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Synthesis of new analogues of diphenylpyraline

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Abstract—1-Unsubstituted 4-dimethylamino-5,6-dihydropyridine-2(1*H*)-thiones were converted to isomeric piperidin-4-ols which were separated and *N*-methylated to 2-substituted 1-methylpiperidin-4-ols. Their 1-phenyl analogues were prepared from 4-dimethylamino-5,6-dihydro-1-phenylpyridine-2(1*H*)-thiones. After their conversion to dihydro-1-phenylpyridin-4(1*H*)-ones the hydrogenation gave isomeric 1-phenylpiperidin-4-ols which were separated. *O*-Alkylation of the 1-substituted piperidin-4-ols by various methods yielded 2-substituted analogues of diphenylpyraline. Their antimycobacterial activity was examined. The configurations and conformations of the piperidine derivatives were investigated by NMR spectroscopy.

1. Introduction

Diphenylpyraline **19** is an antihistaminic agent[1] which is mainly used against nausea, itching and hay fever in medicinal therapy. Besides it possesses bronchospasmolytic[2] and antimycobacterial[3] properties as well as activity against parkinsonism.[4] Some of its metal complexes were reported to have antibacterial and antifungal potency.[5,6] Many derivatives with different substitution on nitrogen or at the aromatic ring system have been prepared.[7–24] Some of them were described to have less sedative side-effects,[22–26] additional antiinflammatory activity[11,13] or antagonistic activity against leukotriene production.[9] Substitution of the piperidine ring was restricted to 3-methyl-,[27] dimethyl-[18,20,27] and trimethylderivatives.[20] Monosubstitution in position 2 of the piperidine ring of diphenylpyraline analogues has not yet been reported. This paper deals with the first syntheses of 2-substituted derivatives of diphenylpyraline and its 1-phenyl analogue. The antimycobacterial activity of the prepared compounds has been investigated.

2. Results and discussion

The synthesis of the 1-methyl compounds is based on the cyclization of an α,β-unsaturated ketone **1** with dimethylammonium rhodanide to a 6-substituted 4-dimethylaminopyridine-2-thione **2**.[28] When the latter is treated with dilute caustic soda the dimethylamino group is replaced by a hydroxy substituent.[29] Compound **2** gives a mixture of the 4-hydroxy derivative **3** and its tautomer **4**. If NMR spectra are recorded in DMSO-d_6 only signals of **3** are visible which was deduced from the singlet of the olefinic proton at 5.5 ppm in the ^{1}H NMR spectrum. When measured in $CDCl_3$ exclusively resonances of **4** can be observed: the Hs at C-5 of **4** resonate as two doublets in the ^{1}H NMR spectrum at ~3.8 ppm. Their ^2J coupling constants were ca. 20 Hz establishing the 6-thioxopiperidin-4-one structure. The catalytic hydrogenation of **3**, **4** with Raney nickel W-7[30] yielded a mixture of the diastereoisomers **5a** and **5b**. Those were separated by LC affording larger amounts of isomer **5a** which is energetically favored due to its equatorial substituent in ring position 4. The piperidinols **5** were treated with formaldehyde and formic acid to afford the 1-methyl-4-piperidinols **6a** and **6b**, respectively, in a Leuckart–Wallach procedure (Scheme 1).

We were not able to prepare their 1-phenyl analogues by reaction of **5a**,**b** with halobenzenes due to the preferred formation of 4-phenoxypiperidines. We did not examine other methods or the protection of the 4-hydroxy group of **5a**,**b** because the dihydro-1-phenylpyridine-2(1*H*)-thiones **9** and **10** were obtained in acceptable yields from the 6-phenylimino-2*H*-thiopyran-4-amines **7** and **8** by a Dimroth rearrangement.[31] In comparison to their 1-unsubstituted analogue **2**, compounds **9** and **10** are stable against caustic soda. However, their methoiodides gave the dihydropyridin-4(1*H*)-ones **11** and **12**. When those were stirred in an inert-gas atmosphere with Raney nickel W-2[32] the methylthio group was removed giving selectively compounds **13** and **14**.[31] For the hydrogenation of **12** the use of the more active Raney nickel catalysts W-4[33] and W-7 was examined. The yielded isomeric 1-phenylpiperidin-4-ols **17a**,**b** were accompanied by high amounts of the pentanol **15**. The latter was prepared in good yields by shaking of **12** with Raney nickel W-7 under hydrogen pressure. The treatment of **11** or **12** with Raney nickel W-2 under the same conditions gave mixtures of the

