2.0, 11.7 Hz), 2.27 (2H, m), 2.98 (2H, m), 4.12 (2H, q, J=7.1 Hz). The free base was converted into its fumarate salt: mp 106 °C (EtOH–Et_2O). *Anal.* Calcd for $C_{23}H_{45}NO_2 \cdot C_4H_4O_4$: C, 67.04; H, 10.21; N, 2.90. Found: C, 66.70; H, 10.11; N, 2.96.

α,α-Dimethyl-1-dodecyl-4-piperidineacetic Acid Hydrochloride (18) NaOH pellets (24.6 g, 0.614 mol) were added to a solution of **17** (22.5 g, 0.061 mol) in 50% EtOH (210 ml), then the resulting mixture was refluxed while stirring for 3 d. The solution was poured while cooling into 5 N HCl (200 ml), the resulting precipitate was filtrated and washed with ether. Recrystallization from 80% EtOH gave **18** as a white solid. (17.8 g, 77%): mp 192 °C. IR (KBr) 1700, 2650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.4 Hz), 1.18 (6H, s), 1.27 (18H, m), 1.82 (5H, m), 2.12 (2H, m), 2.70 (2H, m), 2.94 (2H, m), 3.64 (2H, m), 9.25 (1H, br s), 11.50 (1H, br s). *Anal.* Calcd for $C_{21}H_{41}NO_2 \cdot HCl$: C, 67.07; H, 11.26; N, 3.73. Found: C, 67.02; H, 11.32; N, 3.85.

α,α-Dimethyl-1-dodecyl-4-piperidineacetamide (19a). Method F The compound **18** (17.9 g, 0.048 mol) was added portionwise to $SOCl_2$ (100 ml, 1.37 mol), the mixture was then refluxed for 7.5 h. The solution was evaporated *in vacuo* to afford α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride which was used in the following reactions without purification.

Liquid ammonia (80 ml) at −5 °C was carefully added to a solution of the product obtained in the previous step (8.6 g, 0.022 mol) in a 2/1 mixture of toluene–CH_2Cl_2 (100 ml). After stirring for 72 h at room temperature, the reaction mixture was poured in water then extracted with EtOAc. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated *in vacuo.* Purification of the residue by flash chromatography (EtOAc–CH_3OH–NH_4OH, 9/1/0.5) provided **19a** (5.2 g, 69%) as a colorless powder: mp 123 °C (isopropyl ether). IR (KBr) 1630, 1650, 3220, 3400 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.4 Hz), 1.13 (6H, s), 1.25—1.60 (25H, m), 1.87 (2H, t, J=11.2 Hz), 2.27 (2H, m), 2.99 (2H, m), 5.47 (1H, br s), 5.63 (1H, br s). *Anal.* Calcd for $C_{21}H_{42}N_2O$: C, 74.49; H, 12.51; N, 8.28. Found: C, 74.25; H, 12.55; N, 8.25.

The following compounds were prepared according to Method F.

1-Dodecyl-*N*,α,α-trimethyl-4-piperidineacetamide (19b) The title compound was prepared from α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (25 g, 63 mmol) and methaneamine (300 ml) in $CHCl_3$ (200 ml) to afford **19b** (16 g, 72%) as a solid: mp 78 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t), 1.10 (6H, s), 1.25—1.54 (24H, m), 1.62—1.70 (1H, m), 1.87—1.94 (2H, m), 2.27—2.32 (2H, m), 2.80 (3H, d), 2.98—3.02 (2H, m), 5.66—5.67 (1H, m).

1-Dodecyl-*N*-ethyl-α,α-dimethyl-4-piperidineacetamide (19c) This was obtained from α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (6 g, 15 mmol) and ethaneamine (500 ml) in $CHCl_3$ (50 ml) in 54% yield: mp 67 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.33 Hz), 1.10—1.15 (9H, m), 1.25—1.58 (24H, m), 1.65—1.69 (1H, m), 1.95 (2H, m), 2.34 (2H, m), 3.02—3.06 (2H, m), 3.26—3.31 (2H, m), 5.82 (1H, m).

1-Dodecyl-*N*-propyl-α,α-dimethyl-4-piperidineacetamide (19d) Using propaneamine (21 ml, 0.25 mol) and α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (10 g, 25 mmol) in $CHCl_3$ (100 ml), **19d** was obtained (7.5 g, 79%) as a solid: mp 72—75 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.94 (6H, m), 1.10 (6H, s), 1.25 (19H, m), 1.42—1.57 (7H, m), 1.63—1.67 (1H, m), 1.92 (2H, m), 2.31 (2H, m), 3.00—3.03 (2H, m), 3.17—3.24 (2H, q, J=6.92 Hz), 5.65 (1H, m).

1-Dodecyl-*N*-(1-methylethyl)-α,α-dimethyl-4-piperidineacetamide (19e) α,α-Dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (10 g, 25 mmol) was reacted with isopropylamine (22 ml, 0.25 mol) in $CHCl_3$ (100 ml) to give **19e** as a solid: mp 68 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz), 1.08 (6H, s), 1.13 (6H, d), 1.25 (19H, m), 1.35—1.55 (5H, m), 1.63—1.67 (1H, m), 1.93 (2H, m), 2.32 (2H, m), 3.01—3.03 (2H, m), 4.04—4.11 (1H, m), 5.39—5.42 (1H, m).

1-Dodecyl-*N*-phenylmethyl-α,α-dimethyl-4-piperidineacetamide (19f) The title compound was obtained from α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (10 g, 25 mmol) and benzylamine (8.5 ml, 75 mmol) in $CHCl_3$ (100 ml) as a solid (6.1 g, 57%): mp 74 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz), 1.12 (6H, s), 1.25 (20H, m), 1.34—1.64 (4H, m), 1.62—1.71 (1H, m), 1.86 (2H, m), 2.27 (2H, m), 2.95—2.99 (2H, m), 4.44 (2H, d, J=5.39 Hz), 5.89 (1H, t, J=5.39 Hz), 7.36—7.37 (5H, m).

1-Dodecyl-α,α-dimethyl-*N*,*N*-diethyl-4-piperidineacetamide (19j) The title compound was obtained from α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (18 g, 45 mmol) and diethylamine (40 ml, 0.55 mol) in $CHCl_3$ (300 ml) as a solid: mp <50 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz), 1.13 (6H, s), 1.19 (6H, s), 1.25 (20H, m), 1.48—1.51 (4H, m), 1.64—1.67 (1H, m), 1.83—1.88 (2H, m), 2.27—2.32 (2H, m), 3.01—3.05 (2H, m), 3.39—3.41 (4H, br s).

