Synthesis and Inotropic Activity of 1-(*O*-Aminoalkyloximes) of Perhydroindene Derivatives as Simplified Digitalis-like Compounds Acting on the Na+,K+-ATPase

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A series of 5-substituted (3a*S*,7a*R*)-7a-methylperhydroinden-3a-ol derivatives bearing a 1(*S*)-(ω-aminoalkoxy)iminoalkyl or -alkenyl substituent was synthesized, starting from the Hajos−Parrish ketol **47**, as simplified analogues of very potent 17β-aminoalkyloximes with digitalis skeleton, previously reported. The target compounds were evaluated in vitro for displacement of the specific [³H]ouabain binding from the dog kidney Na+,K+-ATPase receptor. Some of them revealed IC₅₀ values in the micromolar range. The most active compounds possess a cyclohexyl group in the 5(*S*) position and in position 1(*S*) the same aminoalkyloxime groups already reported for the digitoxigenin-like series in position 17β. Although the ring conformation of these derivatives was comparable to that of uzarigenin, the binding affinities of the most active ones were 4/8-fold lower in comparison to that standard. Three compounds among those with the highest affinities were assayed in vitro for their inotropic activity on an electrically driven guinea pig left atrium and were found to be less potent than both digoxin, the most widely used inotropic agent, and the corresponding digitalis 17β-aminoalkyloximes.

Introduction

Digitalis cardiac glycosides are drugs clinically used for the treatment of congestive heart failure, although their major problem is the low therapeutic index due to cardiac pro-arrhythmogenic activity.[1] Among them, digoxin (Chart 1) is the most widely used one. Many efforts have been made to find a safer cardiotonic agent,[2] and our group has been involved (in the last years) in the search for such a positive inotropic agent acting through the inhibition of Na+,K+-ATPase.[3−5]

In the past, several attempts were made to replace the steroidal digitalis skeleton with completely different structures, such as deoxybenzoin,[6] flavone,[6] stilbene,[6] indoline,[7] isoquinoline,[8] benzobicyclo[2,2,2]octane,[9] without obtaining favorable pharmacological results. More recently, San Feliciano et al. reported some compounds structurally derived from a simplification of the steroidal skeleton: diterpene derivatives,[10] in which the D-ring was missing, and cyclohexane derivatives,[11,12] maintaining only the C-ring, both linked to the butenolide ring typically present in digitalis compounds. These compounds did not show any positive inotropic activity.

In the same period, we also started working on simplification of the digitalis skeleton, such as seco-D compounds[13] and perhydroindene derivatives,[14] in order to find the minimum structural requirements for the recognition of the digitalis receptor and, possibly, a safer inotropic agent. Recently, we published the synthesis

Chart 1

R = OH **Digoxin**
R = H   **Digitoxin**

Digitoxigenin

1
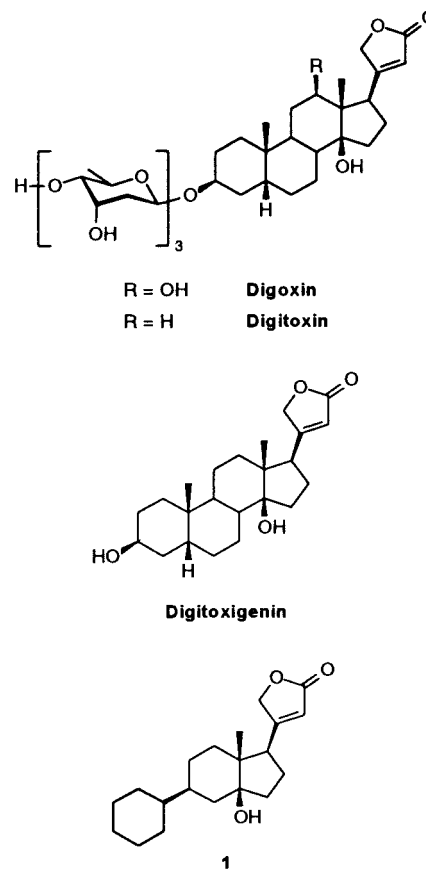
of the butenolide derivative with a hydrindane skeleton **1** (Chart 1), which preserved the most distinctive part of the digitalis skeleton, i.e., the C- and D-rings with a

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Chart 2
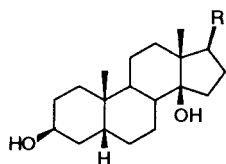
116 R = (*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$

117 R = (*E,E*) CH=CHCH=NO(CH$_2$)$_2$N(CH$_3$)$_2$

118 R = (*E,E*) CH=CHCH=NO(CH$_2$)$_2$NH$_2$

cis junction; this compound showed a weak affinity to the Na$^+$,K$^+$-ATPase receptor.[15] In the same years, we prepared some 17β-aminoalkyloxime derivatives of the digitalis skeleton (Chart 2) showing particularly high inhibitory activity on Na$^+$,K$^+$-ATPase and high inotropic potency on guinea pig atrium; the most active compounds were more potent than digoxin itself.[16] The idea that the replacement of the butenolide ring in compound **1** with the powerful activity inducing aminoalkyloxime chain could enhance the potency of the hydrindane derivatives brought us to prepare the derivatives described in the present article.[17] In the same period, San Feliciano's group published some other hydrindane derivatives acting as inotropic agents:[18,19] a recent paper has been published as a compendium of their work.[20]

Chemistry

The synthetic pathways for the compounds listed in Table 1 are reported in Schemes 1−11.

The oximes or guanylhydrazones **2−12** and **15−46** were synthesized from the corresponding aldehydes and appropriate (*O*-substituted)hydroxylamines or aminoguanidine according to general Scheme 1. Hydroxylamines **13** and **14** were prepared by reduction of the corresponding oximes **10** and **11** with NaBH$_3$CN (Scheme 2).

The oximes and guanylhydrazones reported in Table 1 were obtained as pure or almost pure *E* isomers (*Z* isomer = 10%) except for compounds **35** (50% of *Z* oxime), **36** (25% of *Z* oxime), **37** and **38** (20% of *Z* oxime). Analogously to the corresponding digitalis-like oximes,[16] compounds **2−12**, **15−34** showed no *E/Z* isomerization in D$_2$O/DMSO-d_6 solution at pH 7.4 (phosphate buffer) and 37 °C (^{1}H NMR analysis), while vinylic oximes **39−40** gave a 6/4 *E/Z* equilibrium mixture, after 24 h. Compounds **41** and **42**, with a methyl group on the double bond, were synthesized to stabilize the *E* isomer and prevent isomerization.

The common synthon for all the described compounds was the 1(*S*)-hydroxymethyl derivative **51** (Scheme 3) susceptible of nucleophilic attack to the 5-keto group with the appropriate reagent. Starting material was the Hajos−Parrish ketol[21] **47** which shows the stereochemistry and substitutions at the quaternary carbon atoms corresponding exactly to those of the digitalis C−D-rings. The sequence from **47** to **51** (Scheme 3) was the same described by Sevillano et al.[20] although the reactions were carried out in different conditions. Selective protection of the 5-keto group as dioxolane with excess of ethylene glycol and oxalic acid followed by Wittig reaction on the 1-keto group gave the exomethylenic compound **48**; hydroboration of **48** yielded a 5/2 mixture
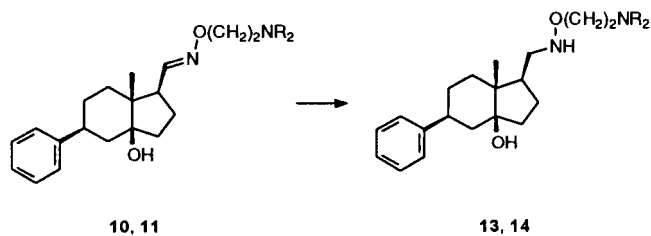
Scheme 1[a]
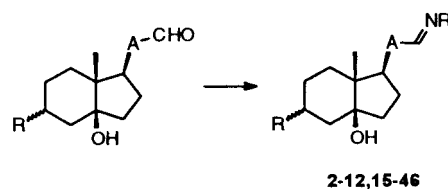
R and R': see Table 1

A = bond, CH$_2$, CH$_2$CH$_2$, (E) - CH=CH, (E) - CH=C(CH$_3$)

[a] Reagents and conditions: compounds **2−11**, **15−33**, **35−38**, **45**, **46**: H$_2$NOR″·xHCl, NaOAc, HCl, dioxane, H$_2$O, pH 4.5; compounds **12**, **34**, **43**, **44**: H$_2$NHC(NH)NH$_2$·H$_2$CO$_3$, dioxane, H$_2$O, HCl; compounds **39−42**: H$_2$NOR″·xHCl, NaOH, dioxane.

Scheme 2[a]

10, 11   13, 14

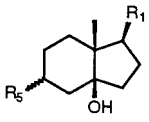10, 13   R = CH$_3$

11, 14   R = H

[a] Reagents and conditions: NaBH$_3$CN, MeOH, H$_2$O, HCl, pH 3.

of 1-epimeric compounds **49** and **50**, which could be easily separated by flash chromatography. Careful hydrolysis of ketal **49** gave the desired synthon **51** together with a small amount of the 3a,4 unsaturated ketone. The undesired epimeric compound **50** could be partially recovered to the useful derivative **49** by IBX oxidation[22] to the corresponding aldehyde **52** which was converted in basic medium to a mixture of the 1-epimers **52** and **53**, the latter being the more stable epimer, followed by in situ NaBH$_4$ reduction to a 2/1 mixture of alcohols **49** and **50**.

The 5-unsubstituted aldehyde **56** (Scheme 4) was obtained by thioketalization of keto alcohol **51** followed by Raney-Ni reduction of **54**; IBX oxidation of the 5-unsubstituted alcohol **55** gave the desired aldehyde **56**.

The preparations of the 5-benzylydene **59** (*E*) and **60** (*Z*), benzyl **63** (*R*) and **64** (*S*), and cyclohexylmethyl **66** (*R*) and **68** (*S*) aldehydes are described in Scheme 5. Wittig reaction on ketol **51** gave approximately a 1:1 *E/Z* mixture of benzylidene derivatives **57** and **58** which could be separated only partially. The purified compounds were oxidized to aldehydes **59** and **60**. Hydrogenation of the mixture of **57** and **58** over Pd/C gave the epimeric mixture of (5*S*) and (5*R*) benzyl derivatives that could be chromatographically separated only by transformation into the corresponding TBDMS ethers **61** and **62**. Hydrolysis of the silyl group and oxidation of the alcohols gave aldehydes **63** and **64**. Hydrogenation of pure **61** and **62**, on Rh/Al$_2$O$_3$ at 4.3 atm, followed by hydrolysis of the silyl group gave the cyclohexyl alcohols **65** and **67**, which were oxidized, respectively, to the aldehydes **66** and **68**.

The introduction of a phenyl group in position 5α or 5β was accomplished by stereospecific β addition of

**Table 1.** Structure, Analytical Data, and Na^+,K^+-ATPase Binding of Compounds **2**−**46**

compd	R_5	R_1	mol formula[a]	Na^+,K^+-ATPase binding, IC_{50},[b] μM
1				$>10^c$
2	H	(*E*) CH=NO(CH$_2$)$_3$NH$_2$	C$_{14}$H$_{26}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	$>100^e$
3	(*E*) =CHC$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{32}$N$_2$O$_2$	50
4	(*Z*) =CHC$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{32}$N$_2$O$_2$	8.0
5	α-CH$_2$C$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	$>100^f$
6	α-CH$_2$C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{40}$N$_2$O$_2$	100
7	β-CH$_2$C$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_2$	3.2
8	β-CH$_2$C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{40}$N$_2$O$_2$	4.0
9	α-C$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{32}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	$>100^g$
10	β-C$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{32}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	3.2
11	β-C$_6$H$_5$	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{19}$H$_{28}$N$_2$O$_2$	4.0
12	β-C$_6$H$_5$	(*E*) CH=NN=C(NH$_2$)$_2$	C$_{18}$H$_{26}$N$_4$O·HCl	$>100^h$
13	β-C$_6$H$_5$	CH$_2$NHO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{34}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]·1.5H$_2$O	10
14	β-C$_6$H$_5$	CH$_2$NHO(CH$_2$)$_2$NH$_2$	C$_{19}$H$_{30}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	20
15	β-(3-H$_3$CC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_2$	5.0
16	β-(3-H$_3$CC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{20}$H$_{30}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	3.2
17	β-(4-H$_3$CC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_2$	10
18	β-(4-H$_3$CC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{20}$H$_{30}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]·0.33H$_2$O	6.3
19	β-(3-HOC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{32}$N$_2$O$_3$	10
20	β-(4-HOC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{32}$N$_2$O$_3$·0.2H$_2$O	2.5
21	β-(3-HOCH$_2$C$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_3$·0.5H$_2$O	5.0
22	β-(3-HOCH$_2$C$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{20}$H$_{30}$N$_2$O$_3$·C$_2$H$_2$O$_4$[d]·0.5H$_2$O	2.5
23	β-(4-HOCH$_2$C$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{34}$N$_2$O$_3$	8.0
24	β-(4-HOCH$_2$C$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{20}$H$_{30}$N$_2$O$_3$·0.5H$_2$O	2.5
25	β-(4-(H$_3$C)$_2$N(CH$_2$)$_2$OC$_6$H$_4$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{25}$H$_{41}$N$_3$O$_3$	1.0
26	β-(3-C$_5$H$_4$N)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{20}$H$_{31}$N$_3$O$_2$	13
27	β-(4-C$_5$H$_4$N)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{20}$H$_{31}$N$_3$O$_2$·0.33H$_2$O	2.5
28	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{38}$N$_2$O$_2$	1.6
29	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_3$N(CH$_3$)$_2$	C$_{22}$H$_{40}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	3.2
30	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_4$N(CH$_3$)$_2$	C$_{23}$H$_{42}$N$_2$O$_2$·0.33H$_2$O	10
31	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_2$NH$_2$	C$_{19}$H$_{34}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	1.0
32	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_3$NH$_2$	C$_{20}$H$_{36}$N$_2$O$_2$·0.25H$_2$O	0.8
33	β-C$_6$H$_{11}$	(*E*) CH=NO(CH$_2$)$_4$NH$_2$	C$_{21}$H$_{38}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	13
34	β-C$_6$H$_{11}$	(*E*) CH=NN=C(NH$_2$)$_2$	C$_{18}$H$_{32}$N$_4$O·1H$_2$O	63
35	β-C$_6$H$_{11}$	(*EZ*) CH$_2$CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{22}$H$_{40}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	1.6
36	β-C$_6$H$_{11}$	(*EZ*) CH$_2$CH=NO(CH$_2$)$_2$NH$_2$	C$_{20}$H$_{36}$N$_2$O$_2$	1.6
37	β-C$_6$H$_{11}$	(*EZ*) (CH$_2$)$_2$CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{23}$H$_{42}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	5.0
38	β-C$_6$H$_{11}$	(*EZ*) (CH$_2$)$_2$CH=NO(CH$_2$)$_2$NH$_2$	C$_{21}$H$_{38}$N$_2$O$_2$·0.5C$_2$H$_2$O$_4$[d]·1H$_2$O	3.2
39	β-C$_6$H$_{11}$	(*E,E*) CH=CHCH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{25}$H$_{42}$N$_2$O$_6$·C$_2$H$_2$O$_4$[d]	1.0
40	β-C$_6$H$_{11}$	(*E,E*) CH=CHCH=NO(CH$_2$)$_2$NH$_2$	C$_{21}$H$_{36}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	1.0
41	β-C$_6$H$_{11}$	(*E,E*) CH=C(CH$_3$)CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{24}$H$_{42}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	2.0
42	β-C$_6$H$_{11}$	(*E,E*) CH=C(CH$_3$)CH=NO(CH$_2$)$_2$NH$_2$	C$_{22}$H$_{38}$N$_2$O$_2$·C$_2$H$_2$O$_4$[d]	1.3
43	β-C$_6$H$_{11}$	(*E,E*) CH=CHCH=NN=C(NH$_2$)$_2$	C$_{20}$H$_{34}$N$_4$O·1H$_2$O	16
44	β-C$_6$H$_{11}$	(*E,E*) CH=C(CH$_3$)CH=NN=C(NH$_2$)$_2$	C$_{21}$H$_{36}$N$_4$O·HCl	$>100^g$
45	β-(*cis*-4-HOC$_6$H$_{10}$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{38}$NO$_3$	1.6
46	β-(*trans*-4-HOC$_6$H$_{10}$)	(*E*) CH=NO(CH$_2$)$_2$N(CH$_3$)$_2$	C$_{21}$H$_{38}$NO$_3$	1.0
116				0.04
117				0.025
118				0.016
digitoxigenin				0.063
uzarigenin				0.25

[a] Analyses for C, H, N, Cl, and H$_2$O are within 0.4% of the theoretical values. [b] Concentrations able to displace 50% of the specific [³H]ouabain binding. Mean of two or three experiments. [c] 30% displacement at 10 μM. [d] Oxalate. [e] 20% displacement at 100 μM. [f] 45% displacement at 100 μM. [g] 30% displacement at 100 μM. [h] 35% displacement at 100 μM.

phenyllithium to the synthon **51** (Scheme 6) and stereoselective hydrogenolysis of **69** with retention or inversion of configuration. Hydrogenolysis over Pd/C in the presence of HClO$_4$ gave a **70**/**72** mixture in 3/1 ratio (the main product showing inversion of configuration) which could be separated by transforming the primary alcohols into their TBDMS ethers. Once separated, the silyl group of the main component was removed, affording **70** again which was oxidized to the aldehyde **71**. The more desired (5*S*)-phenyl derivative **72** was better obtained from **69** by Raney-Ni stereospecific hydro-

genolysis in 82% yield, with retention of configuration. The hydrogenation of the aromatic ring of **72** was carried out over Rh/Al$_2$O$_3$ at 4.3 atm. IBX oxidation of **72** and **74** gave, respectively, **73** and **75**.

The stereochemistry of the new stereocenter and the conformation of the ring system in compounds **70** and **72** could be attributed on the basis of the NMR spectra. In fact, in the derivative **72** the chemical shift of the 7a-methyl is 14.9 ppm (¹³C NMR) as in the corresponding 17β-hydroxymethyl derivative with digitalis skeleton (C-18 at 15.3 ppm),[23] while in the case of **70** the

Scheme 3[a]
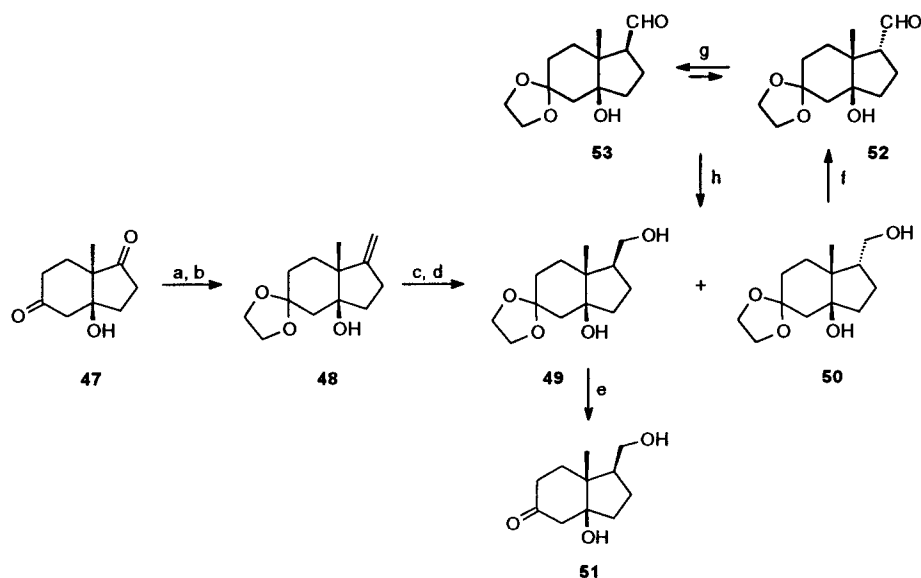
[a] Reagents and conditions: (a) (COOH)$_2$, (CH$_2$OH)$_2$, MeCN; (b) CH$_3$P(C$_6$H$_5$)$_3$Br, *t*-BuOK, *t*-BuOH, THF, reflux, 2 h; (c) 1 M BH$_3$, THF; (d) H$_2$O, NaBO$_3$, 4 N NaOH; (e) 1 N pTSA, MeCN, H$_2$O; (f) IBX, THF, reflux, 1 h; (g) 1.4 M KOH, MeOH; (h) NaBH$_4$, −20 °C, 2.5 h.