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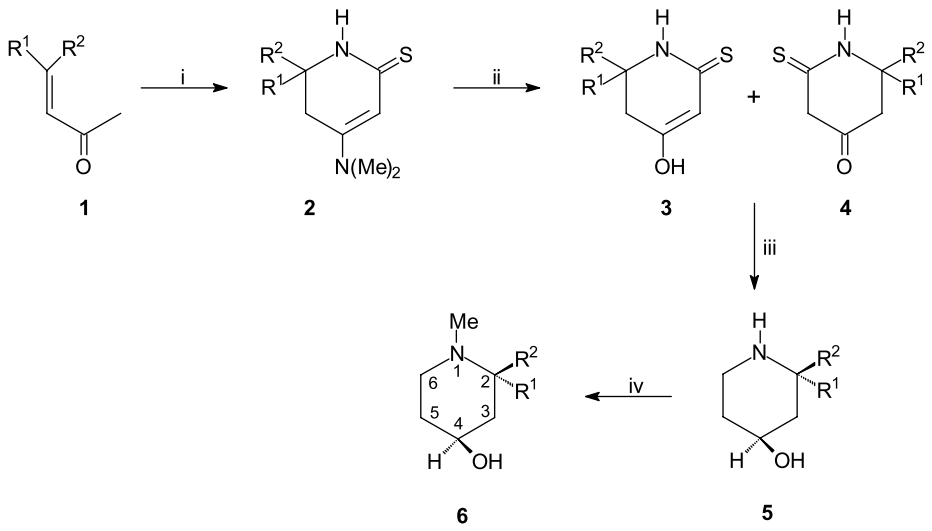
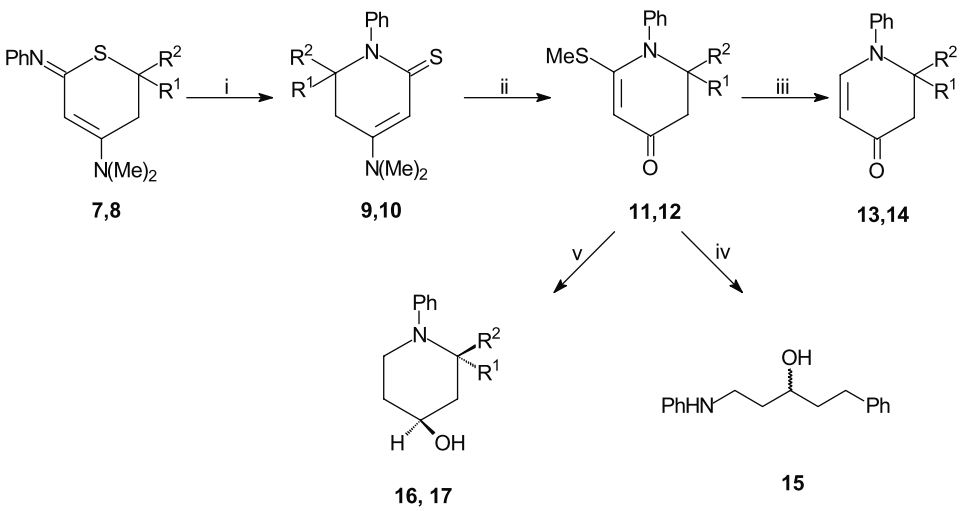


	1-4	5a	5b	6a	6b
R^1	iPr	iPr	H	iPr	H
R^2	H	H	iPr	H	iPr

Scheme 1. *Reagents and reaction conditions*: (i) $NH_2(Me)_2SCN$, PhBr, 170°C, 8 h; (ii) NaOH, 60°C, 72 h; (iii) Raney nickel W-7, ethanol, 45 psi (H_2), room temperature, 96 h; (iv) HCOOH, CH_2O, 100°C.

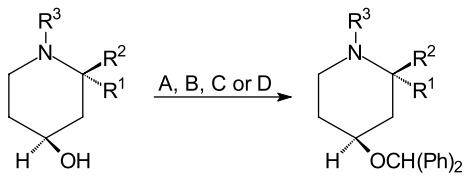
corresponding 1-phenylpiperidin-4-ols **16a**,**b** or **17a**,**b** (Scheme 2). The isomers were separated by LC yielding larger amounts of compounds **16a** and **17a**, which have equatorial substituents in ring position 2.