1-Dodecyl-*N*-phenylmethyl-*N*,α,α-trimethyl-4-piperidineacetamide (19k) The title compound was obtained from α,α-dimethyl-1-dodecyl-4-piperidineacetyl chloride hydrochloride (30 g, 76 mmol) and *N*-methyl benzylamine (29.5 ml, 0.228 mol) in $CHCl_3$ (300 ml) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz), 1.24 (25H, br s), 1.51 (5H, m), 1.80 (3H, m), 2.28 (2H, m), 2.98 (5H, m), 4.84 (2H, s), 7.19—7.38 (5H, m). This compound was converted into its oxalate salt: mp 125 °C. *Anal.* Calcd for $C_{29}H_{50}N_2O \cdot C_2H_2O_4$: C, 69.88; H, 9.84; N, 5.26. Found: C, 69.52; H, 9.95; N, 5.31.

β,β-Dimethyl-1-dodecyl-4-piperidineethanamine (20a). Method G A solution of Red-Al (70% in toluene, 10 ml, 34.3 mmol) was carefully added

to a solution of **19a** (2.95 g, 8.7 mmol) in 80 ml of toluene. The resulting mixture was stirred for 1 h at room temperature, then heated to reflux for 3 h. After cooling, 3 N NaOH (50 ml) was added dropwise and the mixture stirred for 24 h. The organic phase was washed with dilute NaOH, then with brine, dried ($MgSO_4$) and concentrated to dryness to afford a crude product which was purified by chromatography with EtOAc–CH_3OH–NH_4OH (98.5/1/0.5) as eluent to give **20a** as an oil (1.8 g, 64%). This compound was converted into its fumarate salt: mp 100—120 °C. ^{1}H-NMR (CD_3OD) δ: 0.88 (3H, t, J=6.4 Hz), 0.99 (6H, s), 1.29—1.36 (20H, m), 1.57—1.71 (4H, m), 1.87—1.90 (2H, m), 2.95—3.00 (2H, m), 3.53—3.57 (2H, m), 6.63 (2H, s). *Anal.* Calcd for $C_{21}H_{44}N_2 \cdot C_4H_4O_4$: C, 64.84; H, 10.98; N, 6.14. Found: C, 65.24; H, 10.73; N, 5.92.

The following compounds were prepared in a similar fashion.

1-Dodecyl-*N*,β,β-trimethyl-4-piperidineethanamine (20b) Yield: 79%. ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.90 (9H, m), 1.17—1.48 (24H, m), 1.57—1.62 (2H, m), 1.80—1.87 (2H, m), 2.24—2.29 (2H, m), 2.38 (2H, s), 2.42 (3H, s), 2.97—3.01 (2H, m). Fumarate: mp 100—120 °C. *Anal.* Calcd for $C_{22}H_{46}N_2 \cdot 2C_7H_8O_3S$: C, 63.30; H, 9.15; N, 4.10. Found: C, 63.44; H, 9.35; N, 4.03.

1-Dodecyl-*N*-ethyl-β,β-dimethyl-4-piperidineethanamine (20c) Yield: 100%. ^{1}H-NMR ($CDCl_3$) δ: 0.76—0.89 (9H, m), 1.08 (3H, t, J=7.1 Hz), 1.21—1.47 (24H, m), 1.57—1.61 (2H, m), 1.79—1.88 (2H, m), 2.23—2.29 (2H, m), 2.38 (2H, s), 2.62 (3H, q, J=7.1 Hz), 2.96—3.01 (2H, m). Fumarate: mp 160 °C. *Anal.* Calcd for $C_{23}H_{48}N_2 \cdot 2C_4H_4O_4$: C, 63.67; H, 9.65; N, 4.79. Found: C, 63.73; H, 9.56; N, 4.77.

1-Dodecyl-*N*-propyl-β,β-dimethyl-4-piperidineethanamine (20d) Yield: 95%. ^{1}H-NMR ($CDCl_3$) δ: 0.84—0.92 (12H, m), 1.27—1.52 (26H, m), 1.57—1.6 (2H, m), 1.78—1.85 (2H, m), 2.23—2.28 (2H, m), 2.37 (2H, s), 2.53 (3H, t, J=7.2 Hz), 2.96—3.00 (2H, m). Fumarate: mp 186 °C. *Anal.* Calcd for $C_{24}H_{50}N_2 \cdot C_4H_4O_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.51; H, 9.68; N, 4.55.

1-Dodecyl-*N*-(1-methylethyl)-β,β-dimethyl-4-piperidineethanamine (20e) Yield: 80%. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 0.88 (3H, t, J=6.2 Hz), 1.02 (6H, d, J=6.2 Hz), 1.22—1.48 (21H, m), 1.57—1.61 (2H, m), 1.79—1.88 (2H, m), 2.24—2.29 (2H, m), 2.37 (2H, s), 2.63—2.71 (1H, m), 2.97—3.01 (2H, m). Tosylate salt: mp 114 °C. *Anal.* Calcd for $C_{24}H_{50}N_2 \cdot 2C_7H_8O_3S$: C, 64.18; H, 9.36; N, 3.94. Found: C, 63.88; H, 9.33; N, 3.91.

1-Dodecyl-*N*-phenylmethyl-β,β-dimethyl-4-piperidineethanamine (20f) Yield: 95%. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 0.88 (3H, t, J=6.4 Hz), 1.17—1.38 (22H, m), 1.47—1.55 (4H, m), 1.77—1.84 (2H, m), 2.23—2.28 (2H, m), 2.38 (2H, s), 2.95—2.99 (2H, m), 3.77 (1H, s), 7.20—7.32 (5H, m). Fumarate: mp 174 °C. *Anal.* Calcd for $C_{28}H_{50}N_2 \cdot 2C_4H_4O_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 66.65; H, 9.04; N, 4.26.

1-Dodecyl-*N*,*N*-diethyl-β,β-dimethyl-4-piperidineethanamine (20j) Yield: 85%. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (6H, s), 0.85 (3H, t, J=6.4 Hz), 0.92 (6H, t, J=7.0 Hz), 1.13—1.46 (23H, m), 1.59—1.63 (2H, m), 1.80—1.83 (2H, m), 2.16 (2H, s), 2.25—2.30 (2H, m), 2.48 (2H, q, J=7.0 Hz), 2.98—3.02 (2H, m). As fumarate salt: mp 108 °C. *Anal.* Calcd for $C_{25}H_{52}N_2 \cdot 2C_4H_4O_4$: C, 63.96; H, 9.88; N, 4.52. Found: C, 63.66; H, 10.04; N, 4.52.

1-Dodecyl-*N*-phenylmethyl-*N*,β,β-trimethyl-4-piperidineethanamine (20k) Yield: 82%. ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.90 (9H, s), 1.25—1.47 (23H, m), 1.59—1.64 (2H, m), 1.77—1.84 (2H, m), 2.18 (3H, s), 2.23—2.35 (4H, m), 2.98—2.99 (2H, m), 3.54 (2H, s), 7.20—7.38 (5H, m). Fumarate: mp 124 °C. *Anal.* Calcd for $C_{29}H_{52}N_2 \cdot C_4H_4O_4$: C, 72.75; H, 10.36; N, 5.14. Found: C, 72.69; H, 10.45; N, 5.07.

