

Diastereoselective reduction of cyclic bioactive Mannich ketones

Tamás Lóránd,^{a*} Erzsébet Ósz,^a Gyula Kispál,^a Gergely Nagy,^b Edgar Weckert,^c Daniel Luebbert,^c Alke Meents,^c Béla Kocsis,^d and László Prókai^e

^a Department of Biochemistry and Medical Chemistry, Faculty of Medicine, University Pécs, H-7601 Pécs, P.O.Box 99, Hungary

^b Department of Immunology and Biotechnology, Faculty of Medicine, University Pécs, H-7601 Pécs, P.O.Box 99, Hungary

^c HASYLAB at DESY Notkestr. 85, D-22607 Hamburg, Germany¹,

^d Department of Medical Microbiology and Immunology, Faculty of Medicine, University Pécs, H-7601 Pécs, P.O.Box 99, Hungary

^e Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL 32610-0485

E-mail: tamas.lorand@aok.pte.hu

Dedicated to Professor Sándor Antus on his 60th birthday

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Abstract

The reduction of cyclic Mannich ketones having antibacterial activity showed poor stereoselectivity with *L-Selectride*[®], sodium trimethoxyborohydride and diisobutylaluminium hydride, while lithium aluminium hydride and, in particular, sodium borohydride often yielded a single stereoisomer. The size of the ring strongly influenced the stereocomposition of the reaction mixtures. An increased preference for the *trans* isomer was attributed to a weak intramolecular hydrogen bond between the OH and the N, as demonstrated by X-ray crystallography. After reduction, the antibacterial activity of the product decreased dramatically (“S-form”) but was not completely abolished in deep rough mutants of Gram-negative bacteria.

Keywords: Reduction, molecular modelling, X-ray crystallography, NMR spectroscopy, deep rough (Re) mutants.

Introduction

Studies on the mechanism of action for biologically active compounds often have been complex endeavours, with synthetic organic and medicinal chemistry often playing a crucial role in providing invaluable insight into the intricate and previously unrecognised details. Previously we reported the synthesis of some Mannich ketones of 2-arylidencycloalkanones¹ **1-9** (Scheme 1).

Similar derivatives of fused bicyclic ketones such as 1-indanones and 1-tetralones **10-11** also were prepared² (Scheme 1). The majority of these compounds showed antibacterial activity both against standard Gram-positive (*Staphylococcus saprophyticus*, *S. aureus*, *Micrococcus luteus*, *Bacillus subtilis*) and a Gram-negative strain such as *Escherichia coli*. Such compounds have been considered thiol alkylators because under physiological conditions they give reactive methylene ketones (by 1,2-elimination) that can undergo addition reactions with thiol enzymes.³



Comp.	n	R	Ar
1	1	Pip	Ph
2	1	Pip	4'-OCH ₃ -C ₆ H ₄
3	2	Mor	Ph
4	2	Pyr	Ph
5	2	4-Pip	Ph
6	3	Mor	Ph
7	3	Pip	Ph
8	4	Mor	Ph
9	4	Pip	Ph
10	1	Mor	Ph
11	2	Pyr	Ph

Pip: 1-Piperidinyl;

Mor: 4-Morpholinyl;

Pyr: 1-Pyrrolidinyl;

4-Pip: 4-methyl-1-piperidyl.

Scheme 1

Our previous examinations suggested however that the thiol depletion cannot be the only reason for the antibacterial activity.^{1,2} We showed that some compounds were highly active against bacteria, but caused no thiol depletion, others were not active although the free thiol pool decreased significantly when the compounds were administered at the minimum inhibitory concentration (MIC).

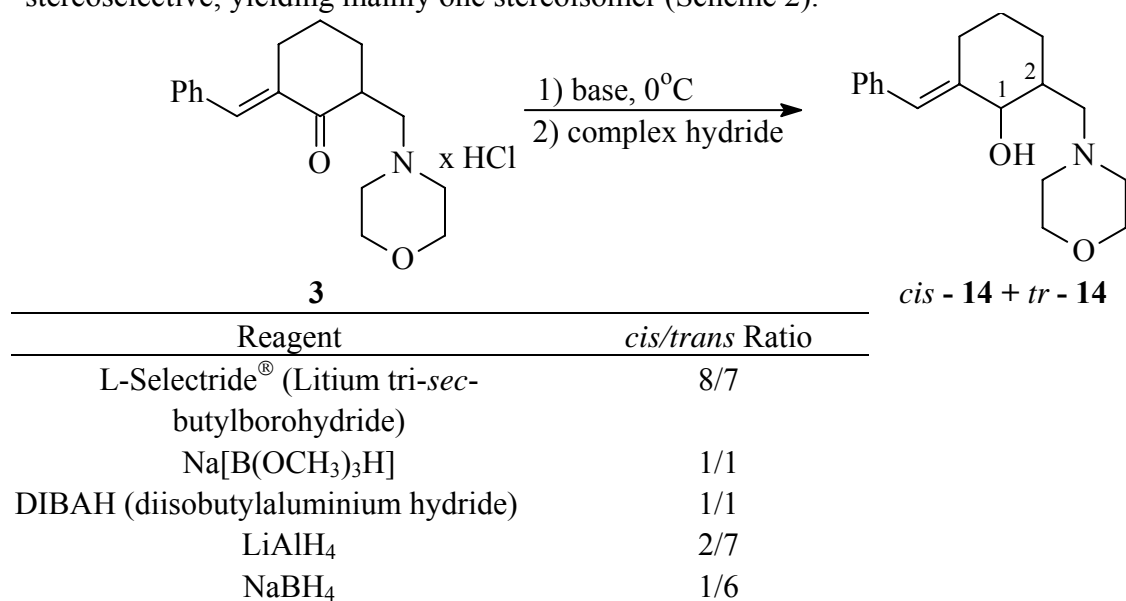
In order to investigate the importance of thiol reactivity in the mechanism of action, we prepared the corresponding amino alcohols from the Mannich ketones mentioned above. Unlike the Mannich ketones, the amino alcohols cannot yield very reactive methylene ketones.

First, we wanted to investigate the stereoselectivity of the reduction using different complex metal hydrides with organic groups. Sodium borohydride is a generally more selective

agent for preparing allylic alcohols than lithium aluminium hydride.⁴ The hydride reduction of α,β -unsaturated Mannich ketones may, however, afford 1,2- or 1,4-addition products. We also aimed at studying the stereocomposition of reduction products depending on the structure of the substrate (size of the ketone ring and the nature of the amine substituent). The starting materials for the reductions were selected as both effective antibacterial agents and less effective ones (*cf.* **1**, **3**, **10** and **6-9**). We also planned to analyse the effect of reduction on the antibacterial activity of our Mannich ketones. The antibacterial activity and the thiol depletion were examined in two *E. coli* strains, in an "S" type (*ATCC 25292*) and in a Re mutant one which has a defective cell wall biosynthesis. The Re mutants are therefore more permeable to some externally added chemicals.

Results and Discussion

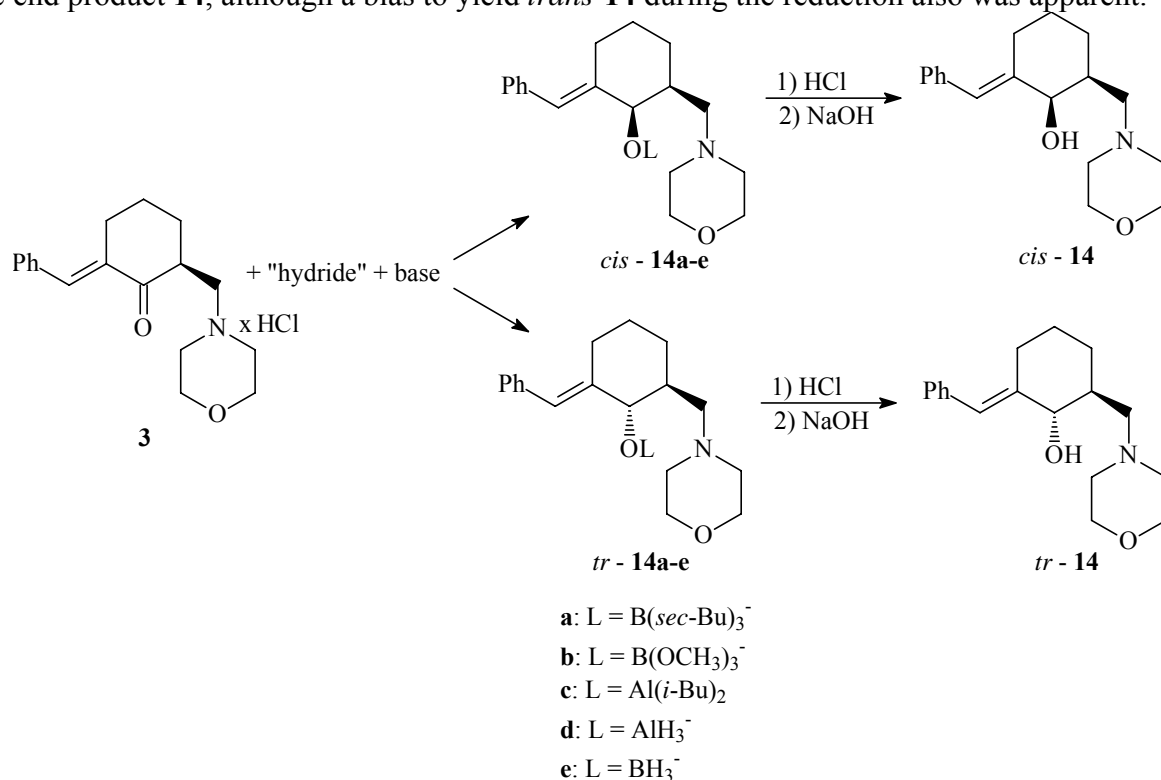
In order to investigate the influence of the reducing agent on the stereocomposition, we explored the reduction of **3** with different complex metal hydrides. These reactions started from the Mannich base liberated from the corresponding hydrochloride **3** under mild conditions (Scheme 2). The complex hydrides applied for the reduction of **3** can be divided into two groups. The first one (*L-Selectride*[®], sodium trimethoxyborohydride, diisobutylaluminium hydride) represents reducing agents showing poor stereoselectivity, while the hydrides of the other group, such as lithium aluminium hydride, produced stereoselective reductions affording the *trans* isomer as a major isomer. In particular, reduction performed with sodium borohydride proved to be rather stereoselective, yielding mainly one stereoisomer (Scheme 2).