2-Substituted 4-piperidinols have already been prepared by other methods. Hydroboration of tetrahydro-2-isopropyl-1-methylpyridine gave a mixture of 3 isomeric isopropyl-1-methylpiperidinols from which small amounts of compounds **6a** and **6b** were separated by means of GLC.[34] Unsubstituted 2-phenyl-4-piperidinols were obtained enantiomerically pure from a 3-hydroxy-5-oxopentanenitrile[35] as well as by stepwise hydrogenation of 6-phenylpiperidine-2,4-dione.[36] Besides, the 4-piperidinols might as well be prepared via the corresponding 2-substituted 4-piperidones. The latter are accessible by acid-catalyzed Mannich reaction of an aldehyde, an amine and an α,β-unsaturated ketone[37–39] or by intermolecular double Michael reaction of α,β-unsaturated γ-ketosulfones with benzylamine.[40–42] Furthermore, cyclizations of appropriate



	7,9,11,13	8,10,12,14	16a	16b	17a	17b
R^1	iPr	Ph	iPr	H	Ph	H
R^2	H	H	H	iPr	H	Ph

Scheme 2. *Reagents and reaction conditions*: (i) DMF, 160°C, 16 h; (ii) CH_3I, $CHCl_3$, room temperature, 18 h; NaOH, 110°C, 2 h; (iii) Raney nickel W-2, ethanol, room temperature; (iv) Raney nickel W-7, ethanol, 45 psi (H_2), room temperature, 8 h; (v) Raney nickel W-2, ethanol, 30 psi (H_2), room temperature, 6 h.



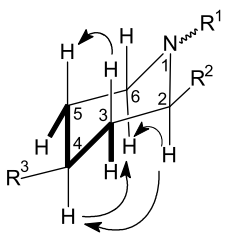
6,16,17,18 **19,20,21,22**

	6a,20a	6b,20b	16a,21a	16b,21b	17a,22a	17b,22b	18,19
R^1	iPr	H	iPr	H	Ph	H	H
R^2	H	iPr	H	iPr	H	Ph	H
R^3	Me	Me	Ph	Ph	Ph	Ph	Me

Scheme 3. *Reagents and reaction conditions*: method A: $(Ph)_2CHBr$, K_2CO_3, 140°C, 5 h; method B: $(Ph)_2CHBr$, NaH, DMF, room temperature, 3 h; method C: $(Ph)_2CN_2$, PhMe, 130°C, 18 h; method D: $(Ph)_2CHOH$, toluene-4-sulfonic acid, PhMe, 130°C, 6 h.

imino acetales[43–45] or of pent-1,4-diene-3-ones with amines[46–49] have been reported. The flash vacuum thermolysis of 4-oxa-5-azaspiro[2.4]heptanes gave mixtures containing 1,2-disubstituted 4-piperidones.[50–52]

Diphenylpyraline **19** has been synthesized from 1-methylpiperidin-4-ol **18** and halodiphenylmethanes[18,21] or diphenyldiazomethanes.[53] The 2-substituted piperidin-4-ols **6**, **16** or **17** were fused together with bromodiphenylmethane and potassium carbonate (method A) yielding the title compounds **20a**,**b** in good and **21a**,**b** and **22a**,**b** in poor yields. The disadvantage of this method is the undesired formation of N-substituted side products which is the main reaction of the 1-phenyl compounds **16** and **17**. Attempts to favor the formation of ethers by deprotonation of the piperidinols **6a**,**b** and **16a** with sodium hydride and subsequent etherification with bromodiphenylmethane (method B) went wrong and only small quantities of **20a**,**b** and **21a** were afforded. Therefore the reactions of **16b** and **17a**,**b** were not examined by this method. Piperidinol **16a** was etherified with diphenyldiazomethane (method C) giving **21a** in acceptable yields. However, the etherification of compounds **16a**,**b** and **17a**,**b** by the reaction with diphenylmethanol in the presence of toluene-4-sulfonic acid (method D) was established as the superior method affording high amounts of the alkoxypiperidines **21a**,**b** and **22a**,**b** (Scheme 3).



	5a	6a	17a	20a	22a
R^1	H	Me	Ph	Me	Ph
R^2	iPr	iPr	Ph	iPr	Ph
R^3	OH	OH	OH	$OCH(Ph)_2$	$OCH(Ph)_2$

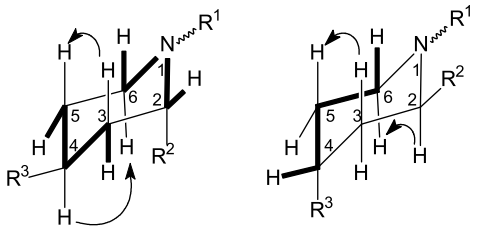
Figure 1. NOEs (arrows) and w-couplings (bold) in ^1H NMR spectra of **5a**, **6a**, **17a**, **20a**, **22a**.