***N*-[2-(1-Dodecyl-4-piperidinyl)-2-methylpropyl]acetamide (20h)** Acetic anhydride (1.9 g, 18.6 mmol) was added dropwise to a solution of **20a** (4 g, 12.4 mmol) and Et_3N (8.6 ml, 62 mmol) in CH_2Cl_2 (50 ml). The resulting mixture was stirred at room temperature for 20 h. The reaction mixture was poured into ice-cooled 1 N NaOH, then extracted with CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to afford the title compound (3.9 g, 86%) as a solid: mp 65 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.84—0.90 (9H, m), 1.03—1.11 (1H, m), 1.25—1.47 (22H, m), 1.62—1.66 (2H, m), 1.81 (2H, m), 2.00 (3H, s), 2.24—2.29 (2H, m), 2.98—3.02 (2H, m), 3.14 (2H, d, J=6.24 Hz), 5.40 (1H, br s). This base was converted into its fumarate (H_2O): mp 113 °C. *Anal.* Calcd for $C_{23}H_{46}N_2O \cdot C_4H_4O_4$: C, 66.11; H, 10.45; N, 5.71. Found: C, 66.09; H, 10.32; N, 5.71.

***N*-[2-(1-Dodecyl-4-piperidinyl)-2-methylpropyl]-*N*-methylacetamide (20g)** The title compound was prepared as described above from **20b** (8 g, 23.8 mmol) in a 97% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.86—0.93 (9H, m), 1.07—1.47 (23H, m), 1.64—1.73 (2H, m), 1.76—1.86 (2H, m), 2.10 (3H, s), 2.24—2.30 (2H, m), 2.98—3.03 (5H, m), 3.22 (0.6H, s), 3.28 (1.4H, s). The base was converted into its tosylate: mp 102 °C. *Anal.* Calcd for $C_{24}H_{48}N_2O \cdot C_7H_8O_3S$: C, 67.34; H, 10.21; N, 5.07. Found: C, 67.18; H, 10.33; N, 4.78.

β,β-Dimethyl-*N*,*N*-dimethyl-4-pyridineethanamine (22i). Method H To a solution of 4-isopropylpyridine (100 g, 0.82 mol), formaldehyde (37% solution in water, 200 ml) in acetic acid (800 ml), dimethylamine (40% solution in water, 300 ml) was added dropwise then the resulting solution was refluxed for 3 d. Upon cooling, formaldehyde (100 ml) and dimethylamine (150 ml) were again added and the reaction mixture was refluxed for 2 extra days. The solvent was concentrated and 35% NaOH solution (400 ml) was carefully added upon cooling. The aqueous solution was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil. This oil was purified by vacuum distillation (bp 64—66 °C/0.3 mmHg) to give **22i** (61.7 g, 42%). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, s), 2.07 (6H, s), 2.45 (2H, s), 7.25—7.30 (2H, m), 8.49—8.51 (2H, m).

1-[2-Methyl-2-(4-pyridinyl)propyl]piperidine (22l) The title compound was prepared following Method H in a 17% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (8H, s), 1.33—1.48 (4H, s), 2.16—2.21 (4H, m, C<u>H</u>$_2$–N), 2.35 (2H, s, N–C<u>H</u>$_2$), 7.30—7.32 (2H, m), 8.47—8.49 (2H, m). The base was converted into its fumarate: mp 177 °C. *Anal.* Calcd for $C_{14}H_{22}N_2 \cdot C_4H_4O_4$: C, 61.21; H, 7.19; N, 7.14. Found: C, 61.29; H, 7.15; N, 7.23.

β,β-Dimethyl-*N*,*N*-dimethyl-4-piperidineethanamine (23i) In a Parr apparatus, **22i** (123 g, 0.69 mol) was dissolved in acetic acid (900 ml) and PtO_2 (12 g) was added. The reaction mixture then was stirred under a 1000 psi hydrogen pressure at 80 °C for 7 h and thereafter the catalyst was filtered. The filtrate was evaporated *in vacuo* to give an oily residue which was dissolved in water, basified under efficient cooling with 35% NaOH and extracted with $CHCl_3$. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford **23i** as an oil (127 g, 100%) pure enough to be used in the next step.

1-[2-Methyl-2-(4-piperidinyl)propyl]piperidine (23l) The compound was prepared from **22l** (10 g, 45.8 mmol) as described above in a quantitative yield and was used in next step without further purification.

***N*,*N*,β,β-Tetramethyl-1-dodecyl-4-piperidineethanamine (20i)** The title compound was prepared in a quantitative yield following the procedure B starting from **23i** (13 g, 70.5 mmol), *n*-bromododecane (19.7 g, 79 mmol), K_2CO_3 (24.4 g, 176 mmol) and NaI (0.5 g) in acetonitrile (150 ml). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, br s), 0.88 (3H, t, J=6.45 Hz), 1.20—1.47 (23H, m), 1.59—1.63 (2H, m), 1.83 (2H, t, J=11.4 Hz), 2.12 (2H, s), 2.23—2.28 (8H, m), 2.96—3.00 (2H, m). It was converted to its fumarate: mp 132 °C. *Anal.* ($C_{23}H_{48}N_2 \cdot 2C_4H_4O_4$) C, H, N.

4-[1,1-Dimethyl-2-(4-piperidinyl)ethyl]-1-dodecyl-piperidine (20l) The title compound was prepared following Method D in a 70% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (6H, s), 0.88 (3H, t, J=6.4 Hz), 1.14—1.37 (22H, m), 1.41—1.54 (7H, m), 1.59—1.64 (2H, m), 1.79—1.87 (2H, m), 2.06 (2H, s), 2.25—2.31 (2H, m), 2.39 (4H, t, J=4.8 Hz), 2.98—3.02 (2H, m). The base was converted into its maleate: mp 129 °C. *Anal.* ($C_{26}H_{52}N_2 \cdot 2C_4H_4O_4$) C, H, N.

β,β,*N*,*N*,1-Pentamethyl-4-piperidineethanamine (20m) The title compound was prepared in a quantitative yield following procedure B from **23i** (1.3 g, 7.05 mmol), iodomethane (1.13 g, 8 mmol) and K_2CO_3 (2.5 g, 1.8 mmol) in acetonitrile (20 ml). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 1.19—1.30 (3H, m), 1.60—1.64 (2H, m), 1.82—1.90 (2H, m), 2.12 (2H, s), 2.24 (3H, s), 2.28 (6H, s), 2.87—2.91 (2H, m). This was converted into its fumarate: mp 160 °C. *Anal.* ($C_{12}H_{26}N_2 \cdot 2C_4H_4O_4$) C, H, N.