Scheme 2

We hypothesized that the relative thermodynamic stability of the respective hydride adducts (*cis*-**14a-e** and *trans*-**14a-e**) should explain the observed selectivity of the metal-hydride

reduction of the Mannich base chosen. To prove this hypothesis, semi-empirical (PM5) quantum chemical calculations were performed to obtain heats of formation (ΔH_f°) for the hydride adducts (Scheme 3). As shown in Table 1, the relative stabilities of the isomeric *cis*-**14a–e** and *trans*-**14a–e** (expressed as $\Delta H_f^\circ_{cis} - \Delta H_f^\circ_{trans}$) correlated well with the observed stereocomposition of the end product **14**, although a bias to yield *trans*-**14** during the reduction also was apparent.



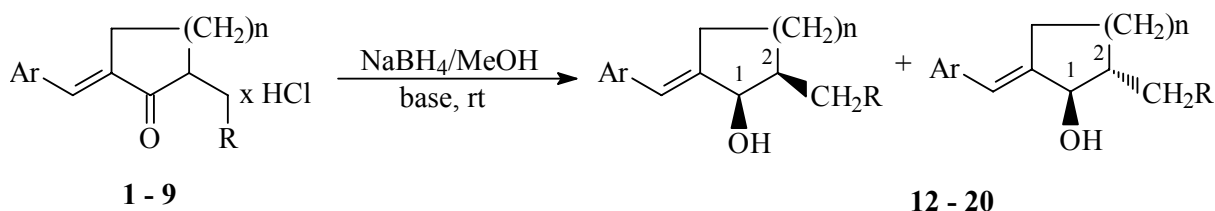
Scheme 3

Table 1. Calculated heats of formation (kcal/mol; by PM5 semi-empirical quantum chemical method) of the intermediates (**14a–14e**)

Compound	ΔH_f° (kcal/mol)	$\Delta(\Delta H_f^\circ_{cis-trans})^a$ (kcal/mol)	<i>trans/cis</i> Ratio in the end-product (14)
<i>cis</i> - 14a	-189.2	-3.4	0.9
<i>trans</i> - 14a	-185.8		
<i>cis</i> - 14b	-347.0	-1.2	1.0
<i>trans</i> - 14b	-345.8		
<i>cis</i> - 14c	-143.7	-0.1	1.0
<i>trans</i> - 14c	-143.6		
<i>cis</i> - 14d	-119.4	0.7	3.5
<i>trans</i> - 14d	-120.1		
<i>cis</i> - 14e	-118.5	2	6.1
<i>trans</i> - 14e	-120.5		

^a $\Delta H_f^\circ_{cis} - \Delta H_f^\circ_{trans}$

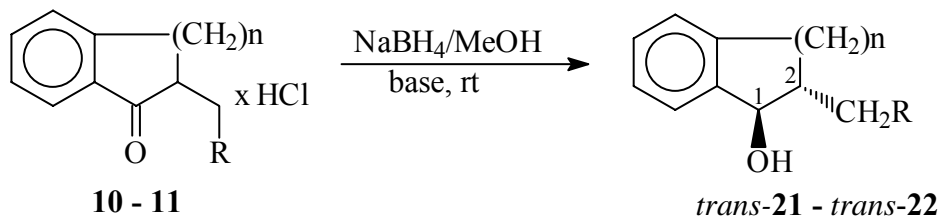
Because of its propensity to produce the highest stereoselectivity based on the preliminary experiments, sodium borohydride was chosen as the reducing agent to study the influence of the substrate on the stereocomposition of the reaction mixture. The reductions were performed in methanolic solutions at room temperature. In all of the starting unsaturated Mannich ketones the configuration was *E* around the C=C bond. From the hydrochlorides of the Mannich ketones (**1-9** and **10-11**) the bases were liberated with equivalent NaOH at 0 °C and they were treated with NaBH₄ (Schemes 4-5).



Comp.	n	R	Ar	Conf.	Cis/trans ratio	Yield (%)	
						<i>cis</i>	<i>trans</i>
<i>trans</i> - 12	1	Pip	Ph	<i>trans</i>	0:100	-	87
<i>trans</i> - 13	1	Pip	4-OCH ₃ -C ₆ H ₄	<i>trans</i>	0:100	-	67
<i>cis</i> - 14	2	Mor	Ph	<i>cis</i>	14:86	12	-
<i>trans</i> - 14	2	Mor	Ph	<i>trans</i>	14:86	-	77
<i>trans</i> - 15 *	2	Pyr	Ph	<i>trans</i>	0:100	-	85
<i>trans</i> - 16	2	4-Pip	Ph	<i>trans</i>	0:100	-	76
<i>cis</i> - 17	3	Mor	Ph	<i>cis</i>	96:4	86	-
<i>trans</i> - 17 *	3	Mor	Ph	<i>trans</i>	96:4	-	-
<i>cis</i> - 18	3	Pip	Ph	<i>cis</i>	65:35	47	-
<i>trans</i> - 18	3	Pip	Ph	<i>trans</i>	65:35	-	25
<i>cis</i> - 19	4	Mor	Ph	<i>cis</i>	100:0	90	-
<i>cis</i> - 20	4	Pip	Ph	<i>cis</i>	100:0	93	-

*Not isolated in pure state

Scheme 4



Comp.	n	R	Conf.	Cis/trans ratio	Yield (%)
<i>trans</i> - 21	1	Mor	<i>trans</i>	0:100	90
<i>trans</i> - 22	2	Pyr	<i>trans</i>	0:100	79

Scheme 5

The composition of the reaction mixture was monitored by ^1H NMR spectroscopy. The diastereoisomers were separated by column chromatography when it was possible. The conversion was always 100 %. The size of the ring strongly influenced the stereocomposition of the reaction mixtures giving only the *trans* isomers with the five membered and only the *cis* with the eight membered rings. Probably, the *trans* diastereoisomer is stabilized by the intramolecular hydrogen bond between OH and the nitrogen atom.

Cis and *trans* indicate the orientation of bonds C1-H1 and C2-H2 as well as of bonds C1-H1 and C7(8)-H7(8) each to other in compounds **12-20** and **21-22**, respectively. The structure verification of our compounds was performed by FT-IR, ^1H -NMR, and ^{13}C -NMR spectroscopy (Fig. 1)** and, in the case of *trans*-**14**, by crystal structure analysis (Table 2).

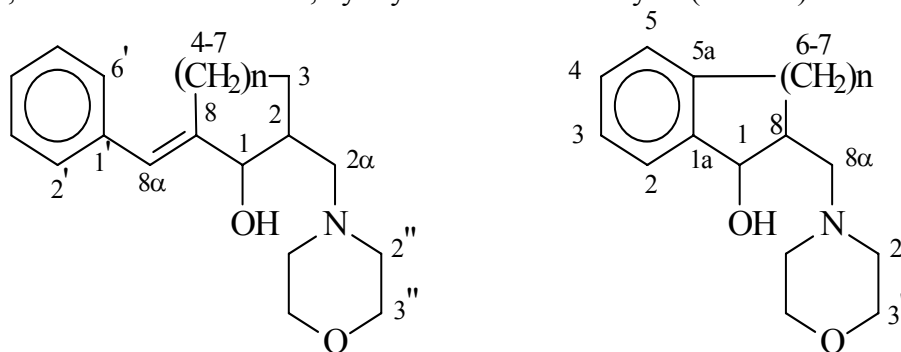


Figure 1. NMR numbering of selected compounds.