The resonances in ^1H and ^{13}C NMR spectra of all new compounds were assigned by means of 2D NMR spectra (gCOSY, gHSQC, gHMQC optimized for long-range couplings of 10 Hz). *O*-Alkylation of the piperidinols **6**, **16** and **17** to compounds **20**, **21** and **22** was established by a long-range coupling from the methine proton of the diphenylmethyl group to the C-4. The OCH carbons of compounds **20**, **21** and **22** typically resonate at 80 ppm in ^{13}C NMR spectra. Due to the introduction of the benzhydryl group the signals for the C-4 in the ^{13}C NMR spectra of compounds **20**, **21** and **22** were shifted ca. 5 ppm to lower field whereas those for the C-3 and the C-5 were shifted 3 ppm upfield in comparison to compounds **6**, **16** and **17**. The shifts of the resonances for the C-2 and C-6 were altered less than 1.5 ppm. Only the signals for the C-5 and the C-6 of compound **21a** were unusually shifted ca. 4 ppm upfield which should be due to its different average conformation as stated below.

The relative configurations of the piperidine derivatives **5**, **6**, **16**, **17**, **20**, **21** and **22** were deduced from the ^3J coupling constants in their ^1H NMR spectra. $^3J_{(2\text{-H, }3\text{-Hax})}$ and $^3J_{(3\text{-Hax, }4\text{-H})}$ coupling constants of ca. 11 Hz indicate axial positions of the involved protons of the piperidine derivatives. Their average conformations were investigated by NOE experiments. Furthermore w-couplings[54] were removed by homodecoupling experiments and detected in this way, but we did not measure their exact values.

The coupling constants of the axial and equatorial protons of compounds **16a** and **17b** make their unambiguous assignment feasible. Instead of the expected 11–12 Hz couplings their diaxial ^3J coupling constants were only ca. 9 Hz revealing a slight deviation from the chair conformation. But their diphenylmethyl ethers **21a** and **22b** do not prefer chair conformations which is indicated by similar coupling constants of the geminal protons in their ^1H NMR spectra.

However, all below-mentioned piperidine derivatives prefer chair conformations as was demonstrated by the following NMR investigations.



	16b	21b
R^1	Ph	Ph
R^2	iPr	iPr
R^3	OH	$OCH(Ph)_2$

	5b	6b	20b
R^1	H	Me	Me
R^2	iPr	iPr	iPr
R^3	OH	OH	$OCH(Ph)_2$

Figure 2. NOEs (arrows) and w-couplings (bold) in ^{1}H NMR spectra of **16b**, **21b** and of **5b**, **6b**, **20b**.

The protons in positions 2 and 4 of compounds **5a**, **6a**, **17a**, and **20a** and **22a** were revealed as axial. NOEs from the axial Hs at C-3 to the axial Hs at C-5 as well as from the Hs at C-4 to the axial Hs at C-2 and C-6 were detected. W-couplings were observed between the equatorial Hs at C-3 and C-5 (Fig. 1) with the exception of **5a** due to the superposition of peaks.

Compounds **16b** and **21b** have equatorial Hs at C-2 and axial Hs at C-4. NOEs were detected from the Hs at C-4 to the axial Hs at C-6 and from the axial H at C-3 of **21b** to its axial H at C-5. The latter NOE was invisible for **16b** because of the superposition of peaks. However, w-couplings between the equatorial protons in positions 2 and 6 and in positions 3 and 5 of **16b** and **21b** were successfully removed by homodecoupling experiments (Fig. 2). Compounds **5b**, **6b** and **20b** have axial protons in position 2 and equatorial protons in position 4. Accordingly, NOEs were determined from the axial Hs at C-2 to the axial Hs at C-6 and from the axial Hs at C-3 to the axial Hs at C-5. The latter was not distinguishable beyond all doubt for compound **20b** due to overlap of the signals of the equatorial proton at C-3 and the axial proton at C-5. W-couplings between the equatorial Hs at C-3 and C-5 were invisible as a result of the superposition of the involved protons, but we could detect them between the equatorial Hs at C-4 and C-6 (Fig. 2).

The antimycobacterial activities of compounds **20**–**22** were preliminarily tested in liquid media by incubating 1:1000 diluted overnight cultures of *M. smegmatis* with increasing concentrations of compounds at 37°C under constant shaking. After 5 h incubation, the growth inhibitory activity was determined from the absorption of the compound-containing media at 600 nm using diphenylpyraline as reference compound. All compounds tested within this set-up showed antimycobacterial activity which will be further investigated against *M. tuberculosis H$_{37}$Rv* by the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF, Southern Research Institute, America).

Isomeric 2-substituted piperidin-4-ols have been prepared via new pathways and separated by CC. Their etherification to new analogues of diphenylpyraline was managed by various methods. The configurations and the preferred conformations of all synthesized piperidine derivatives have been investigated by NMR spectroscopy. The prepared title compounds have antimycobacterial activity.