Scheme 4[a]
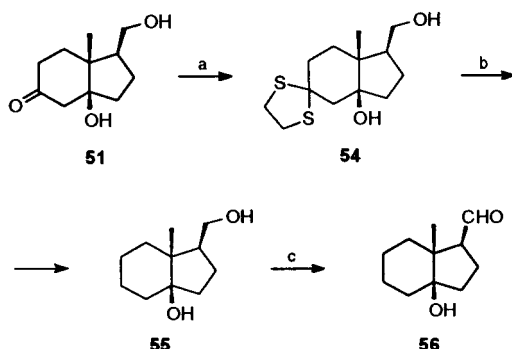
[a] Reagents and conditions: (a) HSCH$_2$CH$_2$SH, CH$_2$Cl$_2$, BF$_3$·Et$_2$O; (b) Raney-Ni, EtOH, reflux, 16 h; (c) IBX, THF, reflux, 2.5 h.

corresponding chemical shift is downfield, 19.4 ppm, diagnostic of a non-digitalis-like conformation (Figure 1). Since the hydrindane skeleton conformation is controlled by the substituent in position 5 which must be always in equatorial conformation (as confirmed by MM2 calculations), the isomer in digitalis-like conformation **72** has the 5β-phenyl group (Figure 1, digitalis-like) while **70** has the 5α-phenyl. As a confirmation of the digitalis-like conformation of **72**, the multiplets of the benzylic protons in the ^{1}H NMR spectra of **70** and **72** at 2.83 and 2.73 ppm, respectively, suggest axial conformations ($W_{h/2} = 25$ Hz) in both cases and, as a consequence, the equatorial position of phenyls.

Compounds **76** and **77** (Scheme 7) were prepared, in the same way, by stereospecific addition of the corresponding aryllithium derivatives to the ketone **51**. Hydrogenolysis over Raney-Ni provided the desired silyl ethers **80** and **81** along with the products of further hydrogenolysis of the benzyl silyl ether to the methyl derivatives **78** and **79**. Again, oxidation of the alcohols **78**−**81** gave the aldehydes **82**−**85**, respectively.

The same sequence, nucleophilic attack of the proper aryllithium derivative to **51**, hydrogenolysis over Raney-Ni of **86**−**89**, and oxidation of the alcohols **90**−**93**, gave the aldehydes **94**−**97** (Scheme 8).

The aromatic aminoether **99** (Scheme 9) was obtained by selective etherification of phenol **98** with 2-chloroethyl-*N,N*-dimethylamine and Ag$_2$CO$_3$; oxidation of compound **99** gave the 1*S* aldehyde **100** which was used rapidly as crude material in order to avoid its partial epimerization to the 1*R* epimer due to the presence of the basic amine.

Homologation of the aldehyde **75** (Scheme 10) was accomplished through the vinyl derivative **101**, hydroboration to **102**, and oxidation to the aldehyde which proved to exist as lactol **103**. Vinylogous aldehydes **105** and **108** (Scheme 10) were obtained by Horner−Emmons reactions of **75** with the appropriate phosphonoacetates to give the esters **104** and **107**, which were reduced with DIBAH to the corresponding allylic alcohols and oxidized to the aldehydes **105** and **108** with MnO$_2$. The saturated aldehyde **106** was obtained by hydrogenation of **105** over Pd/C.

The TBDMS ethers of epimeric cyclohexanols **110** and **115** were obtained as reported in Scheme 11. Hydrogenation of the aromatic ring of **93** over Rh/Al$_2$O$_3$ gave the cis isomer **109** which was oxidized to the aldehyde **110**. The epimeric trans isomer **115** was obtained by first transforming the 1*S* hydroxymethyl derivative **109** into the corresponding acetate **111**. Acidic hydrolysis deprotection of the silyl ether and subsequent oxidation gave the ketone **112**. LiAlH(O*t*But)$_3$ reduction gave selectively the axial alcohol **113** (only 10% of the equatorial isomer) which was protected as TBDMS ether **114**. Basic hydrolysis of the acetate followed by oxidation of the resulting alcohol gave the aldehyde **115**.

All the silyl ethers were deprotected in situ in acidic conditions before the reaction with 2-dimethylaminoethoxyamine at the appropriate pH.

Biological Activity

All compounds were evaluated in vitro for displacement of the specific [^{3}H]ouabain binding from the dog kidney Na$^+$,K$^+$-ATPase receptor;[24,25] data are shown in Table 1. Compounds **28**, **39**, and **40** were chosen among those with the highest affinities, to further investigate

Scheme 5[a]
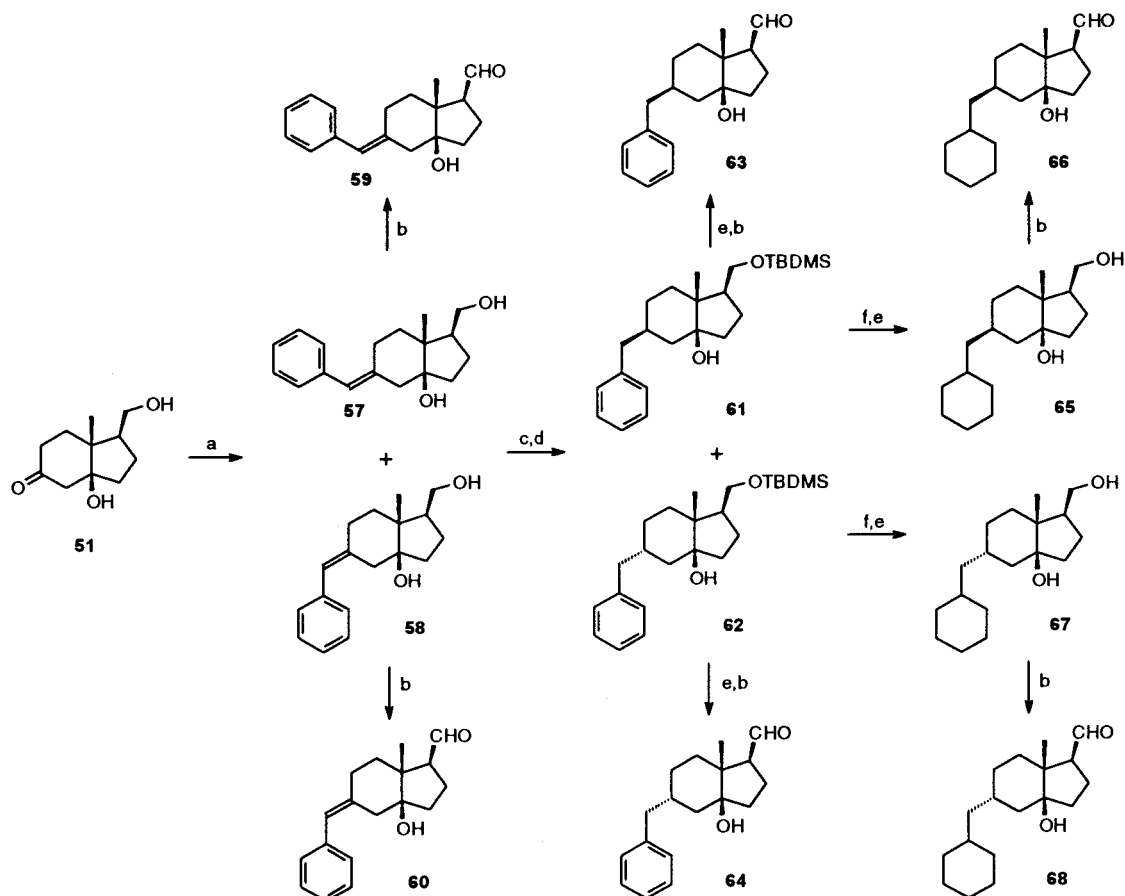
[a] Reagents and conditions: (a) $C_6H_5CH_2P(C_6H_5)_3Br$, $NaNH_2$, THF; (b) IBX, DMSO; (c) H_2, 10% Pd/C, EtOAc; (d) TBDMSCl, imidazole, DMF; (e) 3 N HCl, dioxane, H_2O, pH 1; (f) H_2, 5% Rh/Al_2O_3, MeOH, 4.3 atm.
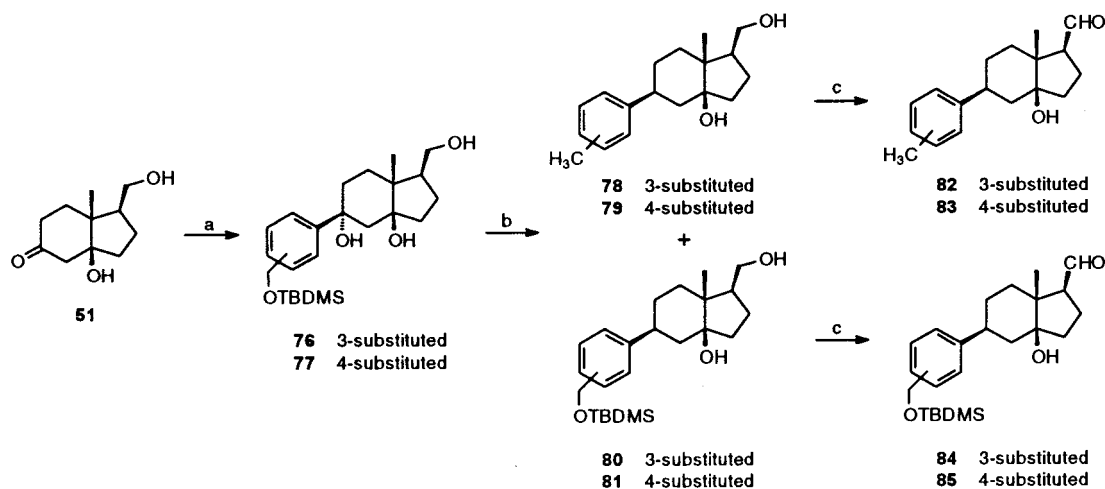
Scheme 6[a]
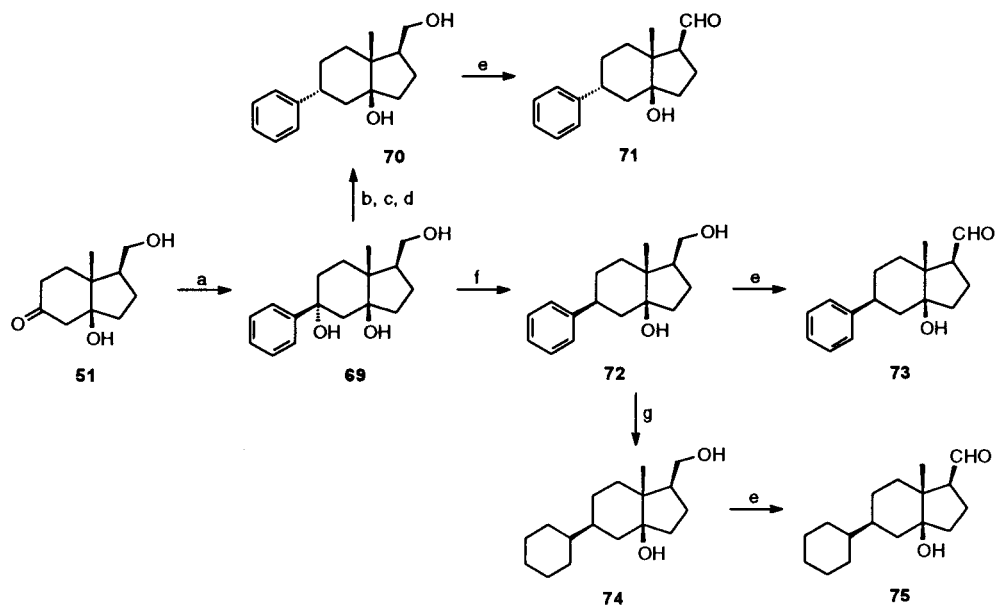
[a] Reagents and conditions: (a) PhLi, THF, −78 °C, 1 h; (b) H_2, 5% Pd/C, $HClO_4$, EtOAc; (c) TBDMSCl, imidazole, DMF; (d) 3 N HCl, dioxane, H_2O, pH 1; (e) IBX, DMSO; (f) Raney-Ni, EtOH, reflux, 3 h; (g) H_2, 5% Rh/Al_2O_3, MeOH, 4.3 atm.

in vitro their inotropic activity by measuring the effects on the contractile force of an electrically driven guinea pig left atrium;[16] data are shown in Table 2.

As reference compounds, digoxin was chosen as the most commonly prescribed cardiac glycoside in the congestive heart failure, digitoxigenin and uzarigenin were taken as models for their aglyconic digitalis skeleton, and oximes **116**−**118** are examples of the potent aminoalkyloximes previously reported (Chart 2).[16]

Scheme 7[a]

78   3-substituted
79   4-substituted

+

80   3-substituted
81   4-substituted

82   3-substituted
83   4-substituted

84   3-substituted
85   4-substituted

51

76   3-substituted
77   4-substituted

[a] Reagents and conditions: (a) 3- or 4-TBDMSOCH$_2$C$_6$H$_4$Br, 1.6 M *n*-BuLi, THF, Et$_2$O, −78 °C, 1.5 h; (b) Raney-Ni, EtOH, reflux, 3 days; (c) IBX, DMSO.
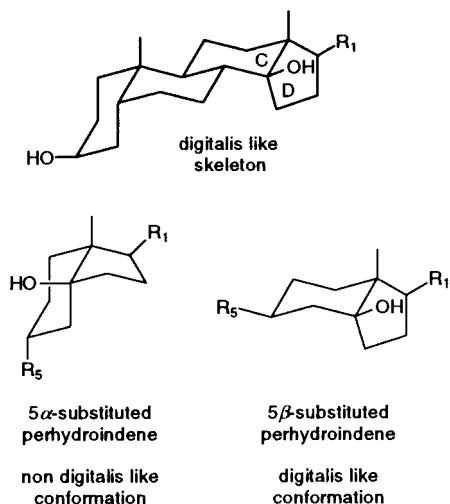

Figure 1. Conformations of epimeric 5-substituted perhydro-indene derivatives.

digitalis like skeleton

5α-substituted perhydroindene

non digitalis like conformation

5β-substituted perhydroindene

digitalis like conformation

Scheme 8[a]

51

86   R = 3-pyridyl
87   R = 4-pyridyl
88   R = 3-TBDMSOC$_6$H$_4$
89   R = 4-TBDMSOC$_6$H$_4$

90   R = 3-pyridyl
91   R = 4-pyridyl
92   R = 3-TBDMSOC$_6$H$_4$
93   R = 4-TBDMSOC$_6$H$_4$

94   R = 3-pyridyl
95   R = 4-pyridyl
96   R = 3-TBDMSOC$_6$H$_4$
97   R = 4-TBDMSOC$_6$H$_4$

[a] Reagents and conditions: (a) RBr, 1.6 M *n*-BuLi or 1.5 M *t*-BuLi, Et$_2$O or *n*-hexane or pentane, THF, −78 °C, 0.5 or 1.5 h; (b) Raney-Ni, EtOH, reflux, 8 h; (c) IBX, DMSO or IBX, THF, reflux, 1.5 h.
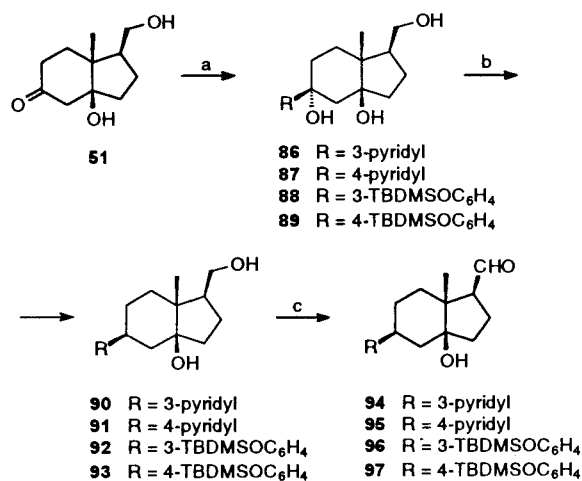
Results and Discussion

The compounds were tested as pure compounds or *E/Z* isomeric mixtures of the iminic double bond when they could not be obtained as pure isomers from the synthesis and any attempt to separate them was unproductive. The biological assays were performed within 1−4 h from the dissolution of the compounds. Since these compounds take a long time to equilibrate at pH 7.4, as reported above, we assume that no important isomerization occurred to the mixtures in the biological systems used.

All the following reasoning is based on the mixtures of components when they were used as such.

Binding to the Na$^+$,K$^+$-ATPase. The structure−activity relationships can be more easily discussed by separating the observations on substituents in positions 5 and 1 of the perhydroindene skeleton.

Position 5. The unsubstituted compound **2** showed a very low affinity; this means that the perhydroindenic skeleton itself does not afford a sufficient recognition with the receptor.

As a consequence, our approach was directed toward the addition of a substituent in position 5 that could

possibly superimpose to the A ring of a steroidal skeleton.

The most striking difference in affinities was afforded by the comparison between 5α and 5β derivatives. 5α-Substituted compounds **5**, **6**, and **9** were 25−30 times less active than the corresponding 5β derivatives **7**, **8**, and **10**. The reason can be found in the different conformations of the two epimeric series. As previously shown in Figure 1, all perhydroindene derivatives have their minimum conformational energy with the 5 substituents in equatorial position, and this results in different conformations for the two epimeric hydrindane derivatives (Figure 1). The 5α-substituted perhydro-indenes present a non-digitalis-like conformation of the CD rings, while the 5β substituted compounds are in the digitalis-like conformation, which is most probably the reason of their higher affinity to the receptor. As previously described for the synthetic intermediates **70** and **72**, such conformations have been demonstrated on the basis of the NMR spectra. In the 5β-substituted derivative **10**, the ^{13}C chemical shift of the 7a-methyl is 15.7 ppm as in the corresponding 17β-aminoalkoxy-

Scheme 9[a]
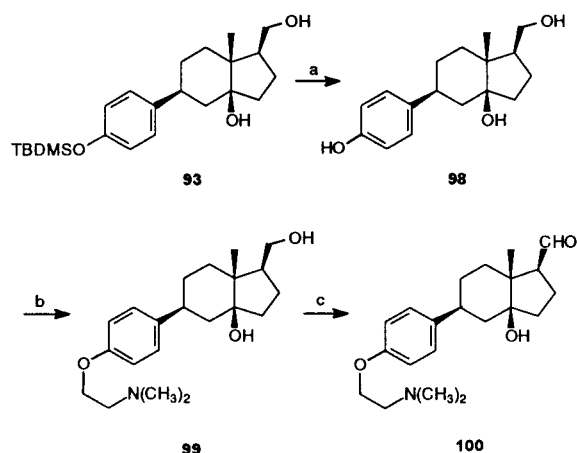
[a] Reagents and conditions: (a) 3 N HCl, dioxane, H_2O, pH 0.9; (b) Ag_2CO_3, $(Me)_2NCH_2CH_2Cl$, 50 °C, 6 h; (c) IBX, THF, reflux, 1 h.

imino derivative with digitalis skeleton (C-18 at 15.7 ppm),[16] while in the 5α-substituted derivative **9** the corresponding signal is downfield at 18.5 ppm. Further evidence is the multiplets of the benzylic protons in the ^{1}H NMR spectra of **9** and **10**, at 2.81 and 2.70 ppm, respectively, in both cases indicating an axial conformation ($W_{h/2} = 25$ Hz).