The molecule shows an intramolecular H-bond O2-H4...N1 with an H4-N1 distance of 1.955 Å and an angle of 151. All distances and angles are within the experimental errors in the expected range.⁵ The C1-C6 as well as the hetero 6-ring are in chair conformations. Ring C1-C6 is slightly distorted from the ideal conformation due to the sp^2 hybridisation of C1. The conformation about the C1-C7 double bond is *E* (*trans*). The interaction between the molecules in the crystal is only of the van der Waals type.

The new compounds were screened against some standard Gram-positive and Gram-negative strains, among them some Re deep rough mutants strains (Table 3). The reduction dramatically decreased the antibacterial activity of the original Mannich ketones both against the Gram-positive and -negative strains (e.g. **3** *S. aureus* MIC: $1.56 \mu\text{g mL}^{-1}$; *cis*-**14** MIC: $>200 \mu\text{g mL}^{-1}$).^{1,2} However, some of the compounds (*trans*-**13**, *cis*-**17**, *trans*-**18**, *trans*-**20**) showed slight activity to Gram-positive strains. With the deep mutant strains, some of the amino alcohols tested (*cis*-**14**, *trans*-**14**, *trans*-**16**, *cis*-**17**, *cis*-**19** and *cis*-**20**) showed moderate activity. The comparison of the antibacterial activity of Mannich ketones¹⁻² and the corresponding amino alcohols proves that the keto group is required for the biological effect in most of the compounds. The slightly increased polarity of the compounds cannot explain their diminished antibacterial activity. The decreased antibacterial effect of the amino alcohols can partly support the thiol alkylation as a mechanism

** The NMR numbering is shown on Fig. 1, displaying the morpholino derivative as an example. The numbering of the unsaturated and fused compounds differs from the IUPAC numbering given in the Experimental because of the better comparison of the data.

of action. However, the existing but weak antibacterial effect on *M. luteus* (*trans*-**13**, *cis*-**20**), *S. saprophyticus* (*cis*-**20**) and Re strains probably can be based on another mechanism of action.

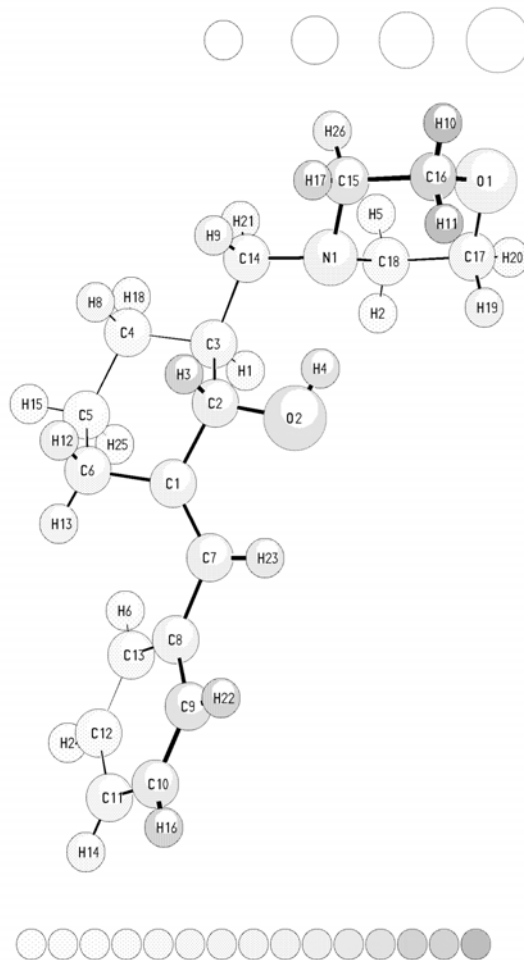


Figure 2. Projection of *trans*-**14** with anisotropic displacement ellipsoids (50% probability) for non-H atoms and an arbitrary small displacement parameter for H-atoms.¹³

A close relationship can be deduced from our data between the permeability and the antibacterial activity of our compounds. We determined the MIC values for “S” form *E. coli* ATCC 25292 and “Re” form *E. coli* ReD31m4, *Salmonella minnesota* Re595, *Shigella sonnei* Re4350. These Re deep rough mutants have modified outer membranes that are more permeable for some chemicals than the “S” form *E. coli* that has a complete outer membrane.⁶⁻⁸ Thus *cis*-**14**, *trans*-**14**, *cis*-**17**, *cis*-**19** and *cis*-**20**, that are only mildly active or non active to “S” form, can kill the Re mutant Gram-negative bacteria.

Table 2. Bond lengths (Å) and angles (°) for *trans*-**14**

C(1)-C(7)	1.3420(6)	O(2)-C(2)-C(3)	111.83(3)
C(1)-C(6)	1.5050(6)	C(1)-C(2)-C(3)	110.48(3)
C(1)-C(2)	1.5095(6)	C(18)-N(1)-C(15)	108.71(3)
O(2)-C(2)	1.4201(6)	C(18)-N(1)-C(14)	110.61(3)
C(2)-C(3)	1.5436(9)	C(15)-N(1)-C(14)	109.78(3)
N(1)-C(18)	1.4672(6)	C(14)-C(3)-C(4)	107.94(3)
N(1)-C(15)	1.4696(6)	C(14)-C(3)-C(2)	111.12(3)
N(1)-C(14)	1.4709(6)	C(4)-C(3)-C(2)	111.02(3)
C(3)-C(14)	1.5291(6)	C(16)-O(1)-C(17)	109.57(3)
C(3)-C(4)	1.5351(6)	C(13)-C(8)-C(9)	117.82(4)
O(1)-C(16)	1.4194(7)	C(13)-C(8)-C(7)	122.67(3)
O(1)-C(17)	1.4231(7)	C(9)-C(8)-C(7)	119.49(3)
C(8)-C(13)	1.3999(6)	N(1)-C(18)-C(17)	110.12(4)
C(8)-C(9)	1.4000(8)	C(1)-C(6)-C(5)	110.42(3)
C(8)-C(7)	1.4765(6)	C(12)-C(13)-C(8)	121.30(4)
C(18)-C(17)	1.5146(7)	C(1)-C(7)-C(8)	126.57(4)
C(6)-C(5)	1.5302(9)	N(1)-C(15)-C(16)	110.46(3)
C(13)-C(12)	1.3926(6)	O(1)-C(17)-C(18)	110.48(3)
C(15)-C(16)	1.5171(8)	C(4)-C(5)-C(6)	109.93(3)
C(5)-C(4)	1.5247(6)	N(1)-C(14)-C(3)	115.08(3)
C(12)-C(11)	1.3884(9)	C(11)-C(12)-C(13)	120.18(4)
C(11)-C(10)	1.3896(8)	C(12)-C(11)-C(10)	119.19(4)
C(9)-C(10)	1.3929(7)	C(5)-C(4)-C(3)	112.65(3)
C(7)-C(1)-C(6)	125.83(3)	O(1)-C(16)-C(15)	111.41(4)
C(7)-C(1)-C(2)	121.78(4)	C(10)-C(9)-C(8)	120.74(4)
C(6)-C(1)-C(2)	112.39(3)	C(11)-C(10)-C(9)	120.70(4)
O(2)-C(2)-C(1)	110.93(3)		

We also observed a relationship between hydrophobicity and the antibacterial effect. The more hydrophobic compounds: *trans*-**14**, *cis*-**17** and *cis*-**20** proved to be the more effective.

Although most of the compounds lost biological activity upon reduction (**3**/*cis*-**14**, **3**/*trans*-**14** from 6.25 to 200 $\mu\text{g mL}^{-1}$), we observed that some of them retained (**6**/*cis*-**17**) or even increased their activity (**9**/*cis*-**20** from 200 to 50 $\mu\text{g mL}^{-1}$).

Determination of the free intracellular thiol content of the “S” and Re mutant *E. coli* treated with these compounds at MIC concentration or at 200 $\mu\text{g mL}^{-1}$ revealed that reduction completely abolished the thiol reactivity (Figs. 3 and 4). This supported our idea, that in some of these compounds the antibacterial activity cannot be explained by a thiol alkylation.