2-[3-[4-[2-(Dimethylamino)-1,1-dimethylethyl]-1-piperidinyl]propyl]-1*H*-isoindole-1,3(2*H*)-dione (20ac) The title compound was prepared as an oil in 59% yield, following Method B starting from **23i** (15 g, 81 mmol), *N*-(3-bromopropyl)phtalimide (24 g, 89.5 mmol) and K_2CO_3 (28 g, 0.2 mol) in acetonitrile (150 ml). ^{1}H-NMR ($CDCl_3$) δ: 0.72 (6H, s), 1.02—1.16 (2H, m), 1.49—1.53 (2H, m), 1.72—1.91 (5H, m), 2.04 (2H, s), 2.25 (6H, s), 2.36 (2H, t, J=6.99 Hz), 2.88—2.92 (2H, m), 3.74 (2H, t, J=6.92 Hz), 7.68—7.72 (2H, m), 7.82—7.85 (2H, m). This was converted into its fumarate (EtOH): mp 127—134 °C. *Anal.* ($C_{22}H_{33}N_3O_2 \cdot 2C_4H_4O_4$) C, H, N.

***N*-[3-[4-[2-(Dimethylamino)-1,1-dimethylethyl]-1-piperidinyl]propyl]-5-methylhexanamide (20o)** A solution of **20ac** (14 g, 37.6 mmol) and hydrazine hydrate (4 ml, 82.5 mmol) in ethanol (100 ml) was heated under reflux for 0.5 h. The reaction mixture was poured into ice-cooled 5 N sodium hydroxide, then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to leave 4-[2-(dimethylamino)-1,1-dimethylethyl]-1-piperidine-propanamine as an oil (7.9 g, 86%). To an ice-cooled solution of 4-[2-(dimethylamino)-1,1-dimethylethyl]-1-piperidine-propanamine (4.2 g, 17.4 mmol) and Et_3N (12 ml, 86 mmol) in CH_2Cl_2 (50 ml) was added dropwise a solution of 5-methyl hexanoyl chloride (2.6 g, 17.5 mmol) in CH_2Cl_2 (25 ml) and the resulting mixture was stirred at room

temperature overnight. Water was added and the organic layer was washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo.* The oily residue was purified by column chromatography eluting with CH_2Cl_2–CH_3OH–NH_4OH (90/9.5/0.5) to afford **20o** (2 g, 32%) as an orange oil. This oil was converted to its corresponding oxalate: mp 87 °C. ^{1}H-NMR (CD_3OD, D_2O) δ: 1.11 (6H, s), 1.64—1.66 (3H, m), 1.95—1.98 (2H, m), 2.12—2.20 (2H, m), 2.90—2.97 (8H, m), 3.07 (2H, t), 3.15—3.21 (4H, m), 3.62—3.66 (2H, m), 6.65 (4H, s). *Anal.* ($C_{21}H_{43}N_3O \cdot 2C_2H_2O_4$) C, H, N.

β,β-Dimethyl-*N*,*N*-dimethyl-1-(6,6-dimethyl-2-hepten-4-yn-1-yl)-4-piperidineethanamine (20p) The title compound was obtained as an oil in 56% yield starting from **23i** (10 g, 54 mmol), 1-bromo-6,6-dimethyl-2-hepten-4-yne (E/Z=3/1, 12 g, 60 mmol), K_2CO_3 (14.9 g, 0.108 mol) in 200 ml of DMF. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 1.17—1.39 (11H, m), 1.59—1.63 (2H, m), 1.88 (2H, t, *J*=11.41 Hz), 2.12 (2H, s), 2.27 (3H, s), 2.28 (3H, s), 2.93—3.00 (5H, m), 5.57—5.62 (1H, m), 5.90—6.11 (1H, m). The maleate was prepared and recrystallized from ethanol: mp 192 °C. *Anal.* ($C_{20}H_{36}N_2 \cdot 2C_4H_4O_4$) C, H, N.

β,β-Dimethyl-*N*,*N*-dimethyl-1-(2,2-dimethylheptyl)-4-piperidineethanamine (20n) A solution of **20p** (4.5 g, 14.7 mmol) in methanol (150 ml) and 10% Pd/C was hydrogenated in a Parr apparatus at 40 °C under 50 psi of hydrogen pressure for 8 h. Catalyst was removed by filtration and the solvent was evaporated *in vacuo* to give **20n** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83—0.87 (15H, m), 1.12—1.64 (13H, m), 1.89 (2H, m), 2.12 (2H, s), 2.28—2.34 (8H, m), 3.02—3.06 (2H, m). The fumarate was prepared in ethanol: mp 138 °C. *Anal.* ($C_{20}H_{42}N_2 \cdot 2C_4H_4O_4$) C, H, N.

4-[2-(Dimethylamino)-1,1-dimethylethyl]-*N*-(4-methylpentyl)-1-piperidinebutanamide 20q A solution of **23i** (12 g, 65 mmol), 4-bromobutanoic acid ethyl ester (15.9 g, 81 mmol)) and K_2CO_3 (22.4 g, 0.16 mol) in CH_3CN (200 ml) was refluxed for 4 h. After cooling, the solvent was evaporated, water was added to the resulting residue and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give 4-[2-(dimethylamino)-1,1-dimethylethyl]-1-piperidinebutanoic acid ethyl ester **20ad** (11.8 g, 61%) as a yellow oil. A solution of **20ad** (4 g, 12 mmol) and 4-methyl pentanamine (9 g, 90 mmol) in toluene (100 ml) was heated in an autoclave at 200 °C for 4 d. After cooling, solvent was evaporated and the oily residue was purified by silica gel column chromatography with CH_2Cl_2–CH_3OH (95/5) as eluent to give **20q** (3 g, 71%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 0.88 (6H, d, *J*=6.60 Hz), 1.15—1.29 (5H, m), 1.50—1.68 (7H, m), 1.83—1.92 (2H, m), 2.12 (2H, s), 2.22 (2H, t, *J*=7.12 Hz), 2.28 (6H, s), 2.33 (2H, t, *J*=6.78 Hz), 2.94—2.98 (2H, m), 3.17—3.23 (2H, m), 6.74 (1H, br s). This was converted to its fumarate in EtOH: mp 140 °C. *Anal.* ($C_{21}H_{43}N_3O \cdot 2C_4H_4O_4$) C, H, N.

β,β-Dimethyl-*N*,*N*-dimethyl-1-[(4-methylpentyl)aminobutyl]-4-piperidineethanamine (20r) The title compound was prepared following procedure G from **20q** (2 g, 5.7 mmol) in 83% yield as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 0.87 (6H, d, *J*=6.6 Hz), 1.1—1.5 (13H, m), 1.59 (2H, t, *J*=10.8 Hz), 1.83 (2H, t, *J*=11.0 Hz), 2.11 (2H, s), 2.28 (6H, s), 2.25—2.35 (2H, m), 2.58 (4H, m), 2.99 (2H, d, *J*=11.5 Hz). This was converted to its corresponding fumarate (EtOH): mp 130—142 °C. *Anal.* ($C_{21}H_{45}N_3 \cdot 3C_4H_4O_4$) C, H, N.