Since also the olefinic compounds **3** and **4** showed affinities between those of the 5α and 5β derivatives **5** and **7**, we focused our attention on the 5β substituted hydrindanes.

Introduction of a substituent into the phenyl ring gave results difficult to rationalize. Lipophilic or hydrophilic substituents did not substantially change affinity. Also, the introduction of a hydroxy group (compounds **19**–**24**), to mimic the 3-hydroxy substituent of the digitalis skeleton, increased little the affinity occasionally and

marginally. A tentative explanation is that orientation of the phenyl ring differs with respect to the A ring of digitalis compounds and, as a consequence, also the hydroxy groups point toward different directions. Noteworthy was the aminoether **25** with a 3-fold higher affinity in comparison with the unsubstituted analogue **10**; the aminoether chain of **25** with a more flexible conformation could probably reach the supposed sites for hydrogen bonding corresponding to the oxygen atoms of the sugars of the digitalis glycosides.

Substitution of the phenyl ring with a cyclohexyl gave 2/4-fold higher affinities: **28**, **31**, and **34** vs **10**, **11**, and **12**, respectively. The cyclohexyl ring could better mimic the A ring of steroids, even though a superimposition to uzarigenin instead of digitoxigenin is more probable (Figure 2). Surprisingly enough, also in this case, the introduction of a hydroxy group in the position 4 of the cyclohexyl ring, mimicking the 3-hydroxy substituent of the digitalis compounds, as in compounds **45** and **46**, was not shown to be very effective. The affinity was slightly improved only in the case of **46** where the 4β-hydroxy substituent resembles better the spatial arrangement of uzarigenin (Figure 2). A higher degree of conformational freedom could explain the 4-fold lower affinity of **46** in comparison with uzarigenin.

Position 1. The highest affinities could be found in simple oximes with primary amines **31** and **32** and vinylic oximes **39** and **40**. The 6−7 bond distance between the basic nitrogen and the hydrindane skeleton in the simple oximes **31** and **32** or the presence of an α,β-unsaturated system, resembling that of the digitalis lactone, in compounds **39** and **40** were singled out as characteristics productive of good affinity. The introduction of an α-methyl in the unsaturated oxime to stabilize the E configuration, compounds **41** and **42**, afforded a slightly lower affinity, perhaps due to some steric hindrance in the interaction with the receptor.

Scheme 10[a]
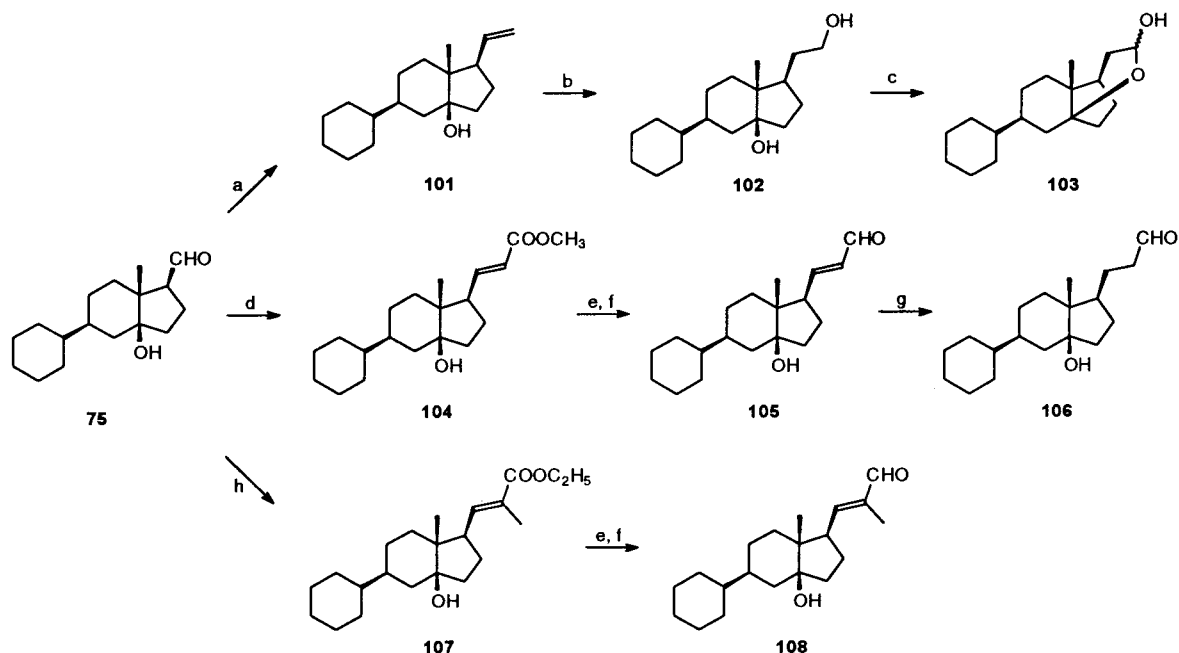
[a] Reagents and conditions: (a) $CH_3P(C_6H_5)_3Br$, t-BuOH, t-BuOK, THF; (b) 1 M BH_3, THF, H_2O, $NaBO_3$, 4 N NaOH; (c) IBX, DMSO; (d) 55% NaH, $(CH_3O)_2P(O)CH_2CO_2CH_3$, THF; (e) 1 M DIBAH, THF, from −78 °C to room temperature; (f) MnO_2, dioxane; (g) 5% Pd/C, H_2, EtOH, (h) 55% NaH, $(C_2H_5O)_2P(O)CH(CH_3)CO_2C_2H_5$, THF.

Scheme 11[a]
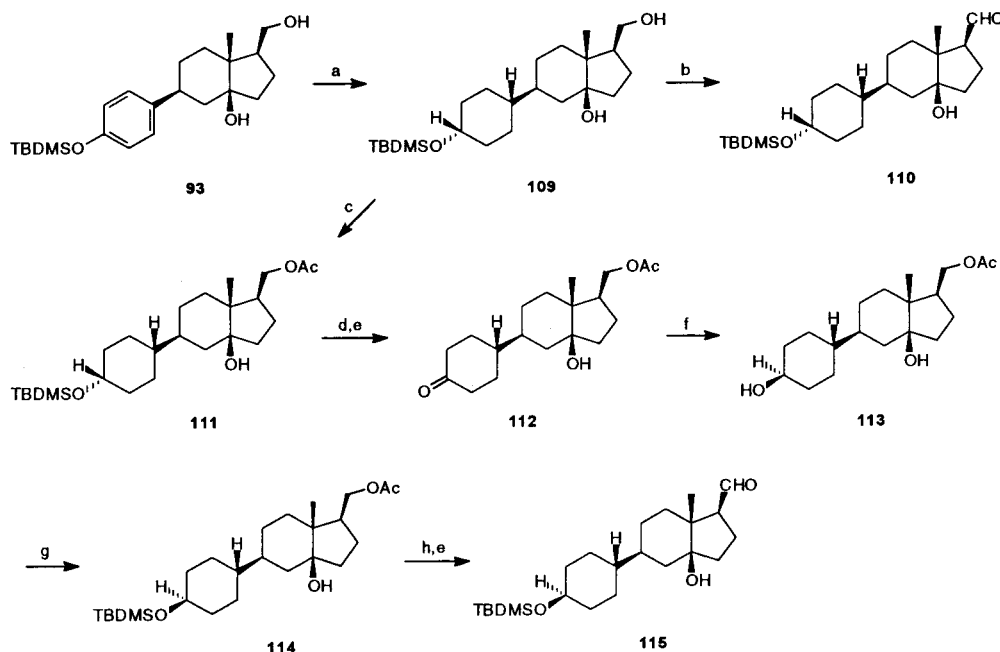
[a] Reagents and conditions: (a) H_2, 5% Rh/Al_2O_3, MeOH, 4.3 atm; (b) IBX, DMSO; (c) DMAP, Ac_2O, Py; (d) 3 N HCl, H_2O, dioxane, pH 1; (e) IBX, THF, reflux; (f) $LiAlH(OtBut)_3$, THF, from -78 °C to room temperature; (g) TBDMSCl, imidazole, DMF; (h) 10% K_2CO_3, MeOH.

Table 2. Inotropic Activity on Electrically Driven Guinea Pig Left Atrium

compd	E_{max},[a] % increase from basal force	concn to obtain E_{max}, μM	EC_{50},[b] μM
28	70	100	12
39	50	100	20
40	90	100	15
116	39	3	nd
117	191	0.3	0.057
118	155	0.3	0.05
digitoxigenin	200	3	0.57
digoxin	184	1	0.38

[a] Maximal increase in force of contraction. [b] Concentrations producing 50% of the maximal increase in force of contraction were calculated from concentration−response curves; nd: not determined.

Homologous oximes **35** and **36** showed a slight decrease in affinity; further elongation, as in **37** and **38**, gave a further small decrease. Again, for the most active of these simple oximes the distance between the skeleton and the amine seems to be 7 bonds.

Reduction of the oxime function to the hydroxylamines **13** and **14** yielded a 3/5-fold decrease of affinity.

As far as the basic center is concerned, primary amines showed slightly higher affinities in comparison with the tertiary amines. A very high decrease in affinity could be revealed for guanylhydrazones **12**, **34**, **43**, and **44**, since they showed 16/80-fold lower affinities than the corresponding oximes.

In general in this perhydroindene series we have found the same structure−activity relationships for the substituent in position 1β seen for the substituents in 17β in the digitalis skeleton[16] but with much more marked differences among the same groups in the latter case.

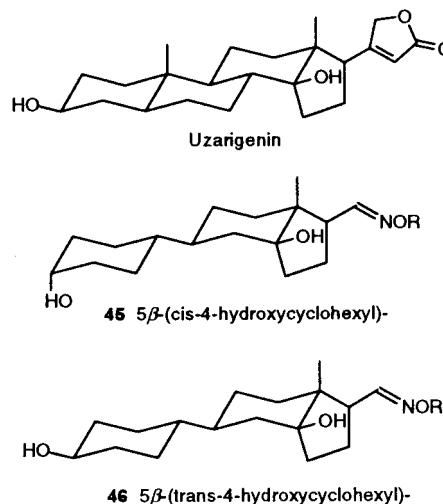A tentative explanation may be that the strong hydrophobic interaction with the receptor is so tight for the rigid and peculiarly shaped $5\beta,14\beta$-androstane

Figure 2. Conformations of uzarigenin and epimeric 5β-(4-hydroxycyclohexyl)perhydroindene derivatives.

skeleton that any variation in the 17β-substituent requires a rearrangment of the oxime chain in order to allow the ionic coupling between the amonium group and the anionic counterpart in the receptor to take place. This may result in more pronounced differences among the corresponding apparent binding energies. In the case of perhydroindene derivatives, the opposite behavior may occur. The best fitting energy could be the result of a compromise between an optimized ionic interaction of the oxime chain and the less stringent hydrophobic bond of the more flexible 5-substituted perhydroindene skeleton, which has more adaptive characteristics. As a result, energy differences in this series are minimized.

Inotropic Activity. Compounds **28**, **39**, and **40** were tested up to their maximum solubility. All showed low positive inotropic effects when compared to the stand-

ards, when considering the concentration producing their maximum effects, suggesting that a higher binding affinity might be requested to produce inotropic activity on the isolated atria. However, the different distribution and biochemical characteristics of the Na^+,K^+-ATPase isoforms in different tissues and species should be considered. In fact, the binding affinity was measured on isolated and purified Na^+,K^+-ATPase from dog kidney, which contains the α1 isoform, whereas the inotropic activity was measured on the whole guinea pig atria, which contains both α1, α2, and α3 isoforms. Besides, it must be reminded that the sensitivity of the Na^+,K^+-ATPase for cardiac glycosides is isoform- and species-dependent (the affinity of the glycosides is higher for the α3 than for the α1 and α2 isoforms, and the canine Na^+,K^+-ATPase is more sensitive than the rat and the guinea pig enzymes). Therefore it cannot be excluded that this series of compounds may differently interact with the Na^+,K^+-ATPase isoforms (α1 and α3).

Conclusions

Some perhydroindenic 1β-aminoalkyloximes presented in this paper showed good binding affinity to Na^+,K^+-ATPase. The most active compounds revealed IC_{50} values in the micromolar range. These compounds were substituted in position 5β with a cyclohexyl group and in position 1β with the same aminoalkyloxime groups already reported with a digitoxigenin-like skeleton.[16] The 5β-cyclohexylperhydroindene derivatives showed a conformation best fitting to that of uzarigenin but the binding affinities of the most active compounds were 4/8-fold lower. This could mean that a strong interaction of the basic amine with the anionic site of the receptor is not sufficient to overcome the reduction in affinity of the perhydroindene skeleton vs a steroidal one, capable of binding to the receptor through van der Waals interactions.

Such a reduction in binding affinities could be the reason some compounds, chosen among those with the highest affinities within this series, showed low positive inotropic effects in the guinea pig left atrium.

Experimental Section

Chemistry. Elemental analyses were performed by Redox, Cologno Monzese, Italy. ^1H NMR spectra were recorded on a Bruker AC-300 spectrometer at 300.13 MHz (^1H NMR) or at 75.48 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane as internal standard and coupling constants (*J* values) are in hertz. NMR assignments were drawn from classical arguments on chemical shift and coupling constant behavior. Mass spectral data were obtained with electron impact ionization technique at 70 eV from a Finnigan INCOS-50 mass spectrometer using the direct exposure probe (DEP). Chromatographies were carried out on silica gel (Baker 7024−02) in all instances. Solvents and reagents were used as purchased from suppliers.

Intermediate hydroxylamines were prepared as previously described.[16]

Preparation of Oximes. Method A. A solution of NaOAc (4 equiv) and the appropriate hydroxylamine (1.05 equiv) in dioxane/water 3:2 (0.1 M) was adjusted to pH 4.5 with 3 N HCl. A solution of the appropriate aldehyde (1 equiv) in dioxane/water 2:1 (0.2 M) was added dropwise at room temperature. After 1 h for compounds **2−11**, **15−33**, **37**, **38**, **45**, and **46**, or 4 h for compound **35**, or 16 h for compound **36**, dioxane was evaporated in vacuo. The residue was diluted with

water and 1 N NaOH added until pH 9.5 was reached. The mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography and, finally, transformed into the salt by adding the stoichiometric amount of the corresponding acid.

Preparation of Oximes. Method B. To a solution of the appropriate hydroxylamine (1.2 equiv) in 1 N NaOH/dioxane 5:2 (1.7 M) was added dropwise a solution of the appropriate aldehyde (1 equiv) in dioxane (0.5 M) at room temperature. After 3 h for compounds **39** and **40** or 2 days for compounds **41** and **42**, the solution was diluted with water and extracted three times with $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography and, finally, transformed into the salt by adding the stoichiometric amount of the corresponding acid.

Preparation of Hydroxylamines. Method C. A solution of crude oxime as a base (1 equiv) in MeOH (0.2 M) was adjusted to pH 3.0 with 1 N HCl under stirring at room temperature. $NaBH_3CN$ (1.5 equiv) was added, followed by water (0.1 mL/equiv). The reaction was continuously kept at pH 3 by a pH-stat controlling the addition of 1 N HCl. After 6 h, $NaBH_3CN$ (0.75 equiv) was added followed by water (0.1 mL/equiv). Additions of $NaBH_3CN$ (0.4 equiv) and water (0.1 mL/equiv) were repeated after 24 and 30 h. After 48 h the solution was brought to pH 1.8 with 1 N HCl. After being stirred for 1 h, the solution was brought to pH 9.5 with 4 N NaOH, and methanol was evaporated in vacuo. The mixture was diluted with water and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography and, finally, transformed into the salt by adding the stoichiometric amount of the corresponding acid.

Preparation of Guanylhydrazones. Method D. A suspension of aminoguanidine hydrogencarbonate (1.2 equiv) in dioxane/water 3:2 was brought to pH 4.5 for compounds **12** and **34** and to pH 3 for **43** and **44** with 1 N HCl. A solution of appropriate aldehyde (1 equiv) in dioxane/water 2:1 was added dropwise at room temperature. After 16 h for compounds **12** and **34** or 6 days for compounds **43** and **44**, the mixture was evaporated to dryness and the crude product purified by flash chromatography.

Preparation of Oximes. Method E. A solution of the appropriate aldehyde in dioxane/water 3:2 was adjusted to pH 1 with 3 N HCl. After 2 h for compounds **84**, **85**, **110**, and **115** or 16 h for compounds **96** and **97**, a solution of NaOAc (4 equiv) and the appropriate hydroxylamine (1.5 equiv) in dioxane/water 3:2, previously adjusted to pH 4.5 with 6 N HCl, was added dropwise. After 0.5 h dioxane was evaporated in vacuo. The residue was diluted with water and 1 N NaOH added until pH 9.5 was reached. The mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography and, finally, transformed into the salt by adding the stoichiometric amount of the corresponding acid.

(1*S*,3a*S*,7a*R*)-1-[3-Aminopropoxy-(*E*)-iminomethyl]-7a-methylperhydroinden-3a-ol Oxalate (2). Prepared following method A starting from **56**. The crude product was purified by chromatography in $CHCl_3$/MeOH/26% w/v aqueous NH_3 (9:1:0.1) followed by salt formation with the stoichiometric amount of oxalic acid in EtOH. After evaporation in vacuo of the resulting solution, the residue was triturated with EtOAc to give a white solid (0.26 g, 47%), mp 128−155 °C. ^1H NMR (DMSO-d_6) δ 0.78 (s, 2.55H, CH_3 (*E*) isomer), 0.84 (s, 0.45H, CH_3 (*Z*) isomer), 2.48 (m, 1H, C*H*CH=N), 2.87 (t, 2H, CH_2N), 3.94 (t, 2H, CH_2O), 6.71 (d, 0.15H, *J* = 7.9, CH=N (*Z*) isomer), 7.40 (d, 0.85H, *J* = 8.5, CH=N (*E*) isomer). MS *m/z* 237 (2), 164 (100).

(1*S*,3a*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-[(*E*)-benzyliden]-7a-methylperhydroinden-3a-ol (3). Prepared following method A starting from **59**. The crude product on chromatography with $CHCl_3$/MeOH/26% w/v aqueous NH_3 (9:1:0.1) followed by trituration with *i*-Pr_2O gave a

white solid (0.26 g, 90%), mp 113−116 °C. ^{1}H NMR (CDCl[3]) δ 0.97 (s, 3H, CH[3]), 2.30 (s, 6H, N(CH[3])[2]), 2.58 (t, 2H, CH[2]N), 2.74 (m, 1H, C*H*CH=N), 4.12 (t, 2H, CH[2]O), 6.30 (s, 1H, CHPh), 7.19−7.35 (m, 5H, Ph), 7.54 (d, 1H, J = 8.6, CH=N). MS *m/z* 356 (7, M[+]), 58 (100).