3. Experimental

3.1. General

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin–Elmer). NMR spectra: Varian Inova 400 (297 K) 5 mm tubes, TMS as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba) at the Microanalytical Laboratory at the Institute of Physical Chemistry, University of Vienna. Hydrogenations were performed in a Parr hydrogenation apparatus shaker type 3911. Chromatography: column chromatography (CC): pump: Labomatic MD-80, silica gel 60 (Merck), 0.015–0.025 mm, pore-diameter 60 Å; column diameter 40 mm, layer thickness 410 mm, rate of flow: 15 ml/min, detection: Wellchrom K-2400 RI detector (Knauer), thin-layer chromatography (TLC): TLC plates (Merck) silica gel 60 F_{254}.

3.2. (*RS*)-(±)-4-Dimethylamino-5,6-dihydro-6-isopropyl-pyridine-2(1*H*)-thione (2)

Ketone **1** (0.2 mol) and dimethylammonium rhodanide (0.1 mol) were suspended in 100 ml of bromobenzene. The mixture was refluxed for 8 h at a water separator and the solvent removed in vacuo. The residue was triturated with propan-2-ol, filtered with suction and recrystallized. Yield: 13.52 g (68.2%); mp 142°C (propan-2-ol); IR (KBr): $\tilde{\nu}$=3169 (s), 2952 (m), 1571 (s), 1525 (s), 1400 (s), 1121 (s), 1057 (s), 976 (s) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 400 MHz): 0.88, 0.90 (2d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 1.89–2.02 (m, 1H, CH(CH$_3$)$_2$), 2.24 (dd, J=16.4, 11.6 Hz, 1H, 5-H), 2.43 (dd, J=16.4, 5.6 Hz, 1H, 5-H), 2.91 (s, 6H, N(CH$_3$)$_2$), 3.20–3.26 (m, 1H, 6-H), 5.16 (s, 1H, 3-H), 8.06 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d$_6$, δ, 100 MHz): 17.50, 18.41 (CH(*C*H$_3$)$_2$), 25.70 (C-5), 29.80 (*C*H(CH$_3$)$_2$), 38.95 (N(CH$_3$)$_2$), 56.67 (C-6), 97.32 (C-3), 154.42 (C-4), 189.78 (C-2) ppm. Anal. calcd for $C_{10}H_{18}N_2S$ (198.33): C, 60.56; H, 9.15; N, 14.12; S, 16.17%. Found: C, 60.62; H, 9.18; N, 14.14; S, 15.91%.

3.3. (*RS*)-(±)-5,6-Dihydro-4-hydroxy-6-isopropyl-pyridine-2(1*H*)-thione (3) resp. (*RS*)-(±)-2-(1-Methyl-ethyl)-6-thioxopiperidin-4-one (4)

Compound **2** (0.050 mol) was suspended in a 2 M solution of sodium hydroxide (0.5 mol) and stirred at 60°C for 72 h. The mixture was cooled and filtered. The ice-cooled solution was acidified with HCl_{conc}. The separated oil was dissolved in dichloromethane. The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent was removed in vacuo. The product may be recrystallized, but smells bad and is readily decomposing. Therefore the oily residue was used for the synthesis of the piperidin-4-oles **5a** and **5b** without further purification. Yield: 6.10 g (71.2%);

mp 56°C (benzene); IR (KBr): $\tilde{\nu}$=3403 (m), 3197 (m), 2963 (m), 1723 (s), 1612 (s), 1339 (m), 1105 (m) cm^{-1}.

Compound **3**. ^1H NMR (DMSO-d_6, δ, 400 MHz): 0.86, 0.88 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.92–2.02 (m, 1H, $CH(CH_3)_2$), 2.23–2.27 (m, 2H, 5-H), 3.33–3.40 (m, 1H, 6-H), 5.50 (s, 1H, 3-H), 8.89 (s, 1H, NH), 10.60 (br, 1H, OH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.35, 18.48 ($CH(CH_3)_2$), 27.47 (C-5), 30.09 ($CH(CH_3)_2$), 57.08 (C-6), 103.58 (C-3), 163.86 (C-4), 192.70 (C-2) ppm.

Compound **4**. ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.02, 1.06 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.93–2.06 (m, 1H, $CH(CH_3)_2$), 2.45 (dd, J=16.8, 9.2 Hz, 1H, 3-H), 2.65 (dd, J=16.8, 4.8 Hz, 1H, 3-H), 3.63–3.69 (m, 1H, 2-H), 3.71, 3.84 (2d, J=20.4 Hz, 2H, 5-H), 9.02 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.79, 18.44 ($CH(CH_3)_2$), 31.74 ($CH(CH_3)_2$), 39.76 (C-3), 54.71 (C-5), 58.98 (C-2), 198.47 (C-6), 201.93 (C-4) ppm.