β,β,*N*,*N*-Tetramethyl-1-(1-oxododecyl)-4-piperidineethanamine (20s) A solution of the acetate salt of **23i** (8.28 g, 45 mmol) and Et_3N (22.7 ml, 0.225 mol) in CH_2Cl_2 (400 ml) was cooled at 5 °C. Dodecanoic acid chloride (15.5 ml, 67 mmol) was added dropwise and the resulting mixture was stirred for 24 h. The reaction mixture was poured into ice-cooled 1 N NaOH solution and extracted with EtOAc. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (eluent CH_2Cl_2–CH_3OH, 98/2) to give **20s** (11 g, 66%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, s), 0.82 (3H, s), 0.87 (3H, t, *J*=6.4 Hz), 1.1—1.4 (20H, m), 1.5—1.7 (4H, m), 2.12 (2H, s), 2.28 (6H, s), 2.30 (1H, m), 2.44 (1H, t, *J*=11.5 Hz), 2.94 (1H, t, *J*=12.3 Hz), 3.90 (1H, d, *J*=12.9 Hz), 4.70 (1H, d, *J*=12.5 Hz). This compound was converted into its oxalate: mp 138 °C. *Anal.* ($C_{23}H_{46}N_2O \cdot C_2H_2O_4$) C, H, N.

β,β,*N*,*N*,*N*-Pentamethyl-1-(1-oxododecyl)-4-piperidineethaniminium Iodide (20t) Methyl iodide (10 ml, 0.15 mol) was added to a solution of **20s** (1 g, 2.72 mmol) in ether (20 ml). The resulting mixture was stirred for 48 h at room temperature and 10 h at reflux. After cooling, the mixture was filtered to give **20t** as a white solid: mp 208 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, *J*=6.4 Hz), 1.1—1.4 (26H, m), 1.28 (6H, s), 1.4—1.65 (4H, m), 1.85 (1H, d, *J*=12.9 Hz), 1.93 (1H, d, *J*=11.0 Hz), 2.33 (2H, t, *J*=7.9 Hz)), 2.44 (1H, t, *J*=12.7 Hz), 2.96 (1H, t, *J*=11.9 Hz), 3.58 (9H, s), 3.70 (1H, d, *J*=13.8 Hz), 3.80 (1H, d, *J*=13.8 Hz), 3.97 (1H, d, *J*=13.4 Hz), 4.70 (1H, d, *J*=12.8 Hz). *Anal.* ($C_{24}H_{49}IN_2O$) C, H, N.

β,β,*N*,*N*-Tetramethyl-1-(1-oxo-3-phenyl-2-propenyl)-4-piperidineethanamine (20u) To an ice-cold solution of cinnamic acid (6.4 g, 43 mmol) in $CHCl_3$ (100 ml) was added 1,3-dicyclohexylcarbodiimide (DCC, 17.9 g, 87 mmol) and the resulting mixture was stirred at 0 °C for 0.5 h. A solution of **23i** (8 g, 43 mmol) in $CHCl_3$ (50 ml) was added dropwise to the above solution. The ice bath was removed and the solution was stirred for 24 h. The reaction mixture was poured into ice-cold 1 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (eluent CH_2Cl_2–CH_3OH, 95/5) to afford 7 g (52%) of the title compound: mp 60 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 1.27 (2H, m), 1.50—1.80 (3H, m), 2.14 (2H, s), 2.29 (6H, s), 2.60 (1H, t, *J*=11.6 Hz), 3.07 (1H, t, *J*=12.4 Hz), 4.16 (1H, d, *J*=12.9 Hz)), 4.79 (1H, d, *J*=12.5 Hz), 6.91 (1H, d, *J*=15.5 Hz), 7.37 (3H, m), 7.52 (2H, m), 7.64 (1H, d, *J*=15.5 Hz). This solid was converted into its fumarate: mp 169 °C (EtOH). *Anal.* ($C_{20}H_{30}N_2O \cdot C_4H_4O_4$) C, H, N.

β,β,*N*,*N*-Tetramethyl-1-(3-phenyl-2-propenyl)-4-piperidineethanamine (20v) The above compound (3.85 g, 12 mmol) was reduced with 3.5 M solution of RedAl (7 ml, 24 mmol) in toluene (70 ml) following method G, to provide **20v** (3.5 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 1.2—1.4 (3H, m), 1.64 (2H, m), 1.92 (2H, t, *J*=11.3 Hz), 2.12 (2H, s), 2.28 (6H, s), 3.04 (2H, d, *J*=17.8 Hz), 3.12 (2H, d, *J*=6.7 Hz), 6.30 (1H, dt, *J*=15.9, 6.7 Hz), 6.49 (1H, d, *J*=15.9 Hz), 7.10—7.45 (5H, m). This oily compound was converted into its fumarate (iso-PrOH): mp 150 °C. *Anal.* ($C_{20}H_{32}N_2 \cdot 2C_4H_4O_4$) C, H, N.

1-[2-(4-Chlorophenoxy)-2-methyl-1-oxopropyl]-β,β,*N*,*N*-tetramethyl-4-piperidineethaneamine (20w) The title compound was prepared as described for **20u**, starting from **23i** (8 g, 43 mmol), DCC (17.95 g, 87 mmol) and 2-(4-chlorophenoxy)-2-methyl-propanoic acid (9.2 g, 43 mmol) in $CHCl_3$ (100 ml) to provide 9.9 g (60%) of **20w**: mp 63 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, s), 0.69 (3H, s), 1.05 (1H, dq, *J*=12.5, 3.6 Hz), 1.42 (2H, m), 1.62 (3H, s), 1.65 (3H, s), 1.60—1.70 (2H, m), 1.97 (1H, d, *J*=13 Hz), 2.03 (1H, d, *J*=13 Hz), 2.23 (6H, s), 2.44 (1H, t, *J*=10.6 Hz), 2.79 (1H, t, *J*=12.7 Hz), 4.70 (2H, t, *J*=12.8 Hz), 6.77 (2H, d, *J*=9.0 Hz), 7.16 (2H, d, *J*=9.0 Hz). This was converted into its fumarate (EtOH): mp 194 °C. *Anal.* ($C_{21}H_{33}ClN_2O_2 \cdot C_4H_4O_4$) C, H, N.

1-[2-(4-Chlorophenoxy)-2-methylpropyl]-β,β,*N*,*N*-tetramethyl-4-piperidineethaneamine (20x) Reduction of **20w** (4.5 g, 11.8 mmol) with 3.5 M solution of RedAl (6.8 ml, 23.6 mmol) following Method G gave 3.6 g (83%) of **20x** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 1.15—1.40 (3H, m), 1.25 (6H, s), 1.55 (2H, d, *J*=12.2 Hz), 2.10 (2H, s), 2.18 (2H, d, *J*=11.2 Hz), 2.28 (6H, s), 2.45 (2H, s), 2.98 (2H, d, *J*=17.5 Hz), 6.92 (2H, d, *J*=8.8 Hz), 7.20 (2H, d, *J*=8.8 Hz). This was transformed into its fumarate: mp 110 °C. *Anal.* ($C_{21}H_{35}ClN_2O \cdot 2C_4H_4O_4$) C, H, N. ^{13}C-NMR (DMSO-d_6) δ: 22.86, 24.50, 26.07, 36.35, 42.06, 47.68, 55.93, 66.74, 67.56, 81.54, 124.86, 126.80, 128.77, 134.21, 153.78, 166.39.