(1*S*,3a*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-[(*Z*)-benzyliden-7a-methylperhydroinden-3a-ol (4). Prepared following method A starting from **60**. The crude product on chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by trituration with *i*-Pr[2]O gave a white solid. (0.15 g, 47%), mp 110−112 °C. ^{1}H NMR (CDCl[3]) δ 0.99 (s, 3H, CH[3]), 2.29 (s, 6H, N(CH[3])[2]), 2.58 (t, 2H, CH[2]N), 2.70 (m, 1H, C*H*CH=N), 4.13 (t, 2H, CH[2]O), 6.41 (s, 1H, CHPh), 7.19−7.34 (m, 5H, Ph), 7.55 (d, 1H, J = 8.6, CH=N). MS *m/z* 356 (9, M[+]), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-benzyl-7a-methylperhydroinden-3a-ol oxalate (5). Prepared following method A starting from **64**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. After evaporation in vacuo of the resulting solution, the residue was triturated with EtOAc to give **5** as white solid (0.23 g, 45%), mp 152−178 °C.^{1}H NMR (CD[3]OD) δ 0.81 (s, 3H, CH[3]), 2.48 (d, 2H, CH[2]Ph), 2.97 (s, 6H, N(CH[3])[2]), 3.44 (m, 2H, CH[2]N), 4.32 (m, 2H, CH[2]O), 7.10−7.30 (m, 5H, Ph), 7.43 (d, 1H, J = 7.5, CH=N). MS *m/z* 358 (6, M[+] base), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (6). Prepared following method A starting from **68**. The crude product on chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by trituration with *n*-hexane gave a white solid (0.081 g, 31%), mp 79−85 °C. ^{1}H NMR (CD[3]OD) δ 0.83 (s, 3H, CH[3]), 2.26 (s, 6H, N(CH[3])[2]), 2.58 (t, 2H, CH[2]N), 2.89 (m, 1H, C*H*CH=N), 4.12 (t, 2H, CH[2]O), 7.34 (d, 1H, J = 7.5, CH=N). MS *m/z* 364 (1, M[+]), 58 (100).

(1*S*,3a*S*,5*R*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-benzyl-7a-methylperhydroinden-3a-ol (7). Prepared following method A starting from **63**. The crude product on chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by trituration with Et[2]O gave a white solid (0.10 g, 42%), mp 122−128 °C. ^{1}H NMR (DMSO-*d*[6]) δ 0.76 (s, 3H, CH[3]), 2.00 (m, 2H, CH[2]Ph), 2.12 (s, 6H, N(CH[3])[2]), 2.25 (m, 1H, C*H*CH=N), 2.40 (t, 2H, CH[2]N), 3.92 (t, 2H, CH[2]O), 4.19 (s, OH), 7.12−7.27 (m, 5H, Ph), 7.40 (d, 1H, J = 9.4, CH=N). MS *m/z* 358 (20, M[+]), 58 (100).

(1*S*,3a*S*,5*R*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (8). Prepared following method A starting from **66**. The crude product on chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (9:1:0.1) followed by trituration with *i*-Pr[2]O gave a white solid (0.065 g, 28%), mp 100−106 °C. ^{1}H NMR (CD[3]OD) δ 0.87 (s, 3H, CH[3]), 2.29 (s, 6H, N(CH[3])[2]), 2.42 (m, 1H, C*H*CH=N), 2.61 (t, 2H, CH[2]N), 4.08 (t, 2H, CH[2]O), 7.54 (d, 1H, J = 9.3, CH=N). MS *m/z* 364 (7, M[+]), 58 (100).

(1*S*,3a*S*,5*R*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-phenyl-7a-methylperhydroinden-3a-ol oxalate (9). Prepared following method A starting from **71**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (97:3:0.3). The purified product (0.40 g) was dissolved in EtOAc, and the stoichiometric amount of oxalic acid was added. After evaporation in vacuo, the residue was triturated with EtOH/Et[2]O to give **9** (0.13 g, 37%), white solid, mp 132−135 °C. ^{1}H NMR (DMSO-*d*[6]) δ 0.78 (s, 3H, CH[3]), 2.71 (s, 6H, N(CH[3])[2]), 2.81 (m, 1H, $W_{1/2h}$ = 25 Hz, CHPh), 2.95 (m, 1H, C*H*CH=N), 3.21 (t, 2H, CH[2]N), 4.24 (t, 2H, CH[2]O), 7.20 (m, 5H, Ph), 7.43 (d, 1H, J = 7.3, CH=N). ^{13}C NMR (DMSO-*d*[6]) δ 18.5 (q), 21.5 (t), 28.5 (t), 30.8 (t), 36.7 (t), 38.4 (d), 40.2 (d), 43.0 (t), 43.1 (q), 43.1 (q), 45.2 (s), 55.4 (t), 67.6 (t), 78.3 (s), 125.7 (d), 126.7 (d), 126.7 (d), 128.2 (d), 128.2 (d), 146.9 (s), 154.4 (d), 164.2 (s), 164.2 (s). MS *m/z* 344 (7, M[+] base), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-phenyl-7a-methylperhydroinden-3a-ol oxalate

(10). Prepared following method A starting from **73**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (9:5:0.5). The purified product (0.4 g) was dissolved in EtOH, and the stoichiometric amount of oxalic acid was added. After evaporation in vacuo, the residue was triturated with Et[2]O to give **10** as a white solid (0.25 g, 44%), mp 112−116 °C. ^{1}H NMR (DMSO-*d*[6]) δ 0.90 (s, 3H, CH[3]), 2.30 (m, 1H, C*H*CH=N), 2.70 (m, 1H, $W_{1/2h}$ = 25 Hz, CHPh), 2.70 (s, 6H, N(CH[3])[2]), 3.21 (t, 2H, CH[2]N), 4.20 (t, 2H, CH[2]O), 7.20 (m, 5H, Ph), 7.57 (d, 1H, J = 9.1, CH=N). ^{13}C NMR (DMSO-*d*[6]) δ 15.7 (q), 24.9 (t), 29.0 (t), 35.3 (t), 37.7 (t), 40.6 (t), 40.7 (d), 43.1 (q), 43.1 (q), 47.4 (s), 49.6 (d), 55.4 (t), 67.4 (t), 80.9 (s), 125.9 (d), 126.7 (d), 126.7 (d), 128.3 (d), 128.3 (d), 146.1 (s), 157.9 (d), 164.2 (s). MS *m/z* 344 (18, M[+] base), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Aminoethoxy-(*E*)-iminomethyl]-5-phenyl-7a-methylperhydroinden-3a-ol (11). Prepared following method A starting from **73**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (9:1:0.1) followed by trituration with Et[2]O to give a white solid, (0.11 g, 11%), mp 92−95 °C. ^{1}H NMR (CD[3]OD) δ 1.01 (s, 3H, CH[3]), 2.42 (m, 1H, C*H*CH=N), 2.76 (m, 1H, CHPh), 2.85 (t, 2H, CH[2]N), 4.00 (t, 2H, CH[2]O), 7.12−7.32 (m, 5H, Ph), 7.62 (d, 1H, J = 9.1, CH=N).

(1*S*,3a*S*,5*S*,7a*R*)-1-(*E*)-Guanidinoiminomethyl-5-phenyl-7a-methylperhydroinden-3a-ol hydrochloride (12). Prepared following method D starting from **73**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (8:2:0.3) followed by trituration with EtOAc to give a white solid, (0.09 g, 25%), mp 231−232 °C. ^{1}H NMR (DMSO-*d*[6]) δ 0.91 (s, 3H, CH[3]), 2.55 (dt, 1H, C*H*CH=N), 2.70 (m, 1H, CHPh), 4.48 (s, OH), 7.14−7.30 (m, 5H, Ph), 7.40 (bb, 4H, guanidine), 7.61 (d, 1H, J = 8.4, CH=N), 11.5 (bb, 1H, guanidine). MS *m/z* 314 (6, M[+] base), 296 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-(2-Dimethylaminoethoxyaminomethyl)-5-phenyl-7a-methylperhydroinden-3a-ol oxalate (13). Prepared following method C starting from **10**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (9:1:0.1). The purified product (0.085 g) was dissolved in EtOAc, and the stoichiometric amount of oxalic acid was added. After evaporation in vacuo, the residue was crystallized from EtOAc/EtOH to give a white solid (0.039 g, 20%), mp 115−130 °C. ^{1}H NMR (CD[3]OD) δ 1.08 (s, 3H, CH[3]), 2.72 (m, 1H, CHPh), 2.93 (s, 6H, N(CH[3])[2]), 2.90−3.25 (m, 2H, CH[2]NO), 3.38 (t, 2H, CH[2]N), 3.98 (t, 2H, CH[2]O), 7.13−7.30 (m, 5H, Ph).

(1*S*,3a*S*,5*S*,7a*R*)-1-(2-Aminoethoxyaminomethyl)-5-phenyl-7a-methylperhydroinden-3a-ol Oxalate (14). Prepared following method C starting from **11**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc/EtOH. After evaporation in vacuo of the resulting solution, the residue was triturated with EtOAc to give a white solid (0.10 g, 13%), mp from 148 °C dec. ^{1}H NMR (DMSO-*d*[6]) δ 1.00 (s, 3H, CH[3]), 2.70 (m, 1H, CHPh), 3.12 (t, 2H, CH[2]N), 3.35 (d, 2H, CH[2]NO), 4.24 (t, 2H, CH[2]O), 7.10−7.30 (m, 5H, Ph), 8.0 (bb, 3H, NH[3][+]). MS *m/z* 240 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-(3-methylphenyl)-7a-methylperhydroinden-3a-ol (15). Prepared following method A starting from **82**. The crude product on chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (95:5:0.5) followed by trituration with *i*-Pr[2]O gave a white solid (0.17 g, 47%), mp 148−152 °C. ^{1}H NMR (CD[3]OD) δ 0.99 (s, 3H, CH[3]), 2.29 (s, 6H, N(CH[3])[2]), 2.30 (s, 3H, CH[3]Ph), 2.40 (dt, 1H, C*H*CH=N), 2.62 (t, 2H, CH[2]N), 2.70 (m, 1H, CHPh), 4.10 (t, 2H, CH[2]O), 6.96−7.17 (m, 4H, Ph), 7.57 (d, 1H, J = 9.3, CH=N). MS *m/z* 358 (6, M[+]), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Aminoethoxy-(*E*)-iminomethyl]-5-(3-methylphenyl)-7a-methylperhydroinden-3a-ol oxalate (16). Prepared following method A starting from **82**. The crude product was purified by chromatography with CHCl[3]/MeOH/26% w/v aqueous NH[3] (97:3:0.3) followed by salt formation with the stoichiometric amount of oxalic acid in Et[2]O. The suspension was filtered to give a white solid (0.17 g, 45%), mp

143−148 °C dec. ¹H NMR (CD₃OD) δ 1.00 (s, 3H, CH₃), 2.30 (s, 3H, CH₃Ph), 2.40 (m, 1H, C*H*CH=N), 2.70 (m, 1H, CHPh), 3.20 (t, 2H, CH₂N), 4.20 (t, 2H, CH₂O), 6.95−7.20 (m, 4H, Ph), 7.67 (d, 1H, *J* = 9.3, CH=N). MS *m/z* 330 (6, M⁺ base), 270 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(4-methylphenyl)-7a-methylperhydroinden-3a-ol (17). Prepared following method A starting from **83**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) followed by trituration with Et₂O gave a white solid (0.24 g, 49%), mp 161−166 °C. ¹H NMR (CDCl₃) δ 1.04 (s, 3H, CH₃), 2.29 (s, 6H, N(CH₃)₂), 2.33 (s, 3H, CH₃Ph), 2.50 (dt, 1H, C*H*CH=N), 2.59 (t, 2H, CH₂N), 2.71 (m, 1H, CHPh), 4.13 (t, 2H, CH₂O), 7.13 (m, 4H, Ph), 7.66 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 358 (4, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Aminoethoxy-(*E*)-iminomethyl]-5-(4-methylphenyl)-7a-methylperhydroinden-3a-ol oxalate (18). Prepared following method A starting from **83**. The crude product was purified by chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. Evaporation in vacuo of the resulting solution gave a white solid (0.25 g, 41%), mp 158−161 °C. ¹H NMR (CD₃OD) δ 1.00 (s, 3H, CH₃), 2.28 (s, 3H, CH₃Ph), 2.45 (dt, 1H, C*H*CH=N), 2.69 (m, 1H, CHPh), 3.20 (m, 2H, CH₂N), 4.17 (t, 2H, CH₂O), 7.11 (m, 4H, Ph), 7.66 (d, 1H, *J* = 9.3, CH=N). MS *m/z* 330 (2, M⁺ base), 270 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(3-hydroxyphenyl)-7a-methylperhydroinden-3a-ol (19). Prepared following method E starting from **96**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) followed by trituration with Et₂O gave a white solid (0.26 g, 36%), mp 142−146 °C. ¹H NMR (CDCl₃) δ 0.95 (s, 3H, CH₃), 2.32 (s, 6H, N(CH₃)₂), 2.45 (dt, 1H, C*H*CH=N), 2.65 (t, 2H, CH₂N), 2.67 (m, 1H, CHPh), 4.15 (t, 2H, CH₂O), 6.65−6.72 (m, 3H, Ph), 7.13 (t, 1H, Ph), 7.57 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 360 (6, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(4-hydroxyphenyl)-7a-methylperhydroinden-3a-ol (20). Prepared following method E starting from **97**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with Et₂O gave a white solid (0.099 g, 16%), mp 211−214 °C. ¹H NMR (DMSO-*d₆*) δ 0.85 (s, 3H, CH₃), 2.12 (s, 6H, N(CH₃)₂), 2.28 (m, 1H, C*H*CH=N), 2.43 (t, 2H, CH₂N), 2.55 (m, 1H, CHPh), 3.95 (t, 2H, CH₂O), 4.30 (s, 1H, OH), 6.65 (d, 2H, Ph), 7.01 (d, 2H, Ph), 7.47 (d, 1H, *J* = 9.3, CH=N), 9.13 (s, 1H, PhOH). MS *m/z* 360 (2, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(3-hydroxymethylphenyl)-7a-methylperhydro-inden-3a-ol (21). Prepared following method E starting from **84**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with Et₂O gave a white solid (0.12 g, 48%), mp 160−164 °C. ¹H NMR (DMSO-*d₆*) δ 0.88 (s, 3H, CH₃), 2.16 (s, 6H, N(CH₃)₂), 2.30 (dt, 1H, C*H*CH=N), 2.45 (t, 2H, CH₂N), 2.69 (m, 1H, CHPh), 3.95 (t, 2H, CH₂O), 4.35 (s, 1H, OH), 4.45 (d, 2H, C*H₂*OH), 5.12 (t, *H*OCH₂), 7.06−7.28 (m, 4H, Ph), 7.48 (d, 1H, *J* = 9.4, CH=N). MS *m/z* 374 (5, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Aminoethoxy-(*E*)-iminomethyl]-5-(3-hydroxymethylphenyl)-7a-methylperhydroinden-3a-ol oxalate (22). Prepared following method E starting from **84**. The crude product was purified by chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by salt formation with the stoichiometric amount of oxalic acid in EtOH. After evaporation in vacuo of the resulting solution, the residue was triturated with *i*-Pr₂O to give a white solid (0.04 g, 16%), mp 140−142 °C. ¹H NMR (CD₃OD) δ 1.02 (s, 3H, CH₃), 2.45 (m, 1H, C*H*CH=N), 3.21 (t, 2H, CH₂N), 4.17 (t, 2H, CH₂O), 4.58 (s, 2H, C*H₂*OH), 7.13−7.28 (m, 4H, Ph), 7.67 (d, 1H, *J* = 9.3, CH=N). MS *m/z* 346 (5, M⁺ base), 286 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(4-hydroxymethylphenyl)-7a-methylperhydro-