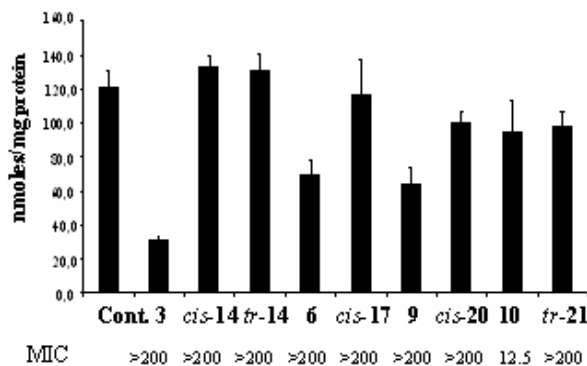


Figure 3. Thiol content in *E. coli* “S” form, the MIC values in $\mu\text{g mL}^{-1}$ are listed under the chart. (Cont.: control)

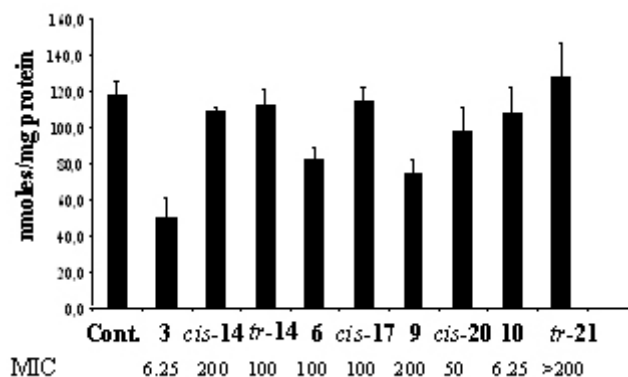


Figure 4. Thiol content in *E. coli* “Re” form, the MIC values in $\mu\text{g mL}^{-1}$ are listed under the chart. (Cont.: control)

Human cytotoxicity of our amino alcohols was evaluated against HeLa cell lines (Table 4). Similarly to the antibacterial effect, the cytotoxicity for most of the compounds diminished by the reduction, as demonstrated in the case of *trans*-13, *trans*-22, *cis*-14 and *cis*-20. On the contrary, the cytotoxicity of *cis*-17 increased and it is the most toxic in this series. It is worth mentioning that the *cis*-14 and *trans*-14 stereoisomers have very different IC_{50} values, but very similar antibacterial activity.

Table 3. Comparison of the in vitro antibacterial activity of the aminoalcohols (**12-22** in the first line, in italics) and starting Mannich ketones (**1-11** in the second line), expressed as minimum inhibitory concentration values (MIC, $\mu\text{g mL}^{-1}$)

No.	<i>S. s.</i>	<i>S. a.</i>	<i>M. l.</i>	<i>B. s.</i>	<i>P. a.</i>	<i>E. c.</i>	<i>E. c.</i> <i>ReD31m4</i>	<i>S. m.</i> <i>Re595</i>	<i>S. s.</i> <i>Re4350</i>
<i>trans -12</i>	>200	>200	>200	>200	>200	>200	>200	>200	>200
1	6.25	6.25	6.25	12.5	>200	100	25	25	6.25
<i>trans -13</i>	>200	>200	200	>200	>200	>200	>200	>200	>200
2	12.5	12.5	12.5	3.125	>200	200	50	12.5	12.5
<i>cis-14</i>	>200	>200	>200	>200	>200	>200	200	100	100
3	6.25	1.56	6.25	12.5	>200	>200	6.25	6.25	3.125
<i>trans -14</i>	>200	>200	>200	>200	>200	>200	100	100	100
3	6.25	1.56	6.25	12.5	>200	>200	6.25	6.25	3.125
<i>trans -16</i>	200	>200	200	200	>200	>200	200	200	200
5	3.125	3.125	6.25	12.5	>200	>200	12.5	6.25	3.125
<i>cis-17</i>	>200	>200	>200	>200	>200	>200	100	100	100
6	12.5	50	25	25	>200	>200	100	100	50
<i>cis-18</i>	100	>200	>200	>200	>200	200	50	50	100
7	25	100	100	50	>200	>200	200	200	200
<i>trans -18</i>	>200	>200	200	>200	>200	>200	>200	>200	>200
7	25	100	100	50	>200	>200	200	200	200
<i>cis-19</i>	>200	>200	>200	>200	>200	>200	200	200	200
8	25	50	25	12.5	>200	>200	200	200	200
<i>cis-20</i>	200	>200	100	>200	>200	>200	50	50	50
9	50	100	100	100	>200	>200	200	200	200
<i>trans -21</i>	>200	>200	>200	>200	>200	>200	>200	>200	>200
10	6.25	6.25	6.25	6.25	200	12.5	6.25	3.125	3.125
<i>trans -22</i>	>200	>200	>200	>200	>200	>200	>200	>200	>200
11	25	25	25	50	>200	>200	25	25	50

S. s.: *Staphylococcus saprophyticus* NIH Hungary 120008;
S. a.: *Staphylococcus aureus* NIH Hungary 118003;
M. l.: *Micrococcus luteus* ATCC 9341;
B. s.: *Bacillus subtilis* ATCC 6633;
E. c.: *Escherichia coli* ATCC 25922;
P. a.: *Pseudomonas aeruginosa* NIH Hungary 170000;
E. c.: *ReD31m4: Escherichia coli* ReD31m4;
S. m.: *Re595: Salmonella minnesota* Re595;
S. s.: *Re4350: Shigella sonnei* Re4350.

Table 4. In vitro cytotoxicity of of aminoalcohols on HeLa cell line, expressed as IC₅₀

Comp.	IC ₅₀ (nM/mL)
<i>trans</i> -12	153,79
<i>trans</i> -13	265,40
<i>cis</i> -14	> 278,35
<i>trans</i> -14	145,19
<i>trans</i> -16	> 267,15
<i>cis</i> -17	60,71
<i>cis</i> -18	260,00
<i>trans</i> -18	> 267,15
<i>cis</i> -19	> 253,60
<i>cis</i> -20	239,28
<i>trans</i> -21	>342,88
<i>trans</i> -22	>345,81

Conclusions

In conclusion, reduction of **3** with various complex hydrides afforded reaction mixtures of very different stereocomposition. Reduction with sodium borohydride was found to be diastereoselective both for α,β -unsaturated- and fused Mannich ketones. The stereocomposition of the reaction mixtures was influenced by the size of the ring. The predominance of the *trans* isomers as *trans*-**14** can be explained by the intramolecular hydrogen bond between the OH and the N as demonstrated by crystal structure analysis. Most of the amino alcohols almost completely lost their biological effect. Two compounds, however, retained or even increased their antibacterial activity on deep rough mutants (**9**/*cis*-**20** MIC: from 200 to 50 $\mu\text{g mL}^{-1}$) and thus emerged as lead compounds for antibacterial agents with a unique, yet currently unknown, activity profile. Since the amino alcohols did not cause thiol depletion, this finding points to a new mechanism of action other than alkylation. The MIC values for deep rough mutants show that the permeability of the outer membrane definitely can influence the antibacterial activity of our compounds. The cytotoxic activities of the amino alcohols also were evaluated using HeLa

cells. Most of the reduced derivatives proved to be less toxic to the HeLa cells than the starting Mannich ketones, consistent with data obtained with bacteria. The effect of two amino alcohols, however, was significantly different in HeLa cells and in bacteria. *Cis-17* increased its toxicity in HeLa but was not active against bacteria, *cis-20* became nontoxic in HeLa but displayed antibacterial activity.

Experimental Section

General Procedures. The diethyl ether used for the reductions was dried by distillation 12 from Na under Ar. Our starting Mannich ketones (**1-9** and **10-11**) are known compounds synthesised according to our methods^{1,2} or literature methods.⁹ In all of the unsaturated Mannich ketones the configuration is *E* around the C=C double bond.¹ Thin-layer chromatography (TLC) was performed on Merck silica gel plates (60 F₂₅₄), using ethyl acetate-benzene (10:1 v/v) as eluent. Melting points were determined on a Boetius apparatus and are uncorrected. The analytical values were within ± 0.4 % of the theoretical values for C, H and N.

The structure elucidation of compounds **12-22** was performed by NMR measurements. NMR spectra were recorded with a Varian ^{UNITY}INOVA 400 WB (400/100 MHz for ¹H/¹³C) spectrometer. Chemical shifts are referenced to Me₄Si (¹H) or to the residual solvent signals (¹³C). Measurements were run at 298K or 300K probe temperatures. The ¹H and ¹³C assignments were based on ¹H-¹H COSY, gradient enhanced ¹³C-¹H HSQC and ¹³C-¹H HMBC experiments executed using standard Varian software.

[The NOE correlations between the corresponding CH₂ proton of the saturated cycloalkane ring and the aromatic protons (H-2',6') in the corresponding NOESY spectra proved the *E* configuration of compounds *trans-12* – *cis-20*.] The *cis/trans* orientation of bonds C1-H1/C2-H2 (in *trans-12* – *cis-20*) and C1-H1/C8-H8 (in *trans-21* and *trans-22*) each to other are evident from the corresponding vicinal ¹H-¹H coupling constant values (see Experimental). The presence of NOE correlations between H-1/H-2 in the corresponding NOESY spectra of *cis-14* and *cis-17* – *cis-20* and the lack of the same correlations for *trans-12* – *trans-18* as well as the lack of NOE correlations between H-1 and H-8 in the corresponding NOESY spectra of *trans-21* and *trans-22* also corroborate the *cis* and *trans* orientations, respectively.

FT-IR spectra were taken on a Nicolet Impact 400 spectrophotometer in KBr pellets.