β,β,*N*,*N*-Tetramethyl-1-[2(*S*)-(6-methoxy-2-naphtalenyl)-1-oxopropyl]-4-piperidineethaneamine (20y) Acylation of **23i** (8 g, 43 mmol) with (*S*)-(+)-6-methoxy-α-methyl naphtaleneacetic acid (9.9 g, 43 mmol) in the presence of DCC (17.5 g, 86 mmol) in $CHCl_3$ (100 ml) provided **20y** as an oil (9.9 g, 58%). This compound was transformed into an oxalate (EtOH): mp 169 °C. ^{1}H-NMR (DMSO-d_6, T: 400 °K) δ: 0.67 (6H, s), 0.6—0.8 (1H, m), 1.03 (1H, dq, *J*=8.7, 3.9 Hz), 1.37 (3H, d, *J*=6.7 Hz), 1.3—1.45 (2H, m), 1.58 (1H, bd), 1.98 (2H, s), 2.05 (3H, s), 2.15 (3H, s), 2.54 (1H, m), 2.66 (1H, m), 3.86 (3H, s), 4.14 (1H, q, *J*=6.7 Hz), 4.27 (2H, m), 7.11 (1H, d, *J*=8.9 Hz), 7.22 (1H, s), 7.34 (1H, d, *J*=8.6 Hz), 7.62 (1H, s), 7.71 (2H, d, *J*=8.6 Hz). *Anal.* ($C_{25}H_{36}N_2O_2 \cdot C_2H_2O_4$) C, H, N.

β,β,*N*,*N*-Tetramethyl-1-[2(*S*)-(6-methoxy-2-naphtalenyl)propyl]-4-piperidineethaneamine (20z) Following Method G, the compound **20y** (6 g, 15 mmol) was reduced with 3.5 M RedAl solution (13 ml, 45 mmol) to afford **20z** (6 g, 100%) as a white solid: mp 70 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.81 (6H, s), 1.2—1.4 (3H, m), 1.33 (3H, d, *J*=6.8 Hz), 1.55 (2H, d, *J*=11.7 Hz), 1.79 (1H, t, *J*=10.3 Hz), 1.96 (1H, t, *J*=10.3 Hz), 2.10 (2H, s), 2.26 (6H, s), 2.49 (2H, m), 2.92 (1H, d, *J*=10.3 Hz), 3.00 (1H, d, *J*=17.9 Hz), 3.06 (1H, m), 3.90 (3H, s), 7.11 (2H, m), 7.32 (1H, d, *J*=8.4 Hz), 7.56 (1H, s), 7.67 (2H, m). This was converted into its fumarate (EtOH): mp 166 °C. *Anal.* ($C_{25}H_{38}N_2O \cdot 2C_4H_4O_4$) C, H, N.

β,β,*N*,*N*-Tetramethyl-1-[2-[4-(2-methylpropyl)phenyl]-1-oxopropyl]-4-piperidineethaneamine (20aa) Acylation of **23i** (8 g, 43 mmol) with 4-isobutyl-α-methylphenylacetic acid (8.95 g, 43 mmol) in $CHCl_3$ (100 ml) in the presence of DCC (17.9 g, 86.8 mmol) gave 12 g (74%) of **20aa** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.17 (0.5H, dq, *J*=8.5, 4.1 Hz), 0.60 (3H, s), 0.63 (3H, s), 0.80 (3H, s), 0.86 (3H, d, *J*=5.8 Hz), 0.91 (3H, d, *J*=5.8 Hz), 1.01 (0.5H, dq, *J*=8.5, 4.1 Hz), 1.15—1.25 (2H, m), 1.40 (1.5H, d, *J*=6.2 Hz), 1.42

(1.5H, d, J=6.2 Hz), 1.40—1.70 (2H, m), 1.75—1.90 (0.5H, m), 1.95 (0.5H, m), 2.21 (3H, s), 2.25 (3H, s), 2.45 (3H, m), 2.83 (0.5H, t, J=10.4 Hz), 3.8—3.95 (1.5H, m), 4.73 (1H, m), 7.05—7.20 (4H, m). This compound was converted into its fumarate (iso-PrOH): mp 172 °C. *Anal.* ($C_{24}H_{40}N_2O \cdot C_4H_4O_4$) C, H, N.

***β,β,N,N*-Tetramethyl-1-[2-[4-(2-methylpropyl)phenyl]propyl]-4-piperidineethaneamine (20ab)** Following Method G, **20aa** (6 g, 16.1 mmol) was reduced with a 3.5 N RedAl solution (14 ml, 48.3 mmol) to provide 5.1 g (88%) of **20ab** as an oil. This compound was converted into its fumarate (EtOH): mp 145 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.78 (6H, s), 0.84 (6H, d, J=6.60 Hz), 1.17 (3H, d, J=6.84 Hz), 1.25 (3H, m), 1.54—1.57 (2H, m), 1.74—1.83 (1H, m), 2.00—2.15 (2H, m), 2.20 (2H, s), 2.28 (6H, s, N($\underline{CH_3}$)$_2$), 2.39 (2H, d, J=7.13 Hz), 2.49—2.50 (2H, m), 2.58—2.59 (2H, m), 2.95—3.10 (3H, m), 6.57 (4H, s), 7.05—7.15 (4H, dd, J=8.04, 22.5 Hz). *Anal.* ($C_{24}H_{42}N_2 \cdot 2C_4H_4O_4$) C, H, N.

3-(4-Pyridinyl)-2-piperidinone (26) A solution of **25** (3 g, 13.8 mmol) and Raney nickel (0.5 g) in EtOH (30 ml) saturated with ammonia was hydrogenated in a Parr apparatus at 50 °C under 50 psi hydrogen pressure for 8 h. Catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give **26** (1.9 g, 80%) as a solid: mp 164 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.80—1.99 (3H, m, H-4, H-5), 2.15—2.25 (1H, m, H-4$_a$), 3.41—3.46 (2H, m, H-6), 3.60—3.65 (1H, dd, J=5.8, 6.9 Hz, H-3), 6.53 (1H, br s, CON$\underline{H}$), 7.17—7.19 (2H, m), 8.55—8.57 (2H, m).

3-(4-Piperidinyl)-2-piperidinone (27) The title compound was hydrogenated from **26** as described for 4-piperidineethanamine derivative in a 93% yield (8.5 g, 48.3 mmol): mp 136 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.29—1.72 (6H, complex m), 1.82—1.92 (2H, m), 2.08 (1H, s, N$\underline{H}$), 2.21—2.32 (2H, m), 3.05—3.13 (2H, m), 2.61 (1H, dd, J=2.45, 11.9 Hz), 2.69 (1H, dd, J=2.9, 11.6 Hz), 3.05—3.13 (2H, m), 3.23—3.28 (2H, m), 6.10 (1H, s, N$\underline{H}$CO).