inden-3a-ol (23). Prepared following method E starting from **85**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) followed by crystallization from EtOAc/EtOH gave a white solid (0.20 g, 38%), mp 179−181 °C. ¹H NMR (CDCl₃) δ 1.03 (s, 3H, CH₃), 2.28 (s, 6H, N(CH₃)₂), 2.52 (dt, 1H, C*H*CH=N), 2.58 (t, 2H, CH₂N), 2.73 (m, 1H, CHPh), 4.12 (t, 2H, CH₂O), 4.67 (s, 2H, C*H₂*OH), 7.21−7.33 (m, 4H, Ph), 7.64 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 374 (3, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Aminoethoxy-(*E*)-iminomethyl]-5-(4-hydroxymethylphenyl)-7a-methylperhydroinden-3a-ol (24). Prepared following method E starting from **85**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with Et₂O/EtOAc gave a white solid (0.20 g, 41%), mp 131−134 °C. ¹H NMR (CDCl₃) δ 1.02 (s, 3H, CH₃), 2.50 (dt, 1H, C*H*CH=N), 2.74 (m, 1H, CHPh), 2.93 (t, 2H, CH₂N), 4.04 (t, 2H, CH₂O), 4.67 (s, 2H, C*H₂*OH), 7.20−7.32 (m, 4H, Ph), 7.63 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 346 (9, M⁺), 286 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-[4-(2-dimethylaminoethoxy)phenyl]-7a-methyl-perhydroinden-3a-ol (25). Prepared following method A starting from **100**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with *i*-Pr₂O/EtOAc gave a white solid (0.08 g, 46%), mp 126−128 °C. ¹H NMR (CDCl₃) δ 1.03 (s, 3H, CH₃), 2.29 (s, 6H, N(CH₃)₂), 2.33 (s, 6H, N(CH₃)₂), 2.50 (dt, 1H, C*H*CH=N), 2.59 (t, 2H, CH₂N), 2.72 (t, 2H, CH₂N), 4.05 (t, 2H, CH₂O), 4.12 (t, 2H, CH₂O), 6.87 (d, 2H, Ph), 7.14 (d, 2H, Ph), 7.64 (s, 1H, *J* = 9.1, CH=N). MS *m/z* 431 (17, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(3-pyridyl)-7a-methylperhydroinden-3a-ol (26). Prepared following method A starting from **94**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (97:3:0.3) followed by trituration with Et₂O gave a white solid (0.09 g, 38%), mp 114−124 °C. ¹H NMR (CDCl₃) δ 1.07 (s, 3H, CH₃), 2.31 (s, 6H, N(CH₃)₂), 2.54 (dt, 1H, C*H*CH=N), 2.60 (t, 2H, CH₂N), 2.77 (m, 1H, CHPy), 4.15 (t, 2H, CH₂O), 7.25 (m, 1H, Py), 7.56 (m, 1H, Py), 7.68 (s, 1H, *J* = 9.1, CH=N), 8.48 (m, 2H, Py). MS *m/z* 345 (9, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-(4-pyridyl)-7a-methylperhydroinden-3a-ol (27). Prepared following method A starting from **95**. The crude product was purified by chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) and triturated with *i*-Pr₂O. The residue was dissolved with EtOAc and filtered through a basic aluminum oxide pad, followed by trituration with *n*-hexane to give a white solid (0.007 g, 20%), mp 131−136 °C. ¹H NMR (CDCl₃) δ 1.04 (s, 3H, CH₃), 2.31 (s, 6H, N(CH₃)₂), 2.54 (dt, 1H, C*H*CH=N), 2.61 (t, 2H, CH₂N), 2.69 (m, 1H, CHPy), 4.14 (t, 2H, CH₂O), 7.15 (m, 2H, Py), 7.64 (s, 1H, *J* = 9.1, CH=N), 8.52 (m, 2H, Py). MS *m/z* 345 (1, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-imino-methyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol (28). Prepared following method A starting from **75**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with Et₂O gave a white solid (0.10 g, 15%), mp 109−120 °C. ¹H NMR (CD₃OD) δ 0.87 (s, 3H, CH₃), 2.28 (s, 6H, N(CH₃)₂), 2.35 (dt, 1H, C*H*CH=N), 2.61 (t, 2H, CH₂N), 4.08 (t, 2H, CH₂O), 7.54 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 350 (4, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[3-Dimethylaminopropoxy-(*E*)-imi-nomethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (29). Prepared following method A starting from **75**. The crude product was purified by chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (95:5:0.5) followed by trituration with *i*-Pr₂O. The purified product as a base was dissolved in EtOAc, and the stoichiometric amount of oxalic acid was added. The suspension was filtered to give a white solid (0.26 g, 44%), mp 140−149 °C. ¹H NMR (CD₃OD) δ 0.87 (s, 3H, CH₃), 2.35 (dt, 1H, C*H*CH=N), 2.87 (s, 6H, N(CH₃)₂), 3.20 (m, 2H, CH₂N), 4.05 (t, 2H, CH₂O), 7.55 (d, 1H, *J* = 9.1, CH=N). MS *m/z* 365 (2, M+1 base), 246 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[4-Dimethylaminobutoxy-(***E***)-imi-nomethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol (30).** Prepared following method A starting from **75**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) gave a white solid (0.35 g, 69%), mp 58−63 °C. ^{1}H NMR (CD$_3$OD) δ 0.90 (s, 3H, CH$_3$), 2.22 (s, 6H, N(CH$_3$)$_2$), 2.28 (m, 2H, CH$_2$N), 2.43 (dt, 1H, C*H*CH=N), 4.00 (t, 2H, CH$_2$O), 7.56 (d, 1H, J = 9.1, CH=N). MS *m/z* 379 (1, M+1), 116 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[2-Aminoethoxy-(***E***)-iminomethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (31).** Prepared following method A starting from **75**. The crude product was purified by chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (9:1:0.1) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. Evaporation in vacuo of the resulting solution gave a white solid (0.10 g, 32%), mp 162−165 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 0.76 (s, 3H, CH$_3$), 2.25 (dt, 1H, C*H*CH=N), 2.94 (t, 2H, CH$_2$N), 4.00 (t, 2H, CH$_2$O), 7.54 (d, 1H, J = 9.1, CH=N). MS *m/z* 322 (2, M$^+$ base), 262 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[3-Aminopropoxy-(***E***)-iminomethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol (32).** Prepared following method A starting from **75**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.20 g, 45%), mp 71−93 °C. ^{1}H NMR (CDCl$_3$) δ 0.90 (s, 3H, CH$_3$), 2.42 (dt, 1H, C*H*CH=N), 2.80 (t, 2H, CH$_2$N), 4.08 (t, 2H, CH$_2$O), 7.57 (d, 1H, J = 9.1, CH=N). MS *m/z* 337 (2, M+1), 246 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[4-Aminobutoxy-(***E***)-iminomethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (33).** Prepared following method A starting from **75**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (9:1:0.1) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.23 g, 35%), mp 110−132 °C dec. ^{1}H NMR (CDCl$_3$) δ 0.86 (s, 2.7H, CH$_3$ (*E*) isomer), 0.95 (s, 0.3H, CH$_3$ (*Z*) isomer), 2.34 (dt, 1H, C*H*CH=N), 2.95 (t, 2H, CH$_2$N), 4.00 (t, 2H, CH$_2$O), 6.83 (d, 0.1H, J = 8.4, CH=N (*Z*) isomer), 7.53 (d, 0.9H, J = 9.6, CH=N (*E*) isomer). MS *m/z* 350 (6, M$^+$ base), 88 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-(***E***)-Guanidinoiminomethyl-5-cyclo-hexyl-7a-methylperhydroinden-3a-ol (34).** Prepared following method D starting from **75**. The crude product on chromatography in CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (80:20:3) followed by trituration with EtOAc gave a white solid (0.07 g, 29%), mp 150−160 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 0.74 (s, 3H, CH$_3$), 2.30 (m, 1H, C*H*CH=N), 4.04 (s, 1H, OH), 5.70 (bb, 4H, guanidine), 7.42 (d, 1H, J = 8.4, CH=N). MS *m/z* 320 (18, M$^+$), 302 (100).

(1*R*,3a*S*,5*S*,7a*R***)-1-[2-Dimethylaminoethoxy-(E,Z)-imi-noethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Ox-alate (35).** Prepared following method A starting from **103**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.07 g, 10%), mp 105−121 °C. ^{1}H NMR (CD$_3$OD) δ 0.93 (s, 1.5H, CH$_3$), 0.94 (s, 1.5H, CH$_3$), 2.92 (s, 3H, N(CH$_3$)$_2$), 2.93 (s, 3H, N(CH$_3$)$_2$), 3.40−3.50 (m, 2H, CH$_2$N), 4.30 (m, 1H, CH$_2$O), 4.36 (m, 1H, CH$_2$O), 6.80 (0.5H, t, CH=N (*Z*) isomer), 7.45 (0.5H, dd, CH=N (*E*) isomer).

(1*R*,3a*S*,5*S*,7a*R***)-1-[2-Aminoethoxy-(E,Z)-iminoethyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (36).** Prepared following method A starting from **103**. The crude product was purified by chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. After evaporation in vacuo of the resulting solution, the residue was triturated with Et$_2$O to give a white solid (0.03 g, 64%), mp 154−159 °C. ^{1}H NMR (CD$_3$OD) δ 0.95 (s, 3H, CH$_3$), 3.20 (m, 2H, CH$_2$N), 4.18 (m, 1.5H, CH$_2$O (*E*) isomer), 4.23 (m, 0.5H, CH$_2$O (*Z*) isomer), 6.76 (0.25H, t, CH=N (*Z*) isomer), 7.45 (0.75H, dd, CH=N (*E*) isomer). MS *m/z* 336 (1, M$^+$ base), 55 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[2-Dimethylaminoethoxy-(***E,Z***)-imi-nopropyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (37).** Prepared following method A starting from **106**. The crude product was purified by chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. After evaporation in vacuo of the resulting solution, the residue was triturated with *i*-Pr$_2$O to give a white solid (0.10 g, 20%), mp 137−139 °C. ^{1}H NMR (CD$_3$OD) δ 0.92 (s, 3H, CH$_3$), 2.92 (s, 6H, N(CH$_3$)$_2$), 3.43 (m, 2H, CH$_2$N), 4.28 (m, 1.6H, CH$_2$O (*E*) isomer), 4.37 (m, 0.4H, CH$_2$O (*Z*) isomer), 6.80 (t, 0.2H, CH=N (*Z*) isomer), 7.50 (t, 0.8H, CH=N (*E*) isomer). MS *m/z* 378 (5, M$^+$ base), 58 (100).

(1*S*,3a*S*,5*S*,7a*R***)-1-[2-Aminoethoxy-(***E,Z***)-iminopropyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Hemiox-alate (38).** Prepared following method A starting from **106**. The crude product was purified by chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (9:1:0.1) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc. After evaporation in vacuo of the resulting solution, the residue was triturated with *i*-Pr$_2$O to give a white solid (0.11 g, 25%), mp 161−163 °C. ^{1}H NMR (CD$_3$OD) δ 0.92 (s, 3H, CH$_3$), 3.20 (m, 2H, CH$_2$N), 4.18 (t, 1.6H, CH$_2$O (*E*) isomer), 4.24 (t, 0.4H, CH$_2$O (*Z*) isomer), 6.77 (t, 0.2H, CH=N (*Z*) isomer), 7.50 (t, 0.8H, CH=N (*E*) isomer). MS *m/z* 350 (2, M$^+$ base), 55 (100).

(1*R*,3a*S*,5*S*,7a*R***)-1-[(***E,E***)-3-(2-Dimethylaminoethoxy-imino)-1-propenyl]-5-cyclohexyl-7a-methylperhydro-inden-3a-ol Oxalate (39).** Prepared following method B starting from **105**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.15 g, 27%), mp 137−144 °C. ^{1}H NMR (DMSO-*d*$_6$) δ 0.72 (s, 3H, CH$_3$), 2.24 (m, 1H, C*H*CH=), 2.68 (s, 6H, N(CH$_3$)$_2$), 3.20 (t, 2H, CH$_2$N), 4.23 (t, 2H, CH$_2$O), 5.85 (dd, 0.9H, J = 9.9, 15.4, C*H*−CH=N (*E*) isomer), 6.33 (dd, 0.9H, J = 10.4, 15.4, C*H*=CH−CH=N (*E*) isomer), 6.40 (m, 0.2H, C*H*=C*H*−CH=N (*Z*) isomer), 7.20 (d, 0.1H, J = 8.9, CH=N (*Z*) isomer), 7.81 (d, 0.9H, J = 9.9, CH=N (*E*) isomer). MS *m/z* 376 (40, M$^+$ base), 95 (100).

(1*R*,3a*S*,5*S*,7a*R***)-1-[(***E,E***)-3-(2-Aminoethoxyimino)-1-propenyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Oxalate (40).** Prepared following method B starting from **105**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.15 g, 28%), 136−140 °C dec. ^{1}H NMR (DMSO-*d*$_6$) δ 0.72 (s, 3H, CH$_3$), 2.24 (m, 1H, C*H*CH=), 3.05 (m, 2H, CH$_2$N), 4.12 (t, 2H, CH$_2$O), 5.84 (dd, 1H, J = 9.9, 15.4, C*H*=CH−CH=N), 6.33 (dd, 1H, J = 10.4, 15.4, CH=C*H*−CH=N), 7.80 (d, 1H, J = 9.9, CH=N), 7.82 (br b, 3H, NH$_3^+$). MS *m/z* 348 (43, M$^+$ base), 95 (100).

(1*R*,3a*S*,5*S*,7a*R***)-1-[(***E,E***)-2-Methyl-3-(2-dimethylamino-ethoxyimino)-1-propenyl]-5-cyclohexyl-7a-methylperhy-droinden-3a-ol Oxalate (41).** Prepared following method B starting from **108**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.21 g, 47%), mp 164−167 °C. ^{1}H NMR (CD$_3$OD) δ 0.82 (s, 3H, CH$_3$), 1.77 (s, 3H, =CCH$_3$), 2.73 (m, 1H, C*H*CH=), 2.92 (s, 6H, N(CH$_3$)$_2$), 3.44 (m, 2H, CH$_2$N), 4.35 (m, 2H, CH$_2$O), 6.04 (d, 1H, CH=C), 7.77 (s, 1H, CH=N). MS *m/z* 390 (21, M$^+$ base), 71 (100).

(1*R*,3a*S*,5*S*,7a*R***)-1-[(***E,E***)-2-Methyl-3-(2-aminoethoxy-imino)-1-propenyl]-5-cyclohexyl-7a-methylperhydro-inden-3a-ol Oxalate (42).** Prepared following method B starting from **108**. The crude product on chromatography with CHCl$_3$/MeOH/26% w/v aqueous NH$_3$ (95:5:0.5) followed by salt formation with the stoichiometric amount of oxalic acid in EtOAc gave a white solid (0.31 g, 74%), mp 164−166 °C. ^{1}H NMR (CD$_3$OD) δ 0.83 (s, 3H, CH$_3$), 1.77 (s, 3H, =CCH$_3$), 2.73 (m, 1H, C*H*CH=), 3.23 (t, 2H, CH$_2$N), 4.24 (t, 2H, CH$_2$O), 6.03 (d, 1H, CH=C), 7.78 (s, 1H, CH=N). MS *m/z* 362 (7, M$^+$ base), 94 (100).

(1*R*,3a*S*,5*S*,7a*R*)-1-[(*E,E*)-3-Guanidinoimino-1-propenyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol (43). Prepared following method D starting from **105**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (85:15:1.5) followed by trituration with *n*-hexane gave a white solid (0.13 g, 36%), mp 95−180 °C dec. ¹H NMR (DMSO-*d*₆) δ 0.72 (s, 3H, CH₃), 2.43 (m, 1H, C*H*CH=), 3.98 (s, 1H, OH), 5.60 (bb, 4H, guanidine), 5.75−6.10 (m, 2H, HC=CH), 7.60 (d, 1H, CH=N). MS *m/z* 346 (0.1, M⁺), 111 (100).

(1*R*,3a*S*,5*S*,7a*R*)-1-[(*E,E*)-2-Methyl-3-guanidinoimino-1-propenyl]-5-cyclohexyl-7a-methylperhydroinden-3a-ol Hydrochloride (44). Prepared following method D starting from **108**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (85:15:1.5) followed by trituration with Et₂O gave a white solid (0.16 g, 44%), mp 226−265 °C. ¹H NMR (CD₃OD) δ 0.84 (s, 3H, CH₃), 1.85 (d, 3H, *J* = 1.2, =CCH₃), 2.78 (m, 1H, C*H*CH=), 6.15 (bd, 1H, *J* = 10.6, CH=C), 7.67 (s, 1H, CH=N). MS *m/z* 360 (present, M⁺ base), 125 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-(4-*cis*-hydroxy-r-1-cyclohexyl)-7a-methylperhydroinden-3a-ol (45). Prepared following method E starting from **110**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (93:7:0.3) followed by trituration with *i*-Pr₂O gave a white solid (0.089 g, 51%), mp 98−121 °C. ¹H NMR (CD₃OD) δ 0.88 (s, 3H, CH₃), 2.28 (s, 6H, N(CH₃)₂), 2.36 (dt, 1H, C*H*CH=N), 2.61 (t, 2H, CH₂N), 3.90 (br s, 1H, C*H*OH), 4.08 (t, 2H, CH₂O), 7.54 (d, 1H, *J* = 9.0, CH=N). MS *m/z* 366 (10, M⁺), 58 (100).

(1*S*,3a*S*,5*S*,7a*R*)-1-[2-Dimethylaminoethoxy-(*E*)-iminomethyl]-5-(4-*trans*-hydroxy-r-1-cyclohexyl)-7a-methylperhydroinden-3a-ol (46). Prepared following method E starting from **115**. The crude product on chromatography with CHCl₃/MeOH/26% w/v aqueous NH₃ (9:1:0.1) followed by trituration with Et₂O gave a white solid (0.094 g, 52%), mp 139−140 °C. ¹H NMR (CD₃OD) δ 0.87 (s, 3H, CH₃), 2.28 (s, 6H, N(CH₃)₂), 2.61 (t, 2H, CH₂N), 3.44 (m, 1H, *W*₁/₂ = 21 Hz, C*H*OH), 4.08 (t, 2H, CH₂O), 7.55 (d, 1H, *J* = 9.0, CH=N).

(3a*S*,7a*R*)-1-Methylen-3a-hydroxy-7a-methylperhydroindene-5-spiro-2′-(1′,3′-dioxolane) (48). To a solution of **47** (100 g, 0.55 mol) and oxalic acid (30.0 g, 0.325 mol) in CH₃CN (1.5 L) was added ethylene glycol (1.1 L, 19.5 mol). After 16 h the mixture was neutralized with 5% aqueous Na₂CO₃, and CH₃CN was evaporated. The residue was extracted with chloroform (3×). The combined organic extracts were dried over Na₂SO₄ and evaporated to dryness under reduced pressure to afford (3a*S*,7a*S*)-3a-hydroxy-5-spiro-2′-(1′,3′-dioxolane)-7a-methyl-1-perhydroindenone (105.0 g, 83%), as an oil. ¹H NMR (CDCl₃) δ 1.01 (s, 3H, CH₃), 2.20 (dt, 1H, H2), 2.53 (ddd, 1H, H2), 3.50 (s, 1H, OH), 3.96 (m, 4H, 2CH₂O). ¹³C NMR (DMSO-*d*₆) (digitalis-like conformation) δ 13.3 (q), 28.3 (t), 29.3 (t), 30.9 (t), 33.2 (t), 42.3 (t), 52.1 (s), 64.0 (t), 64.2 (t), 78.2 (s), 108.0 (s), 220.6 (s). ¹³C NMR (CDCl₃) (non-digitalis-like conformation) δ 18.4 (q), 26.6 (t), 31.1 (t), 31.4 (t), 33.9 (t), 42.6 (t), 52.7 (s), 64.2 (t), 64.5 (t), 78.5 (s), 108.6 (s), 218.6 (s).

To a solution of (3a*S*,7a*S*)-3a-hydroxy-5-spiro-2′-(1′,3′-dioxolane)-7a-methyl-1-perhydroindenone (100 g, 0.44 mol) and methyltriphenylphosphonium bromide (1580 g, 4.42 mol) in THF (1 L) were added potassium *tert*-butoxide (496 g, 4.42 mol) and *tert*-BuOH (18 mL) dropwise at room temperature. The mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was neutralized with glacial acetic acid. The precipitate was filtered off and washed with CH₂Cl₂, and the filtrate was evaporated to dryness to give **48** (76.0 g, 77%) as an oil. ¹H NMR (CDCl₃) δ 1.00 (s, 3H, CH₃), 3.45 (br, 1H, OH), 3.95 (m, 4H, 2CH₂O), 4.80 (t, 1H, =C*H*H), 4.85 (t, 1H, =CH*H*).

(1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-5-spiro-2′-(1′,3′-dioxolane)-7a-methylperhydroinden-3a-ol (49) and (1*R*,3a*S*,7a*R*)-1-Hydroxymethyl-5-spiro-2′-(1′,3′-dioxolane)-7a-methylperhydroinden-3a-ol (50). A 1 M BH₃ solution in THF (0.390 L, 0.39 mol) was dropped into a solution of **48** in THF (0.76 L), maintained at 0 °C under N₂. After being stirred

at room temperature for 1 h, the solution was cooled to 0 °C, and the following were added in order: water (7.0 mL, 0.39 mol), sodium perborate (74.5 g, 0.48 mol), and 4 N NaOH (0.12 L, 0.48 mol). The mixture was stirred at room temperature for 16 h. The organic layer was separated, and the aqueous one was extracted with EtOAc (3×). The combined organic layers were washed with water, dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/acetone/CHCl₃ 4:3:3) to give the 1β isomer **49** (41.14 g, 50%) and the 1α isomer **50** (16.45 g, 20%), as white foams. Isomer **49**: ¹H NMR (CDCl₃) δ 0.91 (s, 3H, CH₃), 3.56 (dd, 1H, C*H*HOH), 3.60 (br, 1H, OH), 3.64 (dd, 1H, CH*H*OH), 3.98 (m, 4H, 2 OCH₂). ¹³C NMR (CDCl₃) δ 16.7 (q), 22.4 (t), 30.3 (t), 30.8 (t), 35.4 (t), 41.5 (t), 44.1 (d), 44.6 (s), 64.2 (t), 64.3 (t), 64.5 (t), 81.6 (s), 109.3 (s). Anal. (C₁₃H₂₂O₄) C, H. Isomer **50**: ¹H NMR (CDCl₃) δ 1.11 (s, 3H, CH₃), 3.59 (dd, 1H, C*H*HOH), 3.78 (dd, 1H, CH*H*OH), 3.95 (m, 4H, 2 OCH₂). ¹³C NMR (CDCl₃) δ 16.9 (q), 24.0 (t), 27.4 (t), 30.1 (t), 34.9 (t), 41.7 (t), 45.6 (s), 50.1 (d), 63.7 (t), 64.3 (t), 64.4 (t), 83.8 (s), 108.8 (s). Anal. (C₁₃H₂₂O₄) C, H.