X-Ray structure determination of *trans-14*. C₁₈H₂₅NO, *M_r* = 287.39, transparent crystal of size 0.3x0.3x0.1 mm³, triclinic, space group P $\bar{1}$ (No. 2 of IT¹). Lattice parameters are *a* = 5.575(3) Å, *b* = 10.207(4) Å, *c* = 14.486(5) Å, α = 74.687(6)°, β = 89.945(6)°, γ = 85.481(9)° and *V* = 792.4(6) Å³ (determined from 17676 reflections, 3° < θ < 30°), *Z* = 2, *d_{calc}* = 1.204 g cm⁻³ and μ_x (λ = 0.49592 Å) = 0.18 cm⁻¹. Reflections were recorded at 100 K using a CCD-detector (MarCCD 165) and monochromatic synchrotron radiation (λ = 0.49592 Å). Reflections were indexed, integrated, corrected and scaled using XDS.¹⁰ The same program was used to refine the lattice parameters. A long and a short exposure time series each with 360° of total oscillation range and with 0.5° per

frame were recorded. Data were integrated for $-11 \leq h \leq 11$, $-20 \leq k \leq 21$ and $-29 \leq l \leq 29$ with $(\sin\theta/\lambda)_{\max} = 1.04$. Total number of observations was 87736 with 13034 unique ($R_{\text{merge}} = 2.1\%$). All unique reflections were used for further analysis. The structure was solved by direct methods¹¹. All non-H atoms were refined anisotropically using full matrix least-square¹² based on F^2 with weights $1/[\sigma^2(F_o^2) + (0.0633 * P)^2 + 0.07 * P]$ where $P = (\text{Max}(F_o^2, 0) + 2 * F_c^2) / 3$. For each H-atom the co-ordinates and an isotropic displacement parameter were refined. The shifts $(\Delta/\sigma)_{\max}$ of the final least square cycle were smaller than 0.002. R-values for $F^2 > 2\sigma(F^2)$ were $R = 0.0393$ (based on $|F|$) and $R_w = 0.1159$ (based on F^2). Goodness of fit was 1.074. The final difference Fourier was featureless with the highest maxima at the positions of the binding electrons ($\Delta\rho_{\min} = -0.32$, $\Delta\rho_{\max} = 0.67$). All relevant crystallographic data have been deposited with the Cambridge Crystallographic Data Center under the number CCDC 197256.

Theoretical calculations. CAChe Worksystem Pro (version 5.04, Fujitsu America, Inc., Beaverton, OR), a personal computer-based molecular modeling program, was used in the computational studies. Geometry-optimized molecular models (*in vacuo*, gradient norm below 0.1 kcal/Å as the criterion for convergence) and ΔH_f° values for *cis/trans-3a-e* were obtained by a semi-empirical quantum mechanical method (PM5 parameters).

Biological procedure. Determination of antibacterial activity. MIC values were determined by the broth macrodilution method¹⁴ as described previously.¹ The water soluble hydrochlorides of the aminoalcohols were screened. The test bacteria were *Pseudomonas aeruginosa* NIH Hungary 170000, *E. coli* ATCC 25922, *E. coli* ReD31m4, *S. minnesota* Re595, *S. sonnei* Re4350, *S. saprophyticus* NIH Hungary 120008, *S. aureus* NIH Hungary 118003, *M. luteus* ATCC 9341 and *B. subtilis* ATCC 6633. The tube dilution method started with making twofold dilution series of test compounds in nutrient broth. The test bacteria were in the logarithmic phase; their final concentration was ca. 5×10^5 colony-forming units mL⁻¹. The MIC values were determined after one night incubation (37 °C) as the lowest concentration of compounds producing no visible bacterial growth. All experiments were performed in triplicate.

In vitro effect of Mannich ketones on HeLa cell line.¹ The HeLa cells were cultured in RPMI-1640 culture medium containing 10% heat-inactivated fetal calf serum with antibiotics streptomycin (25 µg mL⁻¹) and penicillin (50 µg mL⁻¹). The cells were grown as a monolayer, in the logarithmic phase, had viability better than 98 % as proved by Tripian blue exclusion. The growing cells were plated out in 100 µL of medium at concentration of $4-5 \times 10^3$ cells/flat-bottomed well in 96-well microtiter plates. Plates were incubated for 24 hours at 37 °C in a humidified atmosphere of 5% CO₂. 100 µL of media containing the drug dissolved in appropriate solvent were added to each well and incubated for a further 48 hours. MTT was filtered through a 0.22 µm filter and diluted in RPMI-1640 containing antibiotics to 1 mg mL⁻¹. 100 µL of this solution added to each well and incubated for 4 hours. All untransformed MTT (medium) was removed by careful aspiration from the wells. The formazan crystals were dissolved in 100 µL of isopropanol-1 N HCl (24/1 v/v). Then the plate was shaken in order to ensure solubilization of the blue formazan crystals. The absorbance was recorded in an enzyme-linked immunosorbent assay plate reader at a 560 nm test wavelength and a 690 nm reference wavelength.

Determination of free thiol content. The method was published previously.¹ Shortly, the bacterial cells were cultivated in a shaker incubator (37 °C) to the mid log phase and treated with the different compounds at the MIC concentration or at 200 µg mL⁻¹ in cases of ineffective substances (MIC > 200 µg mL⁻¹) for one hour. The treated cells were centrifuged (+4 °C), washed with physiological saline solution and stored at -80 °C as pellets. These cell pellets were resuspended in a buffer containing 50 mM TRIS-HCl, 0.1 % SDS of pH 7.4, and lysed by sonication. The cell lysates were clarified by centrifugation and used immediately for the determination of free thiol by the DTNB assay.¹⁵ The protein concentration was determined by the BCA (bicinchoninic acid) assay.¹⁶ The assay was repeated using eight selected compounds in three parallel cultures. Values represent the average of three independent determinations ± SD.

General procedure for the reductions with NaBH₄

To a methanol solution (50 mL) of the appropriate Mannich ketone (2 mmol), equivalent aqueous NaOH solution (10 mL, 2 mmol) was added at 0 °C under stirring. Then, sodium borohydride (8 mmol) was added in small portions during 20 min. The solution was stirred at room temperature for 24 h. It was cooled to 0 °C and acidified with concentrated HCl. After 20 min its pH was adjusted with aqueous NaOH to pH 10 and evaporated to the half of the original volume. Water was added and the resulting slurry was extracted with chloroform (3 x 80 mL). The chloroform extracts were combined and washed with brine and dried over sodium sulphate. The chloroform solution was evaporated to dryness under reduced pressure. The oily residue was purified by column chromatography using Brockman II neutral Al₂O₃ and different benzene-triethylamine mixtures as eluents as follows: benzene/triethylamine 10/0.2 (*trans*-**15**, *trans*-**21**); 10/0.3 (*trans*-**12**, *trans*-**13**, *cis*-**14**, *trans*-**14**, *cis*-**20**, *trans*-**22**); 10/0.4 v/v (*cis*-**17**- *trans*-**17**).

***trans*-E-2-Phenylmethylene-5-piperidin-1-ylmethyl-cyclopentanol (12).** Colorless crystals; yield 87%; mp 81 °C (from hexane-ether mixture, dec.). Anal. calcd. for C₁₈H₂₅NO: C, 79.66; H, 9.28; N, 5.16; found: C, 79.55; H, 9.39; N, 5.10. IR (KBr) ν_{\max} : 3365, 2941, 2922, 2886, 2854, 2814, 2782, 1597, 1489, 1447, 1409, 1121, 1040, 757 and 695 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.26 (m, 1H, *J*=12.3, 9.6 Hz, CH₂, H-3), 1.45 (m, 2H, CH₂, H-4''), 1.60 (m, 4H, CH₂, H-3'',5''), 1.82 (m, 1H, CH₂, H-3), 1.94 (m, 1H, CH, H-2), 2.33 (bs, 2H, CH₂, H-2'',6''), 2.39 (t, 1H, *J*=12.3 Hz, CH₂, H-2 α), 2.65 (dd, 1H, *J*=12.3, 3.8 Hz, CH₂, H-2 α), 2.66 (m, 2H, CH₂, H-2'',6''), 2.69 (m, 2H, CH₂, H-4), 4.25 (d, 1H, *J*=9.7 Hz, CH, H-1), 5.78 (bs, 1H, -OH), 6.47 (q, 1H, *J*=2.4 Hz, =CH, H-8 α), 7.16 (m, aromatic, 1H, H-4'), 7.30 (m, aromatic, 2H, H-3',5'), 7.36 (m, aromatic, 2H, H-2',6'); ¹³C NMR (100 MHz, CDCl₃) δ_{C} 24.1 (C-4''), 25.1 (C-3), 26.1 (C-3'',5''), 28.0 (C-4), 42.0 (C-2), 55.3 (C-2'',6''), 64.1 (C-2 α), 82.2 (C-1), 120.3 (C-8 α), 126.0 (C-4'), 128.1 (C-3',5'), 128.3 (C-2',6'), 138.0 (C-1'), 145.0 (C-8).