3-(4-(1-Dodecylpiperidin-4-yl)-2-piperidinone (28) The title compound was obtained following Method B from **27** (4 g, 21.8 mmol) as a solid (7 g, 91%): mp 90 °C (iso-Pr_2O). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz, CH_3), 1.25 (20H, complex m), 1.38—1.74 (6H, m), 1.82—1.99 (4H, m), 2.15—2.31 (4H, m), 2.92—3.00 (2H, m), 3.24—3.27 (2H, m), 5.80 (1H, s). *Anal.* ($C_{22}H_{42}N_2O$) C, H, N.

3-(4-(1-Dodecylpiperidin-4-yl)piperidine (21a) To an ice-cooled suspension of $LiAlH_4$ (0.955 g, 25 mmol) in THF (100 ml) was carefully added a solution of **28** (4 g, 11.4 mmol) in THF (50 ml) and the resulting mixture was allowed to warm to ambient temperature then it was stirred under reflux for 3 h. After cooling the mixture was hydrolyzed with a 10% aqueous solution of Rochelle salt. The resulting precipitate was filtered off and washed with THF. The combined filtrates were evaporated to give **21a** as a solid (3.7 g, 97%). This compound was converted to the corresponding fumarate: mp 176 °C. ^{1}H-NMR (DMSO-d_6, D_2O) δ: 0.85 (3H, t, J=6.4 Hz, CH_3), 1.18—1.59 (30H, complex m), 1.76—1.87 (2H, m), 2.33 (6H, s), 2.71—2.83 (2H, m), 2.93—2.98 (2H, m), 3.21—3.26 (2H, m), 3.44—3.48 (2H, m), 7.23 (4H, d, J=8.10 Hz), 7.55 (4H, d, J=8.10 Hz). ($C_{22}H_{44}N_2 \cdot 2C_7H_8O_2S$) C, H, N.

1-Methyl-3-(4-(1-dodecylpiperidinyl)piperidine (21b) A solution of **21a** as a base (2.1 g, 6.25 mmol), formic acid (15 g) and a 37% solution of formaldehyde in methanol (12 g) was stirred at 100 °C overnight. The reaction mixture was evaporated and the residue was carefully basified with 30% sodium hydroxide then the mixture was extracted with EtOAc. The organic phase was washed with water, dried ($MgSO_4$). Evaporation of the solvent left **21b** as an oil (2.1 g, 95%). ^{1}H-NMR ($CDCl_3$) δ: 0.81—0.93 (4H, m), 1.01—1.11 (1H, m), 1.25—1.84 (32H, complex m), 2.24—2.28 (5H, m, $\underline{CH_2}$N, N$\underline{CH_3}$), 2.75—2.86 (2H, m), 2.92—2.96 (2H, m).

This compound was converted into its tosylate (acetone): mp 160 °C $C_{23}H_{46}N_2 \cdot 2C_7H_8O_3S$) C, H, N.

Molecular Modeling Studies Software and Hardware: All simulations were performed with the Insight II 98.0/Discover 2.98 modeling package. The CFF91 force field was used for the building of the 3D OSC model, while the CVFF force field was used in the affinity docking procedure. The homology module was used to build up the three dimensional model of the OSC. The affinity module was used to perform docking calculations. All the calculations were performed on a Silicon Graphics bi-processor Octane workstation, with a main memory size of 256 Mo.

Building of the 3D OSC Model: To build up a three dimensional model of the OSC, we used the classical[22] homology modeling approach. The X-Ray structure of the squalene-hopene cyclase co-crystallized with the so-called LDAO competitive inhibitor was extracted from the PDB database (pdb code 1SQC).[4a] Two other structures were present in the PDB (2SQC and 3SQC), but we decided not to use them because they do not bear a suitable ligand corresponding to our needs. Furthermore, the superimposition of the Cα of the three X-ray structures, revealed that their backbones are absolutely superimposable. We considered then that the 2SQC and 3SQC will not give us more information. Using the sequence alignment of squalene-hopene cyclase and OSC proposed by Wendt *et al.*[4a] we transferred the coordinates in the non-gapped regions from the squalene-hopene cyclase to our OSC model. The gapped regions were processed by adding loops from the PDB, using the functionality loop search of the Homology module. Ten loops propositions were retrieved, and the most suitable one was chosen on the basis of compatibility with the conformation of the flanking regions. The obtained model was submitted to a refinement procedure: a complete relaxation by an energy minimization followed by a succession of mild Molecular Dynamics simulations (10 ps) in order to detect eventual steric constraints or bumps. Finally, a complete relaxation by energy minimization was performed to get our final 3D OSC model.

Docking of the Inhibitors: The Affinity procedure was applied using all the parameters as default values. The first step consisted in defining the active site, and positioning the inhibitor so that its exocyclic nitrogen atom was superimposed to the nitrogen of LDAO, while their cores were aligned with the LDAO alkyl chain. After performing energy minimization and a short molecular dynamics on the protein-inhibitor system to remove bad internal coordinates and contact, the core procedure was performed which gave our 3D OSC-inhibitor models.

Preparation of Rat Liver Microsomal 2,3-Oxidosqualene Cyclase Male Wistar rats weighing 250 g were used. Food was withdrawn 4 h before animals were killed. The livers were quickly removed, minced and homogenized in ice cold 0.25 M sucrose in a Potter-Elvehjem type Teflon homogenizer at 2000 rpm. Homogenates were centrifuged for 15 min at 16000 $\boldsymbol{g}_{max}$, and the supernatants collected were centrifuged again at 16000 $\boldsymbol{g}_{max}$. Then the two-thirds upper part of the supernatant was collected and centrifuged at 1000000 $\boldsymbol{g}_{max}$ for 1 h. Microsomal pellets were resuspended in one-half the initial volume and then centrifuged for 1 h at 100000 $\boldsymbol{g}_{max}$. Pellets of washed microsomes were collected and fractionated in small aliquots stored at −80 °C without loss of activity for at least 2 months.

2,3-Oxidosqualene Cyclase Assay We used the original following procedure: a standard assay mixture consisted of a total volume of 500 μl containing 150 μg of microsomal protein and 100 μM (*R*,*S*)-2,3-oxidosqualene.[23] Incubation was for 1 h at 37 °C; then the reaction was stopped by adding 1 ml of 7% methanolic KOH and 20 ng of stigmasterol as internal standard. After 0.5 h at 80 °C for saponification, nonsaponifiable lipids were extracted twice with *n*-hexane and then evaporated and derivatized with 75 μl of BSTFA–1% TMCS and 25 μl of pyridine. TMCS ethers were chromatographed on a 30 m OV1 column at 260 °C. Retention times of TMCS-lanosterol and -stigmasterol ethers were respectively 17 min and 15.5 min. The inhibitory potencies of compounds were expressed as the concentration at which 50% inhibition of OSC activity was observed.