(1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-3a-hydroxy-7a-methyl-5-perhydroindenone (51). Compound **49** (41.14 g, 0.17 mol) was dissolved in a 1 N solution of PTSA (0.411 L, 0.411 mol) in CH₃CN:H₂O (85:15). After being stirred for 16 h, the mixture was neutralized with solid NaHCO₃, and CH₃CN was evaporated. The residue was extracted with EtOAc (3 ×), and the combined organic layers were dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/CHCl₃/acetone, 4:3:3) to give **51** (22.77 g, 68%) as a thick oil. ¹H NMR (CDCl₃) δ 1.21 (s, 3H, CH₃), 3.53 (dd, 1H, C*H*HOH), 3.79 (dd, 1H, CH*H*OH), 4.20 (br, 1H, OH), 5.10 (br, 1H, OH). ¹³C NMR (CDCl₃) δ 14.5 (q), 22.0 (t), 37.0 (t), 37.2 (t), 37.2 (t), 46.5 (s), 48.5 (t), 49.3 (d), 62.2 (t), 82.9 (s), 209.9 (s).

(1*R*,3a*S*,7a*R*)-3a-Hydroxy-7a-methylperhydroindene-5-spiro-2′-(1′,3′-dioxolane)-1-carboxaldehyde (52). To a solution of **50** (8.00 g, 0.033 mol) in THF (0.16 L) was added IBX (13.86 g, 0.049 mol), and the resulting suspension was heated to reflux for 1 h. After cooling to room temperature, the precipitate was filtered off and the organic solvent evaporated to dryness to give **52** (8.8 g, 100%) as a white foam. ¹H NMR (CDCl₃) δ 1.27 (s, 3H, CH₃), 2.85 (dt, 1H, C*H*CHO), 3.90 (m, 4H, 2 CH₂O), 9.80 (d, 1H, CHO).

(1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-5-spiro-2′-(1′,3′dioxolane)-7a-methylperhydroinden-3a-ol (49). A solution of **52** (24.5 g, 0.102 mol) and 1.4 M methanolic KOH (0.612 L, 0.856 mol) was stirred at room temperature for 0.5 h. After cooling to −20 °C, NaBH₄ (4.05 g, 0.107 mol) was added, and mixture was stirred for 2.5 h. After heating to room temperature, the mixture was neutralized with CH₃COOH and the organic solvent evaporated. The crude product was purified by flash chromatography (*n*-hexane/CHCl₃/acetone, 4:3:3) to give **49** (15.88 g, 64%) and **50** (8.7 g, 35%) as white foams.

(1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-5-spiro-2′-(1′,3′-dithiolane)-7a-methylperhydroinden-3a-ol (54). To a solution of **51** (2.24 g, 0.113 mol) and 1,2-ethanedithiol (1.35 mL, 0.018 mol) in CH₂Cl₂ (20 mL) at 0 °C was added BF₃·Et₂O (0.36 mL, 2.8 mmol). The resulting mixture was stirred at room temperature for 16 h. Then 1 N NaOH was added until neutral pH. The layers were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/CHCl₃/acetone, 6:2:2) to give **54** (1.39 g, 45%) as an oil. ¹H NMR (CDCl₃) δ 0.92 (s, 3H, CH₃), 3.39 (m, 4H, 2 CH₂S), 3.60 (dd, 1H, CH*H*OH), 3.68 (dd, 1H, C*H*HOH). ¹³C (CDCl₃) δ 16.8 (q), 22.3 (t), 33.7 (t), 36.5 (t), 36.9 (t), 38.2 (t), 38.3 (t), 44.1 (s), 44.6 (d), 48.5 (t), 64.4 (t), 66.4 (s), 81.6 (s).

(1*S*,3a*R*,7a*R*)-1-Hydroxymethyl-7a-methylperhydroindene-3a-ol (55). To a solution of **54** (1.24 g, 4.5 mmol) in EtOH (125 mL) was added Raney-Ni (103 g), and the mixture was heated at reflux for 16 h. After cooling to room temperature, the precipitate was filtered off and the organic solvent evaporated to dryness to give **55** (0.61 g, 75%) as a white solid,

mp 112−114 °C. ¹H NMR (CDCl₃) δ 1.01 (s, 3H, CH₃), 3.52 (dd, 1H, CH*H*OH), 3.79 (dd, 1H, C*H*HOH).

(1*S*,3a*R*,7a*R*)-3a-Hydroxy-7a-methylperhydroindene-1-carboxaldehyde (56). A mixture of **55** (0.30 g, 1.6 mmol) and IBX (0.69 g, 2.5 mmol) in THF (30 mL) was heated at reflux for 2.5 h. After cooling to room temperature, the precipitate was filtered off, and the aldehyde solution was directly dropped into the solution at pH 4.5 containing the aminoalkoxyamine to give **2**.

(1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-5-[(*E*)-benzyliden]-7a-methylperhydroinden-3a-ol (57) and (1*S*,3a*S*,7a*R*)-1-Hydroxymethyl-5-[(*Z*)-benzyliden]-7a-methylperhydroinden-3a-ol (58). To a mixture of benzyltriphenylphosphonium bromide and sodium amide (7.50 g, 0.015 mol) in THF (40 mL) was dropped a solution of **51** (2.16 g, 0.01 mol) in THF (20 mL). After 16 h, 10% aqueous NaH₂PO₄ was added, and the resulting mixture was extracted with EtOAc (3×). The combined organic layers were dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/CHCl₃/acetone, 4:3:3) to give the (*E*) isomer **57** (0.51 g, 20%) and the (*Z*) isomer **58** (0.26 g, 10%) as white foams, together with an unseparated *E/Z* mixture (0.40 g, 25%). (*E*) isomer **57**: ¹H NMR (CDCl₃) δ 1.14 (s, 3H, CH₃), 3.56 (dd, 1H, CH*H*OH), 3.79 (dd, 1H, C*H*HOH), 6.40 (s, 1H, CHPh), 7.28 (m, 5H, Ph). (*Z*) isomer **58**: ¹H NMR (CDCl₃) δ 1.12 (s, 3H, CH₃), 3.57 (dd, 1H, CH*H*OH), 3.79 (dd, 1H, C*H*HOH), 6.31 (s, 1H, CHPh), 7.28 (m, 5H, Ph).

(1*S*,3a*S*,7a*R*)-5-(*E*)-Benzyliden-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (59). A solution of IBX (0.62 g, 2.2 mmol) in DMSO (4.4 mL) was added to a flask containing **57** (0.40 g, 1.4 mmol). After 1.5 h, water (5 mL) was added, the precipitate was filtered off and washed with Et₂O, and the organic solvent was evaporated to dryness to give **59** (0.13 g, 33%) as a white foam. ¹H NMR (CDCl₃) δ 1.10 (s, 3H, CH₃), 6.29 (s,1H, CHPh), 7.28 (m, 5H, Ph), 9.72 (d, 1H, CHO, *J* = 3.8).

(1*S*,3a*S*,7a*R*)-5-(*Z*)-Benzyliden-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (60). Prepared as described for compound **59**, starting from compound **58** to give **60** (0.24 g, 98%) as a white foam. ¹H NMR (CDCl₃) δ 1.15 (s, 3H, CH₃), 6.44 (s,1H, CHPh), 7.28 (m, 5H, Ph), 9.78 (d, 1H, *J* = 3.8, CHO).

(1*S*,3a*S*,5*R*,*S*,7a*R*)-1-*tert*-Butyldimethylsilyloxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol (61) and (1*S*,3a*S*,5*S*,*S*,7a*R*)-1-*tert*-Butyldimethylsilyloxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol (62). A mixture of **57** and **58** (0.63 g, 2.3 mmol) was dissolved in EtOAc (10 mL), and 10% Pd/C (0.045 g) was added. After 1.5 h under H₂ at atmospheric pressure, the catalyst was filtered off and the organic solvent evaporated to give a 1/1 mixture of (1*S*,3a*S*,5*R*,7a*R*)-1-hydroxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol and (1*S*,3a*S*,5*S*,7a*R*)-1-hydroxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol (0.60 g, 95%) as an oil.

To a solution of the above mixture (0.60 g, 2.2 mmol) in DMF (9 mL) were added *tert*-butyldimethylsilyl chloride (0.36 g, 2.4 mmol) and imidazole (0.33 g, 4.8 mmol). After being stirred for 16 h at room temperature, the mixture was poured into water and extracted with Et₂O (3×). The combined organic layers were washed with water, dried over Na₂SO₄, and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/Et₂O, 9:1) to give **61** (0.26 g, 32%) and **62** (0.32 g, 38%) as white foams. Isomer **61**: ¹H NMR (CDCl₃) δ 0.10 (s, 6H, Si(CH₃)₂), 0.92 (s, 9H, C(CH₃)₃), 0.98 (s, 3H, CH₃), 2.55 (m, 2H, CH₂Ph), 3.45 (dd, 1H, C*H*HOSi), 3.75 (dd, 1H, CH*H*OSi), 7.10−7.40 (m, 5H, Ph). Isomer **62**: ¹H NMR (CDCl₃) δ 0.10 (s, 6H, Si(CH₃)₂), 0.80 (s, 3H, CH₃), 0.92 (s, 9H, C(CH₃)₃), 2.52 (m, 2H, CH₂Ph), 3.47 (dd, 1H, C*H*HOSi), 3.62 (dd, 1H, CH*H*OSi), 7.10−7.30 (m, 5H, Ph).

(1*S*,3a*S*,5*R*,7a*R*)-3a-Hydroxy-5-benzyl-7a-methylperhydroindene-1-carboxaldehyde (63). A solution of **61** (0.26 g, 0.7 mmol) in dioxane/water 1/1 previously brought to pH 1 with 3 N HCl (9 mL) was stirred for 0.45 h. The mixture was neutralized with 5% aqueous NaHCO₃ and extracted with EtOAc (3×). The combined organic extracts were washed with

aqueous 10% NaH₂PO₄, dried over Na₂SO₄, and evaporated to give (1*S*,3a*S*,5*R*,7a*R*)-1-hydroxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol (0.18 g, 100%) as an oil. ¹H NMR (CDCl₃) δ 0.92 (s, 3H, CH₃), 2.56 (m, 2H, CH₂Ph), 3.48 (dd, 1H, C*H*HOH), 3.77 (dd, 1H, CH*H*OH), 7.20 (m, 5H, Ph).

To a solution of the above-described 1-hydroxymethyl derivative (0.18 g, 0.70 mmol) in DMSO (2 mL) was added IBX (0.28 g, 1 mmol). After the mixture was stirred for 1 h, the aldehyde solution was directly dropped into the buffered solution at pH 4.5 containing the aminoalkoxyamine to give **7**.

(1*S*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-5-benzyl-7a-methylperhydroindene-1-carboxaldehyde (64). Prepared as described for **63** starting from **62** to give (1*S*,3a*S*,5*S*,7a*R*)-1-hydroxymethyl-5-benzyl-7a-methylperhydroinden-3a-ol (0.26 g, 100%) as an oil. ¹H NMR (CDCl₃) δ 0.81 (s, 3H, CH₃), 2.51 (m, 2H, CH₂Ph), 3.51 (dd, 1H, C*H*HOH), 3.72 (dd, 1H, CH*H*OH), 7.2 (m, 5H, Ph).

The above-described 1-hydroxymethyl derivative (0.26 g, 1.0 mmol) was dissolved in a solution of IBX (0.47 g, 1.7 mmol) in DMSO (3 mL). After 1 h water was added and the white precipitate was filtered off. The aqueous phase was extracted with EtOAc. The combined extracts were dried over Na₂SO₄ and evaporated to give **64** (0.26 g, 100%) as an oil. ¹H NMR (CDCl₃) δ 0.90 (s, 3H, CH₃), 2.53 (d, 2H, CH₂Ph), 2.89 (m, 1H C*H*CHO), 7.20 (m, 5H, Ph), 9.72 (d, 1H, CHO).

(1*S*,3a*S*,5*R*,7a*R*)-1-Hydroxymethyl-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (65). A mixture of **61** (0.37 g, 0.95 mmol) and 5% Rh on alumina (0.25 g) in MeOH (10 mL) was hydrogenated in a Parr apparatus at 4.3 atm for 3 h. After this time the catalyst was filtered through a Celite pad and the solution evaporated to give (1*S*,3a*S*,5*R*,7a*R*)-1-*tert*-butyldimethylsilyloxymethyl-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (0.31 g, 83%) as a white foam. ¹H NMR (CDCl₃) δ 0.14 (s, 6H, Si(CH₃)₂), 0.94 (s, 9H, C(CH₃)₃), 0.99 (s, 3H, CH₃), 3.47 (dd, 1H, C*H*HOSi), 3.76 (dd, 1H, CH*H*OSi).

A solution of the compound above-described (0.31 g, 7.8 mmol) in dioxane/water 1/1 was brought to pH 1 with 3 N HCl (15 mL) and was stirred for 2 h. The mixture was neutralized with 5% aqueous Na₂HPO₄ and extracted with EtOAc (3×). The combined organic phases were washed with 5% aqueous NaH₂PO₄, dried over Na₂SO₄, and evaporated to give **65** (0.22 g, 100%) as a glassy solid. ¹H NMR (CDCl₃) δ 1.01 (s, 3H, CH₃), 3.49 (dd, 1H, C*H*HOH), 3.79 (dd, 1H, CH*H*OH).

(1*S*,3a*S*,5*R*,7a*R*)-3a-Hydroxy-5-cyclohexylmethyl-7a-methylperhydroindene-1-carboxaldehyde (66). Prepared by oxidation with IBX as described for compound **64**, starting from compound **65** (0.22 g, 7.8 mmol) to give **66** (0.18 g, 83%) as a white foam. ¹H NMR (CDCl₃) δ 1.04 (s, 3H, CH₃), 2.48 (m,1H, C*H*CHO), 9.74 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (67). Prepared as described for compound **65**, starting from compound **62** (0.68 g, 1.7 mmol) to give (1*S*,3a*S*,5*S*,7a*R*)-1-*tert*-butyldimethylsilyloxymethyl-5-cyclohexylmethyl-7a-methylperhydroinden-3a-ol (0.67 g, 100%) as a white foam. ¹H NMR (CDCl₃) δ 0.09 (s, 6H, Si(CH₃)₂), 0.82 (s, 9H, C(CH₃)₃), 0.90 (s, 3H, CH₃), 2.30 (m, 1H, C*H*CH₂O), 3.48 (dd 1H, C*H*HOSi), 3.63 (dd, 1H, CH*H*OSi). Subsequent hydrolysis (dioxane/water at pH 1) gave **67** (0.42 g, 89%) as a glassy oil. ¹H NMR (CDCl₃) δ 0.90 (s, 3H, CH₃), 2.29 (m,1H, C*H*CH₂O), 3.50 (dd 1H, C*H*HOH), 3.70 (dd, 1H, CH*H*OH).

(1*S*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-5-cyclohexylmethyl-7a-methylperhydroindene-1-carboxaldehyde (68). Prepared as described for compound **64** starting from compound **67** (0.20 g, 0.7 mmol) to give **68** (0.2 g, 100%) as an oil. ¹H NMR (CDCl₃) δ 0.92 (s, 3H, CH₃), 2.89 (m,1H, C*H*CHO), 9.72 (d, 1H, *J* = 1.9, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-phenyl-7a-methylperhydroinden-3a,5-diol (69). To a solution of **51** (20.0 g, 0.10 mol) in dry THF (0.2 L) maintained at −78 °C under nitrogen, was added a solution of 2 M phenyllithium in cyclohexane/ether 70/30 (0.213 L, 0.426 mol) dropwise. After 1 h the mixture was raised to 0 °C, and the solution was treated with 5% aqueus NaH₂PO₄ and extracted with EtOAc.

The organic phase was dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography (*n*-hexane/acetone/CHCl$_3$, 4:3:3) to give **69** (22.6 g, 82%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.91 (m, 1H, C*H*CH$_2$O), 3.25 (br, 1H, OH), 3.58 (dd, 1H, CH*H*OH), 3.81 (dd, 1H, C*H*HOH), 7.23−7.53 (m, 5H, Ph). ^{13}C NMR (CDCl$_3$) δ 14.5 (q), 22.2 (t), 34.4 (t), 35.8 (t), 37.7 (t), 44.2 (t), 46.2 (s), 50.5 (s), 62.8 (t), 74.7 (s), 81.6 (s), 124.4 (d), 127.0 (d), 128.3 (d), 149.0 (s).

(1*S*,3a*S*,5*R*,7a*R*)-1-Hydroxymethyl-5-phenyl-7a-methyl-perhydroinden-3a-ol (70). A mixture of **69** (0.64 g, 2.31 mmol) and 5% Pd/C (0.64 g) in a solution (10 mL) of HClO$_4$ in EtOAc (1 drop of 70% HClO$_4$ in 60 mL of EtOAc) was hydrogenated for 2 h at atmospheric pressure. After this time the catalyst was filtered off through a Celite pad, and the solution was washed with 5% NaHCO$_3$. The aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4 and evaporated to give an approximately 3:1 mixture of **70** and **72** (0.53 g, 88%) as an oil. Compounds **70** and **72** were separated by flash chromatography (*n*-hexane/EtOAc 95/5) of their 1-*tert*-butyldimethylsilyl ethers (prepared as described for compounds **61** and **62**) to give (1*S*,3a*S*,5*R*,7a*R*)-1-*tert*-butyldimethylsilyloxymethyl-5-phenyl-7a-methylperhydroinden-3a-ol (0.32 g, 48%) and (1*S*,3a*S*,5*S*,7a*R*)-1-*tert*-butyldimethylsilyloxymethyl-5-phenyl-7a-methylperhydroinden-3a-ol (0.10 g, 16%). **(5*S*) isomer**: ^{1}H NMR (CDCl$_3$) δ 0.15 (s, 6H, Si(CH$_3$)$_2$), 0.95 (s, 9H, C(CH$_3$)$_3$), 1.10 (s, 3H, CH$_3$), 2.25 (m,1H, CHCH$_2$O), 2.72 (m, 1H, CHPh), 3.50 (m, 1H, C*H*HOSi), 3.63 (m, 1H, CH*H*OSi), 7.20−7.35 (m, 5H, Ph). **(5*R*) isomer**: ^{1}H NMR (CDCl$_3$) δ 0.10 (s, 6H, Si(CH$_3$)$_2$), 0.90 (s, 3H, CH$_3$), 0.92 (s, 9H, C(CH$_3$)$_3$), 2.44 (m,1H, CHCH$_2$O), 2.83 (m, 1H, CHPh), 3.52 (dd, 1H, C*H*HOSi), 3.69 (dd, 1H, CH*H*OSi), 7.18−7.40 (m, 5H, Ph).

Compound **70** was prepared by hydrolysis, in quantitative yield, as described for compound **65**, starting from (1*S*,3a*S*,5*R*,7a*R*)-1-*tert*-butyldimethylsilyloxymethyl-5-phenyl-7a-methylperhydroinden-3a-ol (0.30 g). ^{1}H NMR (CDCl$_3$) δ 0.90 (s, 3H, CH$_3$), 2.45 (m, 1H, CHCH$_2$O), 2.83 (m, 1H, $W_{1/2h}$ = 25 Hz, CHPh), 3.57 (dd, 1H, CH*H*OH) 3.78 (dd, 1H, C*H*HOH), 7.15−7.35 (m, 5H, Ph).