3.4. 2-Isopropylpiperidin-4-ols (5a,b)

15 g of freshly prepared Raney nickel W-7[30] were added to a solution of **3a**, **4a** (0.02 mol) in 200 ml of ethanol. The mixture was shaken at room temperature at 45 psi for 96 h. The reaction mixture was sucked off. The residue was washed with ethanol. The filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane and H_2O. The layers were separated and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over sodium sulfate. The solvent was evaporated and the diastereomeric piperidinols were separated by CC over silica gel eluting with methanol/ethyl acetate (4:1). The hydrochlorides of **5a** and **5b** were afforded by treatment with equivalent amounts of a 1 M solution of hydrogen chloride in diethylether. The solvent was evaporated and the residues were recrystallized.

3.4.1. (2*RS*,4*SR*)-(±)-2-Isopropylpiperidin-4-ol (5a). Yield: 2.24 g (62.3%); mp (HCl): 211°C (acetone); R_f (base)= 0.20 (methanol/ethyl acetate=4:1); IR (base, KBr): $\tilde{\nu}$=3269 (m), 2936 (s), 2858 (s), 1468 (m), 1449 (m), 1366 (m), 1055 (s), 857 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.92, 0.94 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.04 (ddd, J=11.4, 11.4, 11.4 Hz, 1H, 3-H_{ax}), 1.33 (dddd, J= 12.1, 12.1, 12.1, 4.3 Hz, 1H, 5-H_{ax}), 1.57–1.65 (m, 1H, $CH(CH_3)_2$), 1.80 (br, 2H, NH, OH), 1.91–2.02 (m, 2H, 3-H_{equ}, 5-H_{equ}), 2.28 (ddd, J=11.2, 5.8, 2.3 Hz, 1H, 2-H_{ax}), 2.60 (ddd, J=12.5, 12.5, 2.5 Hz, 1H, 6-H_{ax}), 3.14 (ddd, J=12.5, 4.3, 2.5 Hz, 1H, 6-H_{equ}), 3.58–3.66 (m, 1H, 4-H_{ax}) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 18.68, 19.00 ($CH(CH_3)_2$), 32.87 ($CH(CH_3)_2$), 36.14 (C-5), 38.92 (C-3), 44.76 (C-6), 61.12 (C-2), 69.71 (C-4) ppm. Anal. calcd for $C_8H_{18}ClNO$ (179.69): C, 53.47; H, 10.10; Cl, 19.73; N, 7.79%. Found: C, 53.51; H, 9.98; Cl, 19.90; N, 7.68%.

3.4.2. (2*RS*,4*RS*)-(±)-2-Isopropylpiperidin-4-ol (5b). Yield: 0.47 g (13.1%); mp (HCl): 173°C (acetone); R_f (base)= 0.15 (methanol/ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3267 (m), 2944 (m), 2889 (m), 1476 (m), 1371 (m), 1271 (s), 1078 (s), 996 (s), 887 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.89, 0.91 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.41 (ddd, J=13.7, 11.4, 2.8 Hz, 1H, 3-H_{ax}), 1.50–1.76 (m, 4H, $CH(CH_3)_2$, 3-H_{equ}, 5-H_{ax}, 5-H_{equ}), 2.27 (br, 2H, NH, OH), 2.67 (ddd, J=11.4, 6.3, 2.6 Hz, 1H, 2-H_{ax}), 2.88 (ddd, J= 12.0, 4.5, 2.7 Hz, 1H, 6-H_{equ}), 3.03 (ddd, J=12.0, 12.0, 3.6 Hz, 1H, 6-H_{ax}), 4.14–4.19 (m, 1H, 4-H_{equ}) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 18.71, 18.80 ($CH(CH_3)_2$), 32.57 ($CH(CH_3)_2$), 33.15 (C-5), 36.07 (C-3), 40.95 (C-6), 56.13 (C-2), 64.90 (C-4) ppm. Anal. calcd for $C_8H_{18}ClNO$ (179.69): C, 53.47; H, 10.10; Cl, 19.73; N, 7.79%. Found: C, 53.54; H, 10.00; Cl, 19.72; N, 7.72%.

3.5. 1-Methylpiperidin-4-ols (6)

General procedure. Formic acid (0.05 mol) was added to compounds **5a** or **5b** (0.01 mol) at 0°C. The mixture was slowly warmed until solution occurred. A 37% aqueous solution of formaldehyde (0.02 mol) was subsequently added at room temperature. The solution was heated on a steam bath until the generation of carbon dioxide ceased. The solution was cooled, acidified with concentrated hydrochloric acid and the solvent removed in vacuo. The oily residue was dissolved in 2 ml of H_2O, made alkaline with a 25% solution of caustic soda and extracted three times with ether. The combined organic layers were dried over sodium sulfate and the solvent was evaporated. The hydrochlorides of **6a** and **6b** were afforded by treatment with equivalent amounts of a 1 M solution of hydrogen chloride in diethylether. The solvent was evaporated and the residues were recrystallized.