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References and Notes

1) For recent examples of 2,3-oxidosqualene-lanosterol cyclase inhibitors see: *a*) Zheng Y. F., Oehlschlager A. C., Georgopapadakou N. H., Hartman P. G., Scheliga P., *J. Am. Chem. Soc*., **117**, 670—680 (1995); *b*) Viola F., Brusa P., Balliano G., Ceruti M., Boutaud O., Schuber F., Cattel L., *Biochem. Pharmacol*., **50**, 787—796 (1995); *c*) Mark M., Müller P., Maier R., Eisele B., *J. Lipid Res*., **37**, 148—158 (1996); *d*) Eisele B., Budzinski R., Müller P., Maier R., Mark M., *ibid*., **38**, 564—575 (1997); *e*) Morand O. H., Aebi J. D., Dehmlow H., Ji Y. H., Gains N., Lengsfeld H., Himber J., *ibid*., **38**, 373—390 (1997); *f*) Brown G. R., Hollinshead D. M., Stokes E. S. E., Clarke D. S., Eakin M. A., Foubister A. J., Glossop S. C., Griffiths D., Johnson M. C., McTaggart F., Mirrlees D. J., Smith G. J., Wood R., *J. Med. Chem*., **42**, 1306—1311 (1999); *g*) Brown G. R., Hollinshead D. M., Stokes E. S. E., Waterson D., Clarke D. S., Eakin M. A., Foubister A. J., Glossop S. C., McTaggart F., Mirrlees D. J., Smith G. J., Wood R., *ibid*., **43**, 4964—4972 (2000).

2) *a*) Stork G., Burgstahler A. W., *J. Am. Chem. Soc*., **77**, 5068—5077 (1955); *b*) Johnson W. S., *Acc. Chem. Res*., **1**, 1—8 (1968); *c*) van Tamelen E. E., *J. Am. Chem. Soc*., **104**, 6480—6481 (1982); *d*) Abe I., Rohmer M., Prestwich G. D., *Chem. Rev*., **93**, 2189—2206 (1993).

3) *a*) Abe I., Prestwich G. D., *J. Biol. Chem*., **269**, 802—804 (1994); *b*) *Idem*, *Proc. Natl. Acad. Sci. U.S.A*., **92**, 9274—9278 (1995); *c*) Corey

E. J., Daley D. C., Cheng H., *Tetrahedron Lett*., **37**, 3287—3290 (1996); *d*) Stach D., Zheng Y. F., Perez A. L., Oehlschlager A. C., *J. Med. Chem*., **40**, 201—209 (1997); *e*) Corey E. J., Cheng H., Baker C. H., Matsuda S. P. T., Li D., Song X., *J. Am. Chem. Soc*., **119**, 1277—1288 (1997); *f*) *Idem*, *ibid*., **119**, 1289—1296 (1997); *g*) Ceruti M., Rocco F., Viola F., Balliano G., Milla P., Arpicco S., Cattel L., *J. Med. Chem*., **41**, 540—554 (1998).

4) *a*) Wendt K. U., Poralla K., Schulz G. E., *Science*, **277**, 1811—1815 (1997); *b*) Wendt K. U., Lenhart A., Schulz G. E., *J. Mol. Biol*., **286**, 175—187 (1999).
5) *a*) Abe I., Zheng Y. F., Prestwich G. D., *Biochemistry*, **37**, 5779—5784 (1998); *b*) Dang T., Abe I., Zheng Y. F., Prestwich G. D., *Chemistry and Biology*, **6**, 333—341 (1999); *c*) Wendt K. U., Schulz G. E., Corey E. J., Liu D. R., *Angew. Chem. Int. Ed*., **39**, 2812—2833 (2000).
6) Barth M. M., Binet J. L., Thomas D. M., de Fornel D. C., Samreth S., Schuber F. J., Renaut P. P., *J. Med. Chem*., **39**, 2302—2312 (1996).
7) Taton M., Benveniste P., Rahier A., *Biochem. Biophys. Res. Commun*., **138**, 764—770 (1996).
8) Borch M. D., Bernstein M. D., Durst H. D., *J. Am. Chem. Soc*., **93**, 2897—2904 (1971).
9) Pechulis A. D., Bellevue III F. H., Cioffi C. L., Trapp S. G., Fojtik J. P., McKitty A. A., Kinney A. A., Frye L. L., *J. Org. Chem*., **60**, 5121—5126 (1995).
10) Borch M. D., Hassid A. I., *J. Org. Chem*., **37**, 1673—1674 (1972).
11) Olah G. A., Narang B. G., Gupta B. G. B., Malhata R., *J. Org. Chem*., **44**, 1247—1251 (1979).
12) Rissi E., Ebnoether A., (Sandoz Ltd.) Germ. Offen. DE 2429373 750116 (1981) [*Chem. Abstr*., **95**, 24826*m* (1981)].
13) *a*) Manson J. J., Sjogren R. E., Riano M., *J. Org. Chem*., **30**, 307—309 (1965); *b*) Mauli R., Ringold H. J., Djerassi C., *J. Am. Chem. Soc*., **82**, 5494—5500 (1960).
14) Boss A. M., Clissold D. W., Mann J., Markson A. J., Thickitt C. P., *Tetrahedron*, **45**, 6011—6016 (1989).
15) *a*) Eschweiler W., *Ber*., **38**, 880—881 (1905); *b*) Clarke H. T., Gillespie H. B., Weisshaus S. Z., *J. Am. Chem. Soc*., **55**, 1933 (1971); *c*) Cope A. C., Burrows W. D., *J. Org. Chem*., **30**, 2163—2165 (1965).
16) Wannamaker M. W., Waid P. P., Van Sickle W. A., McCarthy J. R., Wilson P., Schatzman G., Moore W. R., *J. Med. Chem*., **35**, 3581—3583 (1992).
17) For a similar approach in the hydroxylated series, see: Wannamaker M. W., Waid P. P., Moore W. R., Schatzman G., Van Sickle W. A., Wilson P., *Bioorg. Med. Chem. Lett*., **3**, 1175—1178 (1993).
18) Binet J., Samreth S., De Fornel D., Boucher T., Renaut P., (Fournier Industrie et Santé) PCT Int. Appl. 1994, WO 9410150 A1 1994440511.
19) Binet J., Samreth S., De Fornel D., (Fournier Industrie et Santé) PCT Int. Appl. 1994, WO 9426713 A1 19941124.
20) Dang T., Prestwich G. D., *Chemistry and Biology*, **7**, 643—649 (2000).
21) Koehl P., Delarue M., *Nat. Struct. Biol*., **2**, 163—170 (1995).
22) Sali A., Blundell T.L., *J. Mol. Biol*., **234**, 719—815 (1993).
23) Ceruti M., Balliano G., Viola F., Cattel L., Gerst N., Schuber F., *Eur. J. Med. Chem*., **22**, 199—208 (1987).
24) Cattel L., Ceruti M., Viola L., Delprino L., Balliano G., Duriatti A., Bouvier-Navé P, *Lipids*, **21**, 3138 (1986).
25) Stütz A., Petranyi G., *J. Med. Chem*., **27**, 1539—1543 (1984).
26) Georgopoulos A., Petranyi G., Mieth H., Drews J., *Antimicrob. Agents Chemother*., **19**, 386—389 (1981).