(1*S*,3a*S*,5*R*,7a*R*)-5-Phenyl-3a-hydroxy-7a-methylper-hydroindene-1-carboxaldehyde (71). Prepared by oxidation with IBX as described for compound **64** starting from compound **70** (0.20 g, 0.8 mmol) to give **71** in quantitative yield. ^{1}H NMR (CDCl$_3$) δ 1.00 (s, 3H, CH$_3$), 2.90 (m, 1H, CHPh), 3.02 (m, 1H, C*H*CHO), 7.18−7.35 (m, 5H, Ph), 9.75 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-phenyl-7a-methyl-perhydroinden-3a-ol (72). A mixture of **69** (22.6 g, 0.082 mol) and 50% Raney-Ni suspension in water (22.6 g) in EtOH (67 mL) was heated at reflux for 3 h. After cooling to room temperature, the mixture was filtered through a Celite pad and the solution evaporated to give **72** (17.48 g, 82%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.31 (m, 1H, C*H*CH$_2$O), 2.73 (m, 1H, $W_{1/2h}$ = 25 Hz, CHPh), 3.53 (dd, 1H, CH*H*OH), 3.81 (dd, 1H, C*H*HOH), 3.85 (br, 1H, OH), 7.17−7.45 (m, 5H, Ph). ^{13}C NMR (CDCl$_3$) δ 14.9 (q), 22.1 (t), 29.8 (t), 39.5 (t), 40.1 (t), 40.1 (t), 41.6 (d), 46.5 (s), 51.1 (d), 62.3 (t), 81.7 (s), 125.9 (d), 125.9 (d), 126.1 (d), 128.4 (d), 128.4 (d), 146.1 (s).

(1*S*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-5-phenyl-7a-methylper-hydroindene-1-carboxaldehyde (73). To a 0.5 M solution of IBX (1.3 g, 4.6 mmol) in DMSO was added **72** (1.00 g, 3.8 mmol). After 1.5 h water was added, and the white precipitate was filtered off. The aqueous phase was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated to give **73** (1.00 g, 100%) as an oil. ^{1}H NMR (CDCl$_3$) δ 1.15 (s, 3H, CH$_3$), 2.75 (m, 1H, CHPh), 7.18−7.38 (m, 5H, Ph), 9.78 (d, 1H, CHO). ^{13}C NMR (CDCl$_3$) δ 16.1 (q), 20.7 (t), 28.9 (t), 36.4 (t), 38.7 (t), 40.1 (t), 41.6 (d), 49.3 (s), 61.7 (d), 82.5 (s), 126.3 (d), 126.8 (d), 126.8 (d), 128.5 (d), 128.5 (d), 145.5 (s), 206.6 (d).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-cyclohexyl-7a-methylperhydroinden-3a-ol (74). A mixture of **72** (12.0 g, 0.046 mol) and 5% Rh on alumina (5.1 g) in MeOH (0.18 L)

was hydrogenated at 4.3 atm for 4 h. After this time the catalyst was filtered off through a Celite pad and the solution evaporated to give **74** (12.30 g, 100%) as an oil. ^{1}H NMR (CDCl$_3$) δ 1.00 (s, 3H, CH$_3$), 2.7−3.7 (br, 2H, OH), 3.50 (dd, 1H, CH*H*OH), 3.79 (dd, 1H, C*H*HOH).

(1*S*,3a*S*,5*S*,7a*R*)-3a-Hydroxy-5-cyclohexyl-7a-methyl-perhydroindene-1-carboxaldehyde (75). Prepared as described for compound **73** starting from compound **74** (12 g, 0.046 mol) to give **75** (11.90 g, 100%) as a white foam. The crude product was sufficiently pure to be used in the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 1.00 (s, 3H, CH$_3$), 9.73 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-*tert*-butyldi-methylsilyloxymethylphenyl)-7a-methylperhydro-inden-3a,5-diol (76). To a solution of 1-bromo-3-[(*tert*-butyl-dimethylsilyl)oxymethyl]benzene (15.5 g, 0.051 mol) (prepared following the preparation of 1-bromo-3-[(*tert*-butyldimethyl-silyl)oxy]benzene in ref 26) in Et$_2$O (20 mL) and THF (30 mL) maintained at −78 °C was dropped 1.6 M *n*-butyllithium in hexane (32.8 mL, 0.051 mol). After the mixture was stirred for 1.5 h, a solution of **51** (1.6 g, 8.6 mmol) in THF (10 mL) was dropped. After 1.5 h at −78 °C, water was added, and the mixture was extracted with EtOAc (3 ×). The organic phase was dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography (*n*-hexane/acetone/CHCl$_3$, 6:2:2) to give **76** (2.5 g, 70%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.12 (s, 6H, Si(CH$_3$)$_2$), 0.95 (s, 9H, C(CH$_3$)$_3$), 1.10 (s, 3H, CH$_3$), 3.55 (m, 1H, C*H*HO), 3.80 (m, 1H, CH*H*O), 4.78 (s, 2H, OCH$_2$Ar), 7.20−7.52 (m, 4H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-*tert*-butyldi-methylsilyloxymethylphenyl)-7a-methylperhydro-inden-3a,5-diol (77). Prepared as described for compound **76** using 1-bromo-4-[(*tert*-butyldimethylsilyl)oxymethyl]benzene instead of 1-bromo-3-[(*tert*-butyldimethylsilyl)oxymethyl]-benzene. The crude product was purified by flash chromatog-raphy (*n*-hexane/acetone/CHCl$_3$, 4:3:3) to give **77** (3.2 g, 65%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.10 (s, 6H, Si(CH$_3$)$_2$), 0.94 (s, 9H, C(CH$_3$)$_3$), 1.10 (s, 3H, CH$_3$), 3.55 (m, 1H, C*H*HO), 3.80 (m, 1H, CH*H*O), 4.72 (s, 2H, OCH$_2$Ar), 7.32 (m, 2H, Ar), 7.48 (m, 2H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-methylphenyl)-7a-methylperhydroinden-3a-ol (78) and (1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-*tert*-butyldimethylsilyloxymeth-ylphenyl)-7a-methylperhydroinden-3a-ol (80). A mixture of **76** (1.30 g, 3.3 mmol) and aqueuos Raney-Ni (ca 100 g) in EtOH (50 mL) was heated at reflux under vigorous stirring for 3 days. After cooling to room temperature, the mixture was filtered through a Celite pad and the solution evaporated. The crude product was purified by flash chromatography (cyclo-hexane/EtOAc 7:3 to 1:1) to give **78** (0.36 g, 40%) and **80** (0.32 g, 26%) as thick oils. **78**: ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 2.70 (m, 1H, CHAr), 3.54 (dd, 1H, C*H*HOH), 3.82 (dd, 1H, CH*H*OH), 7.00−7.25 (m, 4H, Ar). **80**: ^{1}H NMR (CDCl$_3$) δ 0.11 (s, 6H, Si(CH$_3$)$_2$), 0.94 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.72 (m, 1H, CHPh), 3.55 (dd, 1H, C*H*HOH), 3.81 (dd, 1H, CH*H*OH), 4.72 (s, 2H, OCH$_2$Ar), 7.10−7.35 (m, 4H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-methylphenyl)-7a-methylperhydroinden-3a-ol (79) and (1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-*tert*-butyldimethylsilyloxymeth-ylphenyl)-7a-methylperhydroinden-3a-ol (81). Prepared as described for compound **78** and **80**, starting from **77** (3.2 g, 0.0078 mol). The crude product was purified by flash chroma-tography (*n*-hexane/acetone/CHCl$_3$, 6:2:2) to give **79** (0.89 g, 42%) and **81** (1.21 g, 40%) as thick oils. **79**: ^{1}H NMR (CDCl$_3$) δ 1.11 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 2.70 (m, 1H, CHAr), 3.55 (dd, 1H, C*H*HOH), 3.82 (dd, 1H, CH*H*OH), 7.12 (m, 4H, Ar). **81**: ^{1}H NMR (CDCl$_3$) δ 0.11 (s, 6H, Si(CH$_3$)$_2$), 0.92 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.71 (m, 1H, CHAr), 3.55 (dd, 1H, C*H*HOH), 3.81 (dd, 1H, CH*H*OH), 4.72 (s, 2H, OCH$_2$Ar), 7.18−7.32 (m, 4H, Ar).

**(1*S*,3a*S*,5*S*,7a*R*)-5-(3-Methylphenyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (82), (1*S*,3a*S*,5*S*,7a*R*)-5-(4-Methylphenyl)-3a-hydroxy-7a-methylper-

hydroindene-1-carboxaldehyde (83), (1*S*,3a*S*,5*S*,7a*R*)-5-(3-*tert*-Butyldimethylsilyloxymethylphenyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (84) and (1*S*,3a*S*,5*S*,7a*R*)-5-(4-*tert*-Butyldimethysilyloxymethyl-phenyl)-3a-hydroxy-7a-methylperhydroindene-1-carbox-aldehyde (85). Prepared as described for compound 73 to give 82 (0.27 g, 89%), 83 (0.43 g, 100%), 84 (0.27 g, 95%), 85 (0.60 g, 97%) as oils. 82: ^{1}H NMR (CDCl$_3$) δ 1.15 (s, 3H, CH$_3$), 2.34 (s, 3H, CH$_3$), 2.44 (m, 1H, C*H*CHO), 2.70 (m, 1H, CHAr), 7.00–7.29 (m, 4H, Ar), 9.78 (d, 1H, CHO). 83: ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 2.45 (m, 1H, C*H*CHO), 2.72 (m, 1H, CHAr), 7.12 (m, 4H, Ar), 9.78 (d, 1H, CHO). 84: ^{1}H NMR (CDCl$_3$) δ 0.12 (s, 6H, Si(CH$_3$)$_2$), 0.95 (s, 9H, C(CH$_3$)$_3$), 1.17 (s, 3H, CH$_3$), 2.45 (m, 1H, C*H*CHO), 2.74 (m, 1H, CHAr), 4.72 (s, 2H, OCH$_2$Ar), 7.08–7.30 (m, 4H, Ar), 9.78 (d, 1H, *J* = 4.3, CHO). 85: ^{1}H NMR (CDCl$_3$) δ 0.12 (s, 6H, Si(CH$_3$)$_2$), 0.94 (s, 9H, C(CH$_3$)$_3$), 1.17 (s, 3H, CH$_3$), 2.45 (m, 1H, C*H*CHO), 2.72 (m, 1H, CHAr), 4.72 (s, 2H, OCH$_2$Ar), 7.16–7.30 (m, 4H, Ar), 9.78 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-pyridyl)-7a-methylperhydroinden-3a,5-diol (86). To a solution of 1.6 M *n*-butyllithium in hexane (44.19 mL, 0.07 mol) in Et$_2$O (40 mL) maintained at −40 °C was dropped 3-bromopyridine (6.86 mL, 0.07 mol). After 1 h the mixture was cooled to −78 °C, and a solution of 51 (1.4 g, 0.007 mol) in THF (40 mL) was dropped. After 1.5 h the mixture was allowed to warm to room temperature, and a saturated water solution of NH$_4$Cl was added. The aqueous phase was extracted with CH$_2$Cl$_2$/EtOH 9:1 (3×). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated to give 86 (1.94 g, 100%) as an oil. ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 3.55 (m, 1H, C*H*HOH), 3.81 (m, 1H, CH*H*OH), 7.28 (m, 1H, Py), 7.85 (m, 1H, Py), 8.50 (m, 1H, Py), 8.78 (m, 1H, Py).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-pyridyl)-7a-methylperhydroinden-3a,5-diol (87). Prepared as described for compound 86 starting from 4-bromopyridine (8.4 g, 0.052 mol) and 51 (0.80 g, 4.0 mmol). The crude product was purified by flash chromatography (CH$_2$Cl$_2$/MeOH, 93:7 to 8:2) to give 87 (0.86 g, 77%) as a white foam. ^{1}H NMR (DMSO-*d*$_6$) δ 0.98 (s, 3H, CH$_3$), 3.40 (m, 2H, CH$_2$O), 4.64 (s, 1H, OH), 4.90 (t, 1H, OH), 5.10 (s, 1H, OH), 7.44 (m, 2H, Py), 8.46 (m, 2H, Py).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-*tert*-butyldimethylsilyloxyphenyl)-7a-methylperhydroinden-3a,5-diol (88). To a solution of 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]-benzene[26] (8.80 g, 0.032 mol) in Et$_2$O (45 mL) maintained at −78 °C was dropped 1.5 M *tert*-butyllithium in pentane (26 mL, 0.039 mol). After being stirred for 0.5 h at −78 °C and 20 min at 0 °C, the mixture was cooled at −78 °C, and a solution of 51 (1.00 g, 5.4 mmol) in THF (10 mL) was dropped. After 0.5 h the mixture was allowed to warm to room temperature and water was added. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na$_2$SO$_4$ and evaporated. The crude product was purified by flash chromatography (*n*-hexane/acetone/CHCl$_3$, 6:2:2) to give 88 (1.3 g, 61%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.22 (s, 6H, Si(CH$_3$)$_2$), 0.98 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 3.55 (dd, 1H, C*H*HOH) 3.82 (dd, 1H, CH*H*OH), 6.70–7.30 (m, 4H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-*tert*-butyldimethylsilyloxyphenyl)-7a-methylperhydroinden-3a,5-diol (89). To a solution of 1-bromo-3-[(*tert*-butyldimethylsilyl)oxy]-benzene (13.3 g, 0.049 mol; prepared following the method descibed in ref 26) in *n*-hexane (100 mL) maintained at 0 °C was dropped 1.6 M *n*-butyllithium in hexane (33.7 mL, 0.054 mol). After being stirred at room tempearture for 4 h, the mixture was cooled at −78 °C and a solution of 51 (1.50 g, 7.6 mmol) in THF (100 mL) was added. After 1.5 h the reaction was worked up as described for compound 88. To the crude product was added Et$_2$O, and the precipitated white solid was collected by filtration to give 89 (1.38 g, 43%). ^{1}H NMR (CDCl$_3$) δ 0.22 (s, 6H, Si(CH$_3$)$_2$), 0.98 (s, 9H, C(CH$_3$)$_3$), 1.10 (s, 3H, CH$_3$), 3.55 (m, 1H, C*H*HOH) 3.80 (m, 1H, CH*H*OH), 6.82 (m, 2H, Ar), 7.38 (m, 2H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-pyridyl)-7a-methylperhydroinden-3a-ol (90), (1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-pyridyl)-7a-methylperhydroinden-3a-ol (91), (1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(3-*tert*-butyldimethylsilyloxyphenyl)-7a-methylperhydroinden-3a-ol (92), and (1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-*tert*-butyldimethylsilyloxyphenyl)-7a-methylperhydroinden-3a-ol (93). The appropriate starting material was dissolved in EtOH, and Raney-Ni (1:10, w/w) was added. After being stirred at reflux for 8 h, the mixture was filtered through a Celite pad and the solvent evaporated to dryness. The crude products were purified by flash chromatography (CHCl$_3$/MeOH, 95:5) to give 90 (0.18 g, 23%) as a white foam; (CHCl$_3$/MeOH/26%w/v aqueous NH$_3$, 95:5:0.5) to give 91 (0.03 g, 5%) as a white foam; (cyclohexane/EtOAc, 7:3) to give 92 (0.84 g, 66%) as a white foam; (CHCl$_3$/Et$_2$O, 7:3) to give 93 (0.66 g, 53%) as a white foam. 90: ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.74 (m, 1H, CHPy), 3.54 (dd, 1H, C*H*HOH), 3.80 (d, 1H, CH*H*OH), 7.25 (m, 1H, Py), 7.58 (m, 1H, Py), 8.45 (m, 2H, Py). 91: ^{1}H NMR (CDCl$_3$) δ 1.12 (s, 3H, CH$_3$), 2.70 (m, 1H, CHPy), 3.55 (m, 1H, C*H*HOH), 3.80 (m, 1H, CH*H*OH), 7.12 (m, 2H, Py), 8.50 (m, 2H, Py). 92: ^{1}H NMR (CDCl$_3$) δ 0.22 (s, 6H, Si(CH$_3$)$_2$), 1.00 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.68 (m, 1H, CHAr), 3.53 (dd, 1H, C*H*HOH) 3.81 (dd, 1H, CH*H*OH), 6.65–7.20 (m, 4H, Ar). 93: ^{1}H NMR (CDCl$_3$) δ 0.22 (s, 6H, Si(CH$_3$)$_2$), 0.98 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.68 (m, 1H, CHAr), 3.53 (m, 1H, C*H*HOH) 3.80 (m, 1H, CH*H*OH), 6.78 (m, 2H, Ar), 7.08 (m, 2H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-5-(3-Pyridyl)-3a-hydroxy-7a-methyl-perhydroindene-1-carboxaldehyde (94). To solution of 90 (0.18 g, 0.69 mmol) in DMSO (2 mL) was added IBX (0.29 g, 1.03 mmol). After the mixture was stirred for 1 h, the aldehyde solution was directly dropped into the appropriate buffered solution at pH 4.5 containing the aminoalkoxyamine.

(1*S*,3a*S*,5*S*,7a*R*)-5-(4-Pyridyl)-3a-hydroxy-7a-methyl-perhydroindene-1-carboxaldehyde (95). To solution of 91 (0.030 g, 0.1 mmol) in THF (2 mL) was added IBX (0.042 g, 0.15 mmol). The mixture was heated at reflux for 1.5 h. After cooling to room temperature, the aldehyde solution was directly dropped into the appropriate buffered solution at pH 4.5 containing the aminoalkoxyamine.

(1*S*,3a*S*,5*S*,7a*R*)-5-(3-*tert*-Butyldimethylsilyloxyphenyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxalde-hyde (96) and (1*S*,3a*S*,5*S*,7a*R*)-5-(4-*tert*-Butyldimethyl-silyloxyphenyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (97). Prepared as described for compound 73 to give 96 (100%) and 97 (100%) as oils. The crude products were used in the next step without further purification. 96: ^{1}H NMR (CDCl$_3$) δ 0.21 (s, 6H, Si(CH$_3$)$_2$), 1.00 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.45 (m, 1H, C*H*CHO), 2.70 (m, 1H, CHAr), 6.70–7.20 (m, 4H, Ar), 9.78 (d, 1H, CHO). 97: ^{1}H NMR (CDCl$_3$) δ 0.20 (s, 6H, Si(CH$_3$)$_2$), 1.00 (s, 9H, C(CH$_3$)$_3$), 1.12 (s, 3H, CH$_3$), 2.45 (m, 1H, C*H*CHO), 2.70 (m, 1H, CHAr), 6.78 (m, 2H, Ar), 7.08 (m, 2H, Ar), 9.78 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-hydroxyphenyl)-7a-methylperhydroinden-3a-ol (98). A solution of 93 (0.50 g, 1.3 mmol) in dioxane (10 mL) and water (5 mL) was brought to pH 0.9 with 3 N HCl. After being stirred for 16 h, the mixture was brought to pH 5 with 5% aqueous Na$_2$HPO$_4$ solution, dioxane was evaporated, and the aqueous phase was extracted with EtOAc. The organic phase was dried over Na$_2$SO$_4$ and evaporated to dryness to give 98 (0.24 g, 67%) as a white foam. ^{1}H NMR (CD$_3$OD) δ 1.10 (s, 3H, CH$_3$), 2.65 (m, 1H, CHAr), 3.45 (dd, 1H, C*H*HOH), 3.70 (dd, 1H, CH*H*OH), 6.71 (m, 2H, Ar), 7.05 (m, 2H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-[4-(2-dimethylamino-ethoxy)phenyl]-7a-methylperhydroinden-3a-ol (99). A mixture of 98 (0.24 g, 0.87 mmol), silver carbonate (0.48 g, 1.74 mmol), and 1-chloro-2-dimethylaminoethane (4 mL) was stirred at 50 °C in the dark for 6 h. After cooling at room temperature, the mixture was filtered through a Celite pad and the pad was washed with toluene/MeOH, 9:1. The organic solvent was evaporated, and the crude product was purified by flash chromatography (CHCl$_3$/MeOH, 9:1, CHCl$_3$/MeOH/

26% w/v aqueous NH$_3$, 9:1:0.1) to give **99** (0.13 g, 43%) as an oil. ^{1}H NMR (CDCl$_3$) δ 1.10 (s, 3H, CH$_3$), 2.35 (s, 6H, N(CH$_3$)$_2$), 2.65 (m, 1H, CHAr), 2.75 (t, 2H, CH$_2$N), 3.50 (dd, 1H, C*H*HOH), 3.75 (dd, 1H, CH*H*OH), 4.05 (t, 2H, CH$_2$O), 6.71 (m, 2H, Ar), 7.05 (m, 2H, Ar).