***trans*-E-2-(4'-Methoxy-phenylmethylene)-5-piperidin-1-ylmethyl-cyclopentanol (13).**

Colorless crystals; yield 67%; mp 95 °C (from hexane-ether mixture, dec.). Anal. calcd. for C₁₉H₂₇NO₂: C, 75.71; H, 9.03; N, 4.65; found: C, 75.83; H, 9.21; N, 4.51. IR (KBr) ν_{\max} : 3303, 2945, 2936, 2887, 2860, 1604, 1510, 1455, 1294, 1249, 1177, 1114, 1028, 820 and 530 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.25 (m, 1H *J*=12.2, 9.6 Hz, CH₂, H-3), 1.44 (m, 2H, CH₂, H-4''), 1.59 (m, 4H, CH₂, H-3'',5''), 1.81 (m, 1H, CH₂, H-3), 1.92 (m, 1H, CH, H-2), 2.32 (bs, 2H, CH₂,

H-2'',6''), 2.38 (t, 1H, $J=12.2$ Hz, CH₂, H-2 α), 2.63 (dd, 1H, $J=12.2$, 3.8 Hz, CH₂, H-2 α), 2.65 (m, 2H, CH₂, H-2'',6''), 2.65 (m, 2H, CH₂, H-4), 3.78 (s, 3H, -OCH₃), 4.23 (d, 1H, $J=9.7$ Hz, CH, H-1), 5.74 (bs, 1H, -OH), 6.41 (q, 1H, $J=2.5$ Hz, =CH, H-8 α), 6.84 (m, aromatic, 2H, H-3',5'), 7.29 (m, aromatic, 2H, H-2',6'); ¹³C NMR (100 MHz, CDCl₃) δ_c : 24.1 (C-4''), 25.2 (C-3), 26.1 (C-3'',5''), 27.9 (C-4), 42.1 (C-2), 55.2 (-OCH₃), 55.3 (C-2'',6''), 64.1 (C-2 α), 82.2 (C-1), 113.6 (C-3',5'), 119.7 (C-8 α), 129.5 (C-2',6'), 130.9 (C-1'), 142.7 (C-8), 157.8 (C-4').

cis-E-2-Phenylmethylene-6-morpholin-1-ylmethyl-cyclohexanol (14). Colorless crystals; yield 89% for *cis*- and *tr*-**14**; mp 104 °C (hexane-ether, dec.). Anal. calcd. for C₁₈H₂₅NO₂: C, 75.22; H, 8.77; N, 4.87; found: C, 75.32; H, 8.89; N, 4.71. IR (KBr) ν_{\max} : 3153, 2960, 2947, 2931, 2924, 2855, 2825, 1597, 1489, 1291, 1266, 1115, 1005, 985, 869, 747 and 702 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_H : 1.42 (m, 1H, CH₂, H-4), 1.54 (m, 1H, CH₂, H-4), 1.59 (m, 1H, CH₂, H-3), 1.74 (m, 1H, CH₂, H-3), 1.89 (m, 1H, CH₂, H-5), 2.22 (ddd, 1H, $J=12.3$, 2.9, 1.2 Hz, CH₂, H-2 α), 2.36 (m, 2H, CH₂, H-2'',6''), 2.51 (m, 1H, CH, H-2), 2.69 (m, 2H, CH₂, H-2'',6''), 2.89 (m, 1H, CH₂, H-5), 2.95 (t, 1H, $J=12.3$ Hz, CH₂, H-2 α), 3.72 (m, 4H, CH₂, H-3'',5''), 4.39 (d, 1H, $J=4.0$ Hz, CH, H-1), 6.72 (bs, 1H, =CH, H-8 α), 7.21 (m, aromatic, 1H, H-4'), 7.23 (m, aromatic, 2H, H-2',6'), 7.32 (m., aromatic, 2H, H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_c : 23.1 (C-4), 27.8 (C-5), 28.7 (C-3), 36.7 (C-2), 54.0 (C-2'',6''), 60.1 (C-2 α), 66.9 (C-3'',5''), 76.9 (C-1), 121.8 (C-8 α), 126.1 (C-4'), 128.1 (C-3',5'), 128.8 (C-2',6'), 138.1 (C-1'), 142.9 (C-8).

trans-E-2-Phenylmethylene-6-morpholin-1-ylmethyl-cyclohexanol (14). Colorless crystals; mp 73 °C (from hexane-ether mixture dec.). Anal. calcd. for C₁₈H₂₅NO₂: C, 75.22; H, 8.77; N, 4.87; found: C, 75.17; H, 8.91; N, 4.95. IR (KBr) ν_{\max} : 3197, 2972, 2922, 2847, 2825, 1599, 1494, 1461, 1443, 1285, 1116, 864, 747 and 704 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_H : 1.13 (m, 1H, CH₂, H-3), 1.34 (m, 1H, CH₂, H-4), 1.61 (m, 1H, CH₂, H-3), 1.73 (m, 1H, CH₂, H-5), 1.75 (m, 1H, CH, H-2), 1.77 (m, 1H, CH₂, H-4), 2.41 (bs, 2H, CH₂, H-2'',6''), 2.44 (dd, 1H, $J=12.6$, 2.8 Hz, CH₂, H-2 α), 2.56 (ψ t, 1H, $J=12.6$, 11.5 Hz, CH₂, H-2 α), 2.73 (bs, 2H, CH₂, H-2'',6''), 2.95 (m, 1H, CH₂, H-5), 3.74 (m, 4H, CH₂, H-3'',5''), 4.03 (dd, 1H, $J=9.5$, 1.8 Hz, CH, H-1), 6.71 (bs, 1H, =CH, H-8 α), 7.17 (m, aromatic, 1H, H-4'), 7.23 (m, aromatic, 2H, H-2',6'), 7.30 (m., aromatic, 2H, H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_c : 26.6 (C-4), 27.6 (C-5), 29.0 (C-3), 41.2 (C-2), 54.0 (C-2'',6''), 66.3 (C-2 α), 66.8 (C-3'',5''), 79.2 (C-1), 119.4 (C-8 α), 125.8 (C-4'), 127.9 (C-3',5'), 128.9 (C-2',6'), 138.5 (C-1'), 142.4 (C-8).

trans-E-2-Phenylmethylene-6-pyrrolidin-1-ylmethyl-cyclohexanol (15). It was not possible to isolate the pure compound due to instability; yield 85%. ¹H NMR (400 MHz, CDCl₃) δ_H : 1.13 (m, 1H, $J=13.0$, 3.8 Hz, CH₂, H-3), 1.34 (m, 1H, $J=13.0$, 5.4, 3.4 Hz, CH₂, H-4), 1.64 (m, 1H, CH₂, H-3), 1.70 (m, 1H, CH, H-2), 1.74 (m, 1H, CH₂, H-5), 1.77 (m, 1H, CH₂, H-4), 1.80 (m, 4H, CH₂, H-3'',4''), 2.37 (dd, 1H, $J=12.1$, 2.6 Hz, CH₂, H-2 α), 2.53 (m, 2H, CH₂, H-2'',5''), 2.77 (m, 2H, CH₂, H-2'',5''), 2.92 (t, 1H, $J=12.1$ Hz, CH₂, H-2 α), 2.96 (m, 1H, CH₂, H-5), 4.03 (dd, 1H, $J=9.6$, 1.8 Hz, CH, H-1), 6.71 (bs, 1H, =CH, H-8 α), 7.17 (m, aromatic, 1H, H-4'), 7.23 (m, aromatic, 2H, H-2',6'), 7.30 (m, aromatic, 2H, H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_c : 23.5 (C-3'',4''), 26.7 (C-4), 27.6 (C-5), 29.2 (C-3), 43.6 (C-2), 54.4 (C-2'',5''), 63.4 (C-2 α), 79.5 (C-1), 119.1 (C-8 α), 125.7 (C-4'), 127.9 (C-3',5'), 129.0 (C-2',6'), 138.6 (C-1'), 142.9 (C-8).