3.5.1. (2*RS*,4*SR*)-(±)-2-Isopropyl-1-methylpiperidin-4-ol (6a). Yield: 1.72 g (88.8%); mp (HCl): 201°C (acetone); IR (base, KBr): $\tilde{\nu}$=3417 (s), 2959 (s), 2933 (s), 1631 (s), 1602 (m), 1461 (m), 1377 (m), 1072 (m) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.87, 0.90 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.22 (ddd, J=11.4, 11.4, 11.4 Hz, 1H, 3-H_{ax}), 1.58 (dddd, J=12.3, 12.3, 12.3, 4.2 Hz, 1H, 5-H_{ax}), 1.78 (ddd, J=11.4, 4.0, 2.2 Hz, 1H, 2-H_{ax}), 1.82–1.92 (m, 2H, 3-H_{equ}, 5-H_{equ}), 2.02–2.10 (m, 1H, $CH(CH_3)_2$), 2.16 (ddd, J=12.3, 12.3, 2.4 Hz, 1H, 6-H_{ax}), 2.23 (s, 3H, NCH_3), 2.55 (br, 1H, OH), 2.93 (ddd, J=12.3, 3.4, 3.4 Hz, 1H, 6-H_{equ}), 3.54–3.63 (m, 1H, 4-H_{ax}) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.89, 19.99 ($CH(CH_3)_2$), 27.60 ($CH(CH_3)_2$), 33.02 (C-3), 34.85 (C-5), 41.48 (NCH_3), 55.71 (C-6), 67.09 (C-2), 69.59 (C-4) ppm. Anal. calcd for $C_9H_{20}ClNO$ (193.72): C, 55.80; H, 10.41; Cl, 18.30; N, 7.23%. Found: C, 55.95; H, 10.46; Cl, 18.30; N, 7.22%.

3.5.2. (2*RS*,4*RS*)-(±)-2-Isopropyl-1-methylpiperidin-4-ol (6b). Yield: 1.47 g (75.9%); mp (HCl): 159°C (acetone/ether); IR (base, KBr): $\tilde{\nu}$=3339 (m), 2958 (s), 2780 (m), 1460 (m), 1375 (m), 1270 (m), 1074 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.85, 0.88 (2d, J=6.7 Hz, 6H, $CH(CH_3)_2$), 1.49 (ddd, J=13.8, 11.4, 2.7 Hz, 1H, 3-H_{ax}), 1.57–1.69 (m, 2H, 3-H_{equ}, 5-H_{equ}), 1.82–1.92 (m, 1H, 5-H_{ax}), 1.94 (br, 1H, OH), 2.08–2.21 (m, 2H, 2-H_{ax}, $CH(CH_3)_2$), 2.27 (s, 3H, NCH_3), 2.53 (ddd, J=12.2, 12.2, 2.8 Hz, 1H, 6-H_{ax}), 2.70 (ddd, J=12.2, 4.7, 2.7 Hz, 1H, 6-H_{equ}), 4.13–4.18 (m, 1H, 4-H_{equ}) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.88, 19.89 ($CH(CH_3)_2$), 27.16 ($CH(CH_3)_2$), 30.48 (C-3), 32.29 (C-5), 42.41 (NCH_3), 51.38 (C-6), 62.43 (C-2), 64.78 (C-4) ppm. Anal. calcd for $C_9H_{20}ClNO$ (193.72): C, 55.80; H, 10.41; Cl, 18.30; N, 7.23%. Found: C, 55.99; H, 10.17; Cl, 18.16; N, 7.22%.

3.6. (*RS*)-(±)-1-Anilino-5-phenylpentan-3-ol (15)

10 g of freshly prepared Raney nickel W-7[30] were added to a solution of **12** (0.005 mol) in 70 ml of ethanol. The mixture was shaken at room temperature at 45 psi for 8 h. The reaction mixture was sucked off. The residue was washed with ethanol and the filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane and H_2O. The layers were separated and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried over sodium sulfate. The solvent was evaporated and the pentanol **15** was separated from small amounts of **17a** and **17b** by CC over silica gel eluting with toluene/ethyl acetate (9:1). The solvent was evaporated and the oily residue was recrystallized. Yield: 1.02 g (79.9%); mp 90°C (ethanol/water); R_f=0.12 (toluene/ethyl acetate=9:1); IR (KBr): $\tilde{\nu}$=3272 (s), 2946 (m), 2918 (m), 1604 (s), 1507 (s), 1052 (s), 931 (m), 755 (s), 737 (m), 691 (s) cm^{-1}; ^1H NMR (DMSO-d_6, δ, 400 MHz): 1.54–1.73 (m, 4H, 2-H, 4-H), 2.54–2.62 (m, 1H, 5-H), 2.68–2.75 (m, 1H, 5-H), 3.00–3.14 (m, 2H, 1-H), 3.53–3.61 (m, 2H, 3-H), 4.58 (d, J=5.6 Hz, 1H, OH), 5.45 (d, J=5.4 Hz, 1H, NH), 6.47–7.28 (m, 10H, aromatic H) ppm. ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 31.54 (C-5), 36.47 (C-2), 39.41 (C-4), 39.85 (C-1), 67.46 (C-3), 111.87, 115.27, 125.52, 128.23, 128.26, 128.82, 142.46, 149.07 (aromatic C) ppm. Anal. calcd for $C_{17}H_{21}NO$ (255.36): C, 79.96; H, 8.29; N, 5.49%. Found: C, 79.70; H, 8.11; N, 5.37%.