(1*S*,3a*S*,5*S*,7a*R*)-5-[4-(2-Dimethylaminoethoxy)phenyl]-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (100). To a solution of **99** (0.18 g, 0.51 mmol) in THF (3.5 mL) was added IBX (0.30 g, 1.1 mmol). After being stirred at reflux for 1 h, the mixture was cooled to room temperature, diluted with CHCl$_3$, and filtered trough a Celite pad, washing with THF. The organic solvent was evaporated to give **100** (0.21 g, 100%) as an oil. The crude product contained an equimolar amount of *o*-iodoso benzoic acid and was used in the next step without further purification. ^{1}H NMR (CD$_3$OD) δ 1.10 (s, 3H, CH$_3$), 2.70 (m, 1H, CHAr), 2.90 (s, 6H, N(CH$_3$)$_2$), 3.50 (t, 2H, CH$_2$N), 4.30 (t, 2H, CH$_2$O), 6.90 (m, 2H, Ar), 7.20 (m, 2H, Ar), 9.68 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Vinyl-5-cyclohexyl-7a-methylperhydroindene-3a-ol (101). The following were added in order to a solution of **75** (1.93 g, 7.0 mmol) in dry THF (96.5 mL): methyltriphenylphosphonium bromide (4.64 g, 0.01 mol), *tert*-butyl alcohol (0.16 mL, 0.001 mol), and potassium *tert*-butoxide (1.63 g, 0.01 mol). After being stirred at room tempearature for 40 min, the mixture was diluted with 5% aqueous NaH$_2$PO$_4$ solution and extracted with Et$_2$O (3×). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/EtOAc, 95:5) to give **101** (0.88 g, 45%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.86 (s, 3H, CH$_3$), 4.84 (m, 2H, =CH$_2$), 5.99 (m, 1H, =CH).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxyethyl-5-cyclohexyl-7a-methylperhydroinden-3a-ol (102). Prepared as described for compound **49** using the following amounts of reagents: 1 M BH$_3$ solution in THF (4.4 mL, 3.4 mmol), **100** (0.88 g, 3.0 mmol) in THF (22 mL), water (4 mL, 0.39 mol), sodium perborate (0.92 g, 5.0 mmol), and 4 N NaOH (1.4 mL, 5.0 mmol) to give **102** (0.88 g, 45%) as a white foam. The crude product was used in the next step without purification. ^{1}H NMR (CDCl$_3$) δ 0.92 (s, 3H, CH$_3$), 3.50−3.75 (m, 2H, CH$_2$O).

(1*R*,3a*S*,5*S*,7a*R*)-5-Cyclohexyl-α,3a-oxide-7a-methylperhydroindene-1-ethanol (103). To a solution of **102** (0.89 g, 3 mmol) in DMSO (7.7 mL) was added IBX (1.06 g, 3.7 mmol) over 1 h. When **102** disappeared (NMR), the reaction mixture was directly dropped into the appropriate buffered solution at pH 4.5 containing the aminoalkoxyamine. ^{1}H NMR (DMSO-*d*$_6$) δ 0.93 (s, 3H, CH$_3$), 5.00 (m, 1H, CHOH), 5.90 (d, 1H, OH).

Methyl (1*R*,3a*S*,5*S*,7a*R*)-5-Cyclohexyl-3a-hydroxy-7a-methylperhydroindene-1-yl-(*E*)-acrylate (104). To a suspension of NaH (55% dispersion in mineral oil) (1.04 g, 0.024 mol) in dry THF, maintained at 0 °C under nitrogen, was dropped trimethyl phosphonoacetate (3.89 mL, 0.027 mol).

After the mixture was stirred for 1 h, a solution of **75** (3.00 g, 0.011 mol) in THF (30 mL) was added. After the mixture was stirred for 2 h at room temperature, 5% aqueous NaH$_2$PO$_4$ was added and the mixture was extracted with EtOAc (3×). The combined organic layers were dried on Na$_2$SO$_4$ and evaporated to dryness to give **104** (3.50 g, 100%) as an oil. The crude product was used in the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 0.85 (s, 3H, CH$_3$), 2.33 (m, 1H, C*H*CH=), 3.72 (s, 3H, OCH$_3$), 5.63 (d, 1H, *J* = 16.0, =CHCO), 7.14 (dd, 1H, *J* = 10.0, 16.0, CHC*H*=).

(1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-Acrylaldehyde-5-cyclohexyl-7a-methylperhydroindene-3a-ol (105). To a solution of **104** (4.8 g, 0.015 mol) in dry THF (0.218 L) maintained at −78 °C, under nitrogen, was dropped 1 M DIBAH in THF (77 mL, 0.077mol). The mixture was allowed to warm to −20 °C, and DIBAH (33 mL) was added. After being stirred at room temperature for 16 h, the mixture was cooled to 0 °C, a solution of citric acid (34.6 g, 0.18 mol) in water (0.3 L) was slowy added, and the mixture was diluted with Et$_2$O. The jelly-like suspension was stirred for 1 h and extracted with EtOAc. The organic phase was washed with 5% aqueous Na$_2$HPO$_4$, dried

over Na$_2$SO$_4$, and evaporated to dryness to give (1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-allyl alcohol-5-cyclohexyl-7a-methylperhydroindene-3a-ol (3.4 g) as an oil. The crude product was used in the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 0.84 (s, 3H, CH$_3$), 2.33 (m, 1H, C*H*CH=), 4.11 (d, 2H, CH$_2$O), 5.48 (dt, 1H, C*H*CH$_2$OH), 5.89 (dd, 1H, CHC*H*=).

To a solution of (1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-allyl alcohol-5-cyclohexyl-7a-methylperhydroindene-3a-ol (3.4 g, 9.7 mmol) in dioxane (100 mL), maintained at 0−5 °C, was added MnO$_2$ (20.4 g, 0.23 mol). After being stirred for 3 h at room temperature, the mixture was filtered through a Celite pad. The filtrate was washed with acetone and the organic solvent evaporated to dryness to give **105** (3.19 g, 96% from **75**). ^{1}H NMR (CDCl$_3$) δ 0.86 (s, 3H, CH$_3$), 2.49 (m, 1H, C*H*CH=), 5.92 (dd, 1H, *J* = 8.1, C*H*CH=O) 7.09 (dd, 1H, *J* = 10.0, CHC*H*=), 9.49 (d, 1H, *J* = 8.0, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Propionaldehyde-5-cyclohexyl-7a-methylperhydroindene-3a-ol (106). A mixture of **105** (1.0 g, 3.4 mmol) and 5% Pd/C (0.3 g) in EtOH (0.2 L) was hydrogenated at room temperature for 3 h. After this time the catalyst was filtered through a Celite pad and washed with EtOH, and the organic solvent evaporated to give **106** (0.96 g, 97%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.94 (s, 3H, CH$_3$), 2.20−2.60 (m, 2H, C*H*$_2$CHO), 9.76 (t, 1H, CHO).

Ethyl (1*R*,3a*S*,5*S*,7a*R*)-5-Cyclohexyl-3a-hydroxy-7a-methylperhydroinden-1-yl-(*E*)-metacrylate (107). Prepared as described for compound **104** using the following amounts of reagents: 55% (dispersion in mineral oil) NaH (0.54 g, 0.01 mol), THF (45 mL), and triethyl 2-phosphonopropionate (3.21 mL, 0.01 mol). After the mixture was stirred at room temperature for 0.5 h and cooled to 0 °C, the aldehyde was added. At the end **107** was obtained (3.29 g). The crude product was used in the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 0.81 (s, 3H, CH$_3$), 1.28 (t, 3H, CH$_2$C*H*$_3$), 1.79 (d, 3H, =CCH$_3$), 2.63 (m, 1H, C*H*CH=), 4.17 (m, 2H, OCH$_2$), 6.92 (br d, 1H, CH=).

(1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-Metacrylaldehyde-5-cyclohexyl-7a-methylperhydroindene-3a-ol (108). To a solution of **107** (2.22 g) in dry THF (50 mL) maintained at −78 °C, under nitrogen, was dropped 1 M DIBAH in THF (44 mL, 0.044 mol), in three portions, every hour from the start of the reaction. After 16 h at room temperature, the mixture was cooled at 0 °C and 1 N H$_2$SO$_4$ (90.26 mL) was added. The jelly-like suspension was stirred for 1 h and extracted with EtOAc. The organic phase was dried over Na$_2$SO$_4$ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/EtOAc, 7:3) to give (1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-allyl alcohol-5-cyclohexyl-7a,α-dimethylperhydroindene-3a-ol (0.89 g, 30% from **75**) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.83 (s, 3H, CH$_3$), 1.68 (d, 3H, =CCH$_3$), 2.55 (m, 1H, C*H*CH=), 4.03 (br s, 2H, CH$_2$OH), 5.59 (br d, 1H, CH=).

Compound **108** (0.85 g, 100%) was prepared as described for compound **106** using the following amounts of reagents: (1*R*,3a*S*,5*S*,7a*R*)-1-(*E*)-allyl alcohol-5-cyclohexyl-7a,α-dimethylperhydroindene-3a-ol (0.89 g, 2.0 mmol), MnO$_2$ (6.09 g, 0.07 mol), dioxane (23 mL). ^{1}H NMR (CDCl$_3$) δ 0.86 (s, 3H, CH$_3$), 1.72 (d, 3H, =CCH$_3$), 2.82 (m, 1H, C*H*=CH), 6.79 (dq, 1H, CH=), 9.41 (s, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Hydroxymethyl-5-(4-*cis*-*tert*-butyldimethylsilyloxycyclohexyl)-7a-methylperhydroindene-3a-ol (109). Prepared as described for compound **74** starting from **93** (5.00 g, 0.013 mol), 5% Rh on alumina (7.14 g) in MeOH (100 mL), in a Parr apparatus for 24 h. The crude product was purified by flash chromatography (CH$_2$Cl$_2$/2-propanol, 96:4) to give **109** (2.53 g, 50%) as a white foam. ^{1}H NMR (CDCl$_3$) δ 0.03 (s, 6H, Si(CH$_3$)$_2$), 0.91 (s, 9H, C(CH$_3$)$_3$), 0.99 (s, 3H, CH$_3$), 3.48 (dd, 1H, CH*H*OH), 3.77 (dd, 1H, CH*H*OH), 3.92 (m, 1H, $W_{1/2h}$ = 10 Hz, TBDMSOCH).

(1*S*,3a*S*,5*S*,7a*R*)-5-(4-*cis*-*tert*-Butyldimethylsilyloxycyclohexyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (110). Prepared as described for compound **73** starting from compound **109** (0.72 g, 2.0 mmol) to give **110** (0.70 g, 100%) as an oil. The crude product was used in the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 0.05

(s, 6H, Si(CH₃)₂), 0.92 (s, 9H, C(CH₃)₃), 1.00 (s, 3H, CH₃), 3.92 (m, 1H, TBDMSOCH), 9.73 (d, 1H, CHO).

(1*S*,3a*S*,5*S*,7a*R*)-1-Acetoxymethyl-5-(4-*cis*-*tert*-butyldimethylsilyloxycyclohexyl-7a-methylperhydroindene-3a-ol (111). To a solution of **109** (1.48 g, 3 mmol) in pyridine (4 mL) were added DMAP (8 mg) and acetic anhydride (0.4 mL, 4 mmol). After being stirred for 16 h at room temperature, the mixture was diluted with 5% aqueous NaH₂PO₄ and extracted with chloroform. The organic phase was dried over Na₂SO₄ and evaporated to dryness to give **111** (1.60 g, 100%) as a white foam. ¹H NMR (CDCl₃) δ 0.05 (s, 6H, Si(CH₃)₂), 0.90 (s, 9H, C(CH₃)₃), 0.96 (s, 3H, CH₃), 2.08 (s, 3H, OAc), 3.92 (m, 1H, $W_{1/2h}$ = 10 Hz, TBDMSOCH), 4.06 (dd, 1H, C*H*HOAc), 4.22 (dd, 1H, CH*H*OAc).

(1*S*,3a*S*,5*S*,7a*R*)-1-Acetoxymethyl-5-(4-oxo-1-cyclohexyl)-7a-methylperhydroindene-3a-ol (112). A solution of **111** (1.60 g, 3.0 mmol) in a 2/1 dioxane/water solution (24 mL) was brought to pH 1 with 3 N HCl. After being stirred for 1.5 h at room temperature, the mixture was neutralized with 5% Na₂HPO₄ and extracted with EtOAc. The organic phase was dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by flash chromatography (*n*-hexane/chloroform/acetone, 6:2:2) to give (1*S*,3a*S*,5*S*,7a*R*)-1-acetoxymethyl-5-(4-cis-hydroxy-1-cyclohexyl)-7a-methylperhydroindene-3a-ol (0.68 g, 58%) as a white foam. ¹H NMR (CDCl₃) δ 0.95 (s, 3H, CH₃), 2.08 (s, 3H, OAc), 3.98 (m, 1H, C*H*OH), 4.06 (dd, 1H, C*H*HOAc), 4.22 (dd, 1H, CH*H*OAc). ¹³C NMR (CDCl₃) δ 14.4 (q), 21.1 (q), 23.9 (t), 24.1 (t), 24.3 (t), 25.2 (t), 32.6 (t), 32.7 (t), 35.8 (t), 36.9 (t), 39.5 (d), 39.9 (t), 41.8 (d), 46.2 (s), 48.1 (d), 66.7 (d), 67.8 (t), 82.9 (s), 170.9 (s).

To a solution of the above-described alcohol (0.68 g, 2.0 mmol) in THF (20 mL) was added IBX (0.704 g, 2.5 mmol), and the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and filtered on a Celite pad. The organic solvent was evaporated to dryness to give **112** (0.68 g, 100%) as a glassy solid. ¹H NMR (CDCl₃) δ 0.98 (s, 3H, CH₃), 2.08 (s, 3H, OAc), 4.08 (dd, 1H, C*H*HOAc), 4.22 (dd, 1H, CH*H*OAc).

(1*S*,3a*S*,5*S*,7a*R*)-1-Acetoxymethyl-5-(4-trans-hydroxy-1-cyclohexyl)-7a-methylperhydroindene-3a-ol (113). To a solution of **112** (0.68 g, 2.0 mmol) in THF (40 mL) maintained at −78 °C, under nitrogen was dropped a solution of LiAlH(O*t*But)₃ (1.08 g, 4.0 mmol) in THF (40 mL). After the mixture was stirred for 3 h at −78 °C, a solution of LiAlH(O*t*But)₃ (0.54 g, 2.0 mmol) in THF (20 mL) was added, and the mixture was allowed to warm to room temperature over 1 h. Acetic acid was added (2.16 mL), and the mixture was diluted with brine and extracted with EtOAc. The organic phase was dried over Na₂SO₄ and evaporated to dryness to give **113** (0.68 g, 100%) as a glassy oil, containing 10% of the isomer *cis*-alcohol. ¹H NMR (CDCl₃) δ 0.95 (s, 3H, CH₃), 2.08 (s, 3H, OAc), 3.54 (m, 1H, $W_{1/2h}$ = 21 Hz, C*H*OH), 4.07 (dd, 1H, C*H*HOAc), 4.22 (dd, 1H, CH*H*OAc). ¹³C NMR (CDCl₃) δ 14.4 (q), 21.1 (q), 24.3 (t), 25.3 (t), 28.2 (t), 28.3 (t), 35.7 (t), 35.7 (t), 35.7 (t), 36.9 (t), 39.9 (t), 40.1 (d), 41.8 (d), 46.2 (s), 48.0 (d), 66.7 (d), 71.2 (d), 82.9 (s), 170.9 (t).

(1*S*,3a*S*,5*S*,7a*R*)-1-Acetoxymethyl-5-(4-trans-*tert*-butyldimethylsilyloxy-1-cyclohexyl)-7a-methylperhydroindene-3a-ol (114). To a solution of **113** (0.68 g, 2.0 mmol) in DMF (8 mL) were added imidazole (0.64 g, 8.0 mmol) and *tert*-butyldimethylsilyl chloride (0.56 g, 3.0 mmol). After being stirred for 3 h, the mixture was diluted with 5% aqueous NaHCO₃ and extracted with EtOAc. The organic phase was dried over Na₂SO₄ and evaporated to dryness to give **114**. The crude product, containing *tert*-butyldimethylsilanol, was used directly in the next step without further purification.

(1*S*,3a*S*,5*S*,7a*R*)-5-(4-*trans*-*tert*-Butyldimethylsilyloxy-1-cyclohexyl)-3a-hydroxy-7a-methylperhydroindene-1-carboxaldehyde (115). The crude product **114** was dissolved in MeOH (20 mL) and stirred for 2 h at room temperature with 10% aqueous K₂CO₃. After this time the mixture was diluted with 5% aqueous NaH₂PO₄ and extracted with EtOAc. The organic phase was dried over Na₂SO₄ and evaporated to dryness to give (1*S*,3a*S*,5*S*,7a*R*)-1-hydroxymethyl-5-(4-trans-

tert-butyldimethylsilyloxy-1-cyclohexyl)-7a-methylperhydroindene-3a-ol (0.80 g, 100% from **113**) as a white foam. ¹H NMR (CDCl₃) δ 0.05 (s, 6H, Si(CH₃)₂), 0.89 (s, 9H, C(CH₃)₃), 1.00 (s, 3H, CH₃), 3.47 (m, 1H, TBDMSOCH), 3.50 (dd, 1H, C*H*HOH), 3.78 (dd, 1H, CH*H*OH).

Compound **115** was oxidized, in quantitative yield, as described for compound **112** starting from the above-described 1-hydroxymethyl derivative (0.80 g, 2.0 mmol) and IBX (0.68 g, 2.0 mmol) in THF (16 mL). ¹H NMR (CDCl₃) δ 0.05 (s, 6H, Si(CH₃)₂), 0.89 (s, 9H, C(CH₃)₃), 1.01 (s, 3H, CH₃), 3.48 (m, 1H, TBDMSOCH), 9.72 (d, 1H, CHO).

Biology. Na⁺,K⁺-ATPase Binding. The affinity for the receptor site of Na⁺,K⁺-ATPase was evaluated by the displacement of the specific [³H]ouabain binding from Na⁺,K⁺-ATPase receptor[24] isolated from dog kidney purified according to Jørgensen.[25] The IC₅₀ values (concentration that inhibits ouabain binding by 50%) represent the means of values determined in two to three separate experiments in duplicate and were calculated using a nonlinear least-squares fitting algorithm.

Inotropic Activity in Guinea Pig Atria. Isolated guinea pig left atria (from 300 to 500 g male animals) were placed in 20 mL organ baths containing a solution of the following composition (mM): NaCl 131.6, KCl 5.6, CaCl₂ 1.8, NaH₂PO₄ 1.036, NaHCO₃ 24.99, glucose 11, sucrose 13; under 500 mg resting tension, at 32 °C. The solution was continuously bubbled with a mixture of 95% O₂ and 5% CO₂. The preparations were stimulated by platinum electrodes by square-wave pulses at a frequency of 1 Hz (1 ms duration, voltage twice the treshold). After a 60 min equilibration period, cumulative concentrations of the compounds were added, each concentration being left in contact until the maximal response or arrhythmias were observed.

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