trans-E-2-Phenylmethylene-6-(4'-methyl-piperidin)-1-ylmethyl-cyclohexanol (16). Colorless crystals; yield 76%; mp 79°C (from hexane-ether mixture, dec.). Anal. calcd. for C₂₀H₂₉NO C, 80.22; H, 9.76; N, 4.68; found: C, 80.31; H, 9.92; N, 4.58. IR (KBr) ν_{\max} : 3126, 2945, 2921, 2883, 2863, 2768, 1596, 1493, 1441, 1119, 1103, 972, 846 and 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 0.91 (d, 3H, *J*=6.2 Hz, CH₃), 1.10 (m, 1H, *J*=13.0, 3.7 Hz, CH₂, H-3), 1.25 (m, 1H, CH₂, H-5''), 1.30 (m, 1H, CH₂, H-3''), 1.33 (m, 1H, CH₂, H-4), 1.37 (m, 1H, CH, H-4''), 1.58 (m, 1H, CH₂, H-3), 1.63 (m, 1H, CH₂, H-5''), 1.64 (m, 1H, CH₂, H-3''), 1.71 (m, 1H, CH₂, H-5), 1.73 (m, 1H, CH, H-2), 1.76 (m, 1H, CH₂, H-4), 1.81 (m, 1H, CH₂, H-6''), 2.17 (t, 1H, *J*= 10.9 Hz, CH₂, H-2''), 2.37 (dd, 1H, *J*=12.5, 2.9 Hz, CH₂, H-2 α), 2.53 (t, 1H, *J*=12.5 Hz, CH₂, H-2 α), 2.89 (m, 1H, CH₂, H-2''), 2.94 (m, 1H, CH₂, H-5), 3.19 (d, 1H, *J*=10.9 Hz, CH₂, H-6''), 4.00 (dd, 1H, *J*=9.7, 2.0 Hz, CH, H-1), 6.71 (bs, 1H, =CH, H-8 α), 7.16 (m, aromatic, 1H, H-4'), 7.23 (m, aromatic, 2H, H-2',6'), 7.29 (m, aromatic, 2H, H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 21.6 (CH₃), 26.6 (C-4), 27.6 (C-5), 29.0 (C-3), 30.5 (C-4''), 33.8 (C-5''), 34.5 (C-3''), 41.7 (C-2), 52.9 (C-6''), 55.9 (C-2''), 66.0 (C-2 α), 79.1 (C-1), 119.2 (C-8 α), 125.7 (C-4'), 127.9 (C-3',5'), 129.0 (C-2',6'), 138.6 (C-1'), 142.8 (C-8).

cis-E-2-Phenylmethylene-7-morpholin-1-ylmethyl-cycloheptanol (17). Colorless crystals; yield 90% for *cis*- and *tr*-**17**; mp 79 °C (from hexane-ether mixture, dec.). Anal. calcd. for C₁₉H₂₇NO₂: C, 75.71; H, 9.03; N, 4.65; found: C, 75.81; H, 9.16; N, 4.52. IR (KBr) ν_{\max} : 3213, 2956, 2927, 2853, 2831, 1599, 1489, 1459, 1290, 1269, 1115, 1006, 866, 759 and 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.31 (m, 1H, CH₂, H-3), 1.51 (m, 2H, CH₂, H-4), 1.65 (m, 2H, CH₂, H-3 and H-5), 1.75 (m, 1H, CH₂, H-5), 2.18 (dd, 1H, *J*=12.6, 3.0 Hz, CH₂, H-2 α), 2.18 (m, 1H, CH₂, H-6), 2.40 (m, 2H, CH₂, H-2'',6''), 2.42 (m, 1H, CH, H-2), 2.67 (m, 2H, CH₂, H-2'',6''), 2.71 (m, 1H, CH₂, H-6), 2.79 (ψ t, 1H, *J*=12.6, 11.4 Hz, CH₂, H-2 α), 3.73 (m, 4H, CH₂, H-3'',5''), 4.54 (d, 1H, *J*=4.5 Hz, CH, H-1), 6.69 (bs, 1H, =CH, H-8 α), 7.21 (m, aromatic, 1H, H-4'), 7.28 (m, aromatic, 2H, H-2',6'), 7.32 (m, aromatic, 2H, H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 23.9 (C-4), 27.5 (C-5), 29.0 (C-6), 29.9 (C-3), 37.4 (C-2), 53.9 (C-2'',6''), 61.0 (C-2 α), 66.9 (C-3'',5''), 78.3 (C-1), 125.4 (C-8 α), 126.2 (C-4'), 128.1 (C-3',5'), 128.8 (C-2',6'), 138.0 (C-1'), 143.8 (C-8).

trans-E-2-Phenylmethylene-7-morpholin-1-ylmethyl-cycloheptanol (17). We were not able to separate this minor isomer. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.13 (m, 1H, CH₂, H-3), 1.39 (m, 1H, CH₂, H-3), 1.49 (m, 1H, CH₂, H-5), 1.51 (m, 1H, CH₂, H-6), 1.71 (m, 1H, CH₂, H-5), 1.79 (m, 1H, CH, H-2), 1.82 (m, 1H, CH₂, H-6), 2.37 (m, 1H, CH₂, H-4), 2.40 (m, 2H, CH₂, H-2'',6''), 2.42 (m, 1H, CH₂, H-2 α), 2.43 (m, 1H, CH₂, H-4), 2.55 (m, 1H, CH₂, H-2 α), 2.67 (m, 2H, CH₂, H-2'',6''), 3.70 (m, 4H, CH₂, H-3'',5''), 4.05 (d, 1H, *J*=8.7 Hz, CH, H-1), 6.67 (bs, 1H, =CH, H-8 α), 7.14-7.37 (m, aromatic region, 5H, H-4', H-2',6' and H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ : 26.8 (C-4), 27.0 (C-5), 28.0 (C-6), 28.8 (C-3), 42.0 (C-2), 53.8 (C-2'',6''), 66.6 (C-3'',5''), 67.0 (C-2 α), 83.3 (C-1), 126.0 (C-4'), 127.3 (C-8 α), 127.8 (C-3',5'), 128.4 (C-2',6'), 137.7 (C-1'), 143.6 (C-8).

cis-E-2-Phenylmethylene-7-piperidin-1-ylmethyl-cycloheptanol (18). Colorless crystals; yield 72% for *cis*-**18** and *tr*-**18**; mp 71°C (from hexane-ether mixture, dec.). Anal. calcd. for C₂₀H₂₉NO: C, 80.22; H, 9.76; N, 4.68; found: C, 80.14; H, 9.91; N, 4.78. IR (KBr) ν_{\max} : 3170,

2939, 2925, 2875, 2851, 2776, 1489, 1443, 1129, 1115, 1087, 857 and 698 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.28 (m, 1H, CH_2 , H-3), 1.45 (m, 2H, CH_2 , H-4''), 1.48 (m, 2H, CH_2 , H-4), 1.62 (m, 6H, CH_2 , H-3, H-5 and H-3'',5''), 1.73 (m, 1H, CH_2 , H-5), 2.11 (dd, 1H, $J=12.6, 2.9$ Hz, CH_2 , H-2 α), 2.16 (m, 1H, CH_2 , H-6), 2.35 (m, 2H, CH_2 , H-2'',6''), 2.45 (m, 1H, CH, H-2), 2.64 (m, 2H, CH_2 , H-2'',6''), 2.70 (m, 1H, CH_2 , H-6), 2.76 (t, 1H, $J=12.6$ Hz, CH_2 , H-2 α), 4.53 (d, 1H, $J=4.5$ Hz, CH, H-1), 6.70 (bs, 1H, =CH, H-8 α), 7.19 (m, aromatic, 1H, H-4'), 7.28 (m, aromatic, 2H, H-2',6'), 7.32 (m, aromatic, 2H, H-3',5'). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 23.8 (C-4), 24.1 (C-4''), 25.9 (C-3'',5''), 27.6 (C-5), 29.1 (C-6), 30.1 (C-3), 37.5 (C-2), 54.9 (C-2'',6''), 61.0 (C-2 α), 77.3 (C-1), 125.3 (C-8 α), 126.1 (C-4'), 128.0 (C-3',5'), 128.8 (C-2',6'), 138.3 (C-1'), 143.9 (C-8).

trans-E-2-Phenylmethylene-7-piperidin-1-ylmethyl-cycloheptanol trans-18. Colorless crystals; mp 73°C (from hexane-ether mixture, dec.). Anal. calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}$: C, 80.22; H, 9.76; N, 4.68; found: C, 80.11; H, 9.94; N, 4.53. IR (KBr) ν_{max} : 3269, 2938, 2923, 2897, 2859, 2781, 1494, 1444, 1122, 1016, 975, 863 and 698 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.14 (m, 1H, CH_2 , H-3), 1.38 (m, 1H, CH_2 , H-3), 1.45 (m, 3H, CH_2 , H-4 and H-4''), 1.50 (m, 1H, CH_2 , H-5), 1.62 (m, 4H, CH_2 , H-3'', 5''), 1.78 (m, 1H, CH_2 , H-4), 1.80 (m, 1H, CH, H-2), 1.84 (m, 1H, CH_2 , H-5), 2.37 (m, 2H, CH_2 , H-2'',6''), 2.39 (dd, 1H, $J=12.6, 3.0$ Hz, CH_2 , H-2 α), 2.39 (m, 1H, CH_2 , H-6), 2.45 (m, 1H, CH_2 , H-6), 2.54 (t, 1H, $J=12.6$ Hz, CH_2 , H-2 α), 2.71 (m, 2H, CH_2 , H-2'',6''), 4.06 (d, 1H, $J=8.8$ Hz, CH, H-1), 6.70 (bs, 1H, =CH, H-8 α), 7.18 (m, aromatic, 1H, H-4'), 7.29 (m, aromatic, 4H, H-2',6' and H-3',5'); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 24.0 (C-4''), 25.8 (C-3'',5''), 27.0 (C-6), 27.3 (C-4), 28.3 (C-5), 29.1 (C-3), 42.5 (C-2), 55.1 (C-2'',6''), 67.4 (C-2 α), 83.3 (C-1), 126.1 (C-4'), 127.4 (C-8 α), 128.0 (C-3',5'), 128.6 (C-2',6'), 138.1 (C-1'), 144.1 (C-8).

cis-E-2-Phenylmethylene-8-morpholin-1-ylmethyl-cyclooctanol cis-19. Colorless crystals; yield 90%; mp 76°C (from hexane-ether mixture, dec.). Anal. calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_2$: C, 76.15; H, 9.27; N, 4.44; found: C, 76.26; H, 9.46; N, 4.31. IR (KBr) ν_{max} : 3168, 2959, 2916, 2877, 2853, 2767, 1451, 1131, 1115, 1009, 974, 866 and 699 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.38 (m, 1H, CH_2 , H-3), 1.43 (m, 1H, CH_2 , H-5), 1.45 (m, 1H, CH_2 , H-4), 1.48 (m, 1H, CH_2 , H-3), 1.60 (m, 1H, CH_2 , H-5), 1.66 (m, 2H, CH_2 , H-6), 1.69 (m, 1H, CH_2 , H-4), 2.24 (dd, 1H, $J=12.7, 3.3$ Hz, CH_2 , H-2 α), 2.36 (m, 1H, CH, H-2), 2.44 (m, 2H, CH_2 , H-2'',6''), 2.54 (m, 2H, CH_2 , H-7), 2.67 (m, 2H, CH_2 , H-2'',6''), 2.77 (t, 1H, $J=12.7$ Hz, CH_2 , H-2 α), 3.73 (m, 4H, CH_2 , H-3'',5''), 4.70 (d, 1H, $J=3.4$ Hz, CH, H-1), 6.63 (bs, 1H, =CH, H-8 α), 7.19 (m, aromatic, 1H, H-4'), 7.29 (m, aromatic, 2H, H-2',6'), 7.32 (m., aromatic, 2H, H-3',5'); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} : 24.7 (C-4), 25.2 (C-6), 27.6 (C-3), 28.7 (C-5), 29.9 (C-7), 38.4 (C-2), 54.1 (C-2'',6''), 61.9 (C-2 α), 66.7 (C-3'',5''), 74.9 (C-1), 125.4 (C-8 α), 126.1 (C-4'), 128.0 (C-3',5'), 128.9 (C-2',6'), 138.1 (C-1'), 143.8 (C-8).

cis-E-2-Phenylmethylene-8-piperidin-1-ylmethyl-cyclooctanol cis-20 Colorless crystals; yield 93%; mp 96 °C (from hexane-ether mixture, dec.). Anal. calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}$: C, 80.45; H, 9.97; N, 4.47; found: C, 80.52; H, 10.18; N, 4.50. IR (KBr) ν_{max} : 3140, 2946, 2930, 2921, 2878, 2848, 1598, 1490, 1446, 1302, 1102, 1044, 974, 749 and 703 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.29 (m, 1H, CH_2 , H-3), 1.42 (m, 1H, CH_2 , H-5), 1.44 (m, 2H, CH_2 , H-4''), 1.50 (m, 1H, CH_2 , H-

3), 1.60 (m, 4H, CH₂, H-3'',5''), 1.65 (m, 1H, CH₂, H-5), 1.66 (m, 2H, CH₂, H-4), 1.70 (m, 2H, CH₂, H-6), 2.17 (dd, 1H, *J*=12.8, 3.1 Hz, CH₂, H-2α), 2.33 (m, 2H, CH₂, H-2'',6''), 2.39 (m, 1H, CH, H-2), 2.56 (m, 2H, CH₂, H-7), 2.61 (m, 2H, CH₂, H-2'',6''), 2.72 (dd, 1H, *J*=12.8, 10.7 Hz, CH₂, H-2α), 4.73 (d, 1H, *J*=3.8 Hz, CH, H-1), 6.65 (bs, 1H, =CH, H-8α), 7.19 (m, aromatic, 1H, H-4'), 7.28-7.36 (m, aromatic, 4H, H-2',6' and H-3',5'); ¹³C NMR (100 MHz, CDCl₃) δ_C: 24.2 (C-4''), 24.4 (C-6), 25.0 (C-4), 26.1 (C-3'',5''), 28.1 (C-3), 29.5 (C-5), 30.8 (C-7), 38.9 (C-2), 55.2 (C-2'',6''), 62.0 (C-2α), 75.0 (C-1), 125.3 (C-8α), 126.0 (C-4'), 128.0 (C-3',5'), 129.1 (C-2',6'), 138.5 (C-1'), 144.1 (C-8).

trans-2-Morpholin-4-ylmethyl-indan-1-ol trans-21. Colorless crystals; yield 90%; mp 68 °C (from hexane-ether mixture, dec.). Anal. calcd. for C₁₄H₁₉NO₂: C, 72.06; H, 8.21; N, 6.01; found: C, 72.21; H, 8.29; N, 5.92. IR (KBr) ν_{max}: 3409, 2954, 2927, 2850, 2817, 1454, 1304, 1264, 1117, 1058, 1005, 867 and 751 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_H: 2.46 (m, 2H, CH₂, H-2'',6''), 2.48 (m, 1H, CH₂, H-6), 2.52 (m, 1H, CH, H-8), 2.66 (m, 2H, CH₂, H-8α), 2.70 (m, 2H, CH₂, H-2'',6''), 2.95 (m, 1H, CH₂, H-6), 3.73 (m, 4H, CH₂, H-3'',5''), 5.00 (d, 1H, *J*=7.5 Hz, CH, H-1), 7.18 (m, aromatic, 1H, H-3), 7.19 (m, aromatic, 1H, H-5), 7.22 (m, aromatic, 1H, H-4), 7.37 (m, aromatic, 1H, H-2); ¹³C NMR (100 MHz, CDCl₃) δ_C: 33.7 (C-6), 47.1 (C-8), 54.2 (C-2'',6''), 63.0 (C-8α), 67.0 (C-3'',5''), 81.6 (C-1), 123.2 (C-2), 124.5 (C-3), 126.7 (C-4), 127.6 (C-5), 140.8 (C-5a), 144.4 (C-1a).

trans-2-Pyrrolidin-1-ylmethyl-1,2,3,4-tetrahydronaphthalen-1-ol trans-22. Colorless crystals; yield 79%; mp 48 °C (from hexane-ether mixture, dec.). Anal. calcd. for C₁₅H₂₁NO: C, 77.87; H, 9.16; N, 6.06; found: C, 77.71; H, 9.29; N, 6.28. IR (KBr) ν_{max}: 3180, 2965, 2945, 2871, 2799, 1464, 1345, 1136, 1040 and 738 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ_H: 1.44 (m, 1H, *J*=12.4, 5.9 Hz, CH₂, H-7), 1.72 (m, 1H, CH₂, H-7), 1.79 (m, 4H, CH₂, H-3'',4''), 1.93 (m, 1H, CH, H-8), 2.48 (dd, 1H, *J*=12.1, 2.9 Hz, CH₂, H-8α), 2.52 (m, 2H, CH₂, H-2'',5''), 2.77 (m, 2H, CH₂, H-2'',5''), 2.81 (m, 1H, CH₂, H-6), 2.89 (m, 1H, CH₂, H-6), 2.92 (t, 1H, *J*=12.1 Hz, CH₂, H-8α), 4.67 (d, 1H, *J*=9.4 Hz, CH, H-1), 7.06 (m, aromatic, 1H, H-5), 7.15 (m, aromatic, 1H, H-4), 7.21 (m, aromatic, 1H, H-3), 7.60 (m, aromatic, 1H, H-2); ¹³C NMR (100 MHz, CDCl₃) δ_C: 23.4 (C-3'',4''), 25.3 (C-7), 28.9 (C-6), 39.2 (C-8), 54.5 (C-2'',5''), 63.1 (C-8α), 76.1 (C-1), 125.8 (C-2), 126.1 (C-3), 126.5 (C-4), 128.1 (C-5), 135.1 (C-5a), 139.4 (C-1a).

General procedure for the reductions of **3** with other complex hydrides

A solution of **3** (0.20g, 0.62 mmol) in methanol (20 mL) was treated with aqueous (10 mL) Na₂CO₃ (0.033g, 0.31 mmol) at 0 °C with stirring. After 2 min of mixing, ice and water were added and the mixture was extracted with chloroform (3x25 mL). The chloroform extracts were combined and washed with brine (2x20 mL) and dried over Na₂SO₄ for 1 hour in a refrigerator. The solution was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in anhydrous ether (40 mL) and cooled to 0 °C. The reducing agent was added and the mixture was stirred for 5 hours at 0 °C, then for 15 hours at room temperature. The excess of hydride was quenched with methanol at 0 °C, and the mixture was treated with solid NaOH to decompose the complex. The organic phase was washed first with 10% NaOH (3x), with saturated NaHCO₃ solution (3x) and with brine (3x). It was dried over Na₂SO₄, filtered, and the