3.7. 1-Phenylpiperidin-4-ols (16, 17)

General procedure. 10 g of freshly prepared Raney nickel W-2[32] were added to a solution of compounds **11** or **12** (0.01 mol) in 50 ml of ethanol. The mixture was shaken at room temperature at 30 psi for 6 h. The reaction mixture was sucked off. The residue was washed repeatedly with ethanol. The filtrate was concentrated in vacuo. The isomers were separated by CC over silica gel eluting with toluene/ethyl acetate (6:3) or toluene/ethyl acetate (9:1), respectively. The hydrochlorides of **16**, **17** were afforded by treatment with equivalent amounts of a 1 M solution of hydrogen chloride in diethylether. The solvent was evaporated and the residues recrystallized.

3.7.1. (2*RS*,4*SR*)-(±)-2-Isopropyl-1-phenylpiperidin-4-ol (16a). Yield: 1.54 g (60.2%); mp (HCl): 230°C (ethanol/ethyl acetate); R_f (base)=0.22 (toluene/ethyl acetate=6:3); IR (KBr): $\tilde{\nu}$=3337 (s), 2972 (m), 2538 (s), 1495 (m), 1090 (s) 1030 (m), 756 (m), 694 (m) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.83 (d, J=6.7 Hz, 6H, $CH(CH_3)_2$), 1.53 (ddd, J=12.7, 9.1, 9.1 Hz, 1H, 3-H_{ax}), 1.63 (dddd, J= 12.7, 9.0, 9.0, 4.0 Hz, 1H, 5-H_{ax}), 1.79 (br, 1H, OH), 1.86–2.00 (m, 3H, 3-H_{equ}, 5-H_{equ}, $CH(CH_3)_2$), 2.93 (ddd, J=12.7, 9.0, 3.4 Hz, 1H, 6-H_{ax}), 2.94–3.00 (m, 1H, 2-H_{ax}), 3.23 (ddd, J=12.7, 5.7, 4.0 Hz, 1H, 6-H_{equ}), 3.80–3.88 (m, 1H, 4-H_{ax}), 6.96–7.29 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 16.55, 19.30 ($CH(CH_3)_2$), 28.41 ($CH(CH_3)_2$), 32.96 (C-3), 34.32 (C-5), 50.38 (C-6), 62.22 (C-2), 68.69 (C-4), 122.15, 128.98, 151.78 (aromatic C) ppm. Anal. calcd for $C_{14}H_{22}ClNO$ (255.79): C, 65.74; H, 8.67; Cl, 13.86; N, 5.48%. Found: C, 65.76; H, 8.66; Cl, 13.88; N, 5.35%.

3.7.2. (2*RS*,4*RS*)-(±)-2-Isopropyl-1-phenylpiperidin-4-ol (16b). Yield: 0.54 g (21.1%); mp (HCl): 165°C (ethanol/ethyl acetate); R_f (base)=0.27 (toluene/ethyl acetate=6:3); IR (KBr): $\tilde{\nu}$=3345 (s), 2966 (m), 2612 (m), 1495 (m), 1427 (m), 1393 (s), 1374 (s), 981 (s), 776 (m), 757 (m), 698 (m) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.88, 0.99 (2d, J=6.6 Hz, 6H, $CH(CH_3)_2$), 1.41 (ddd, J=13.6, 11.3, 5.1 Hz, 1H, 3-H_{ax}), 1.44 (br, 1H, OH), 1.49 (dddd, J=11.8, 11.8, 11.8, 4.4 Hz, 1H, 5-H_{ax}), 1.86–1.93 (m, 1H, 5-H_{equ}), 2.02–2.12 (m, 2H, 3-H_{equ}, $CH(CH_3)_2$), 3.07 (ddd, J=14.4, 12.0, 2.7 Hz, 1H, 6-H_{ax}), 3.49–3.55 (m, 1H, 2-H_{equ}), 3.62–3.69 (m, 1H, 6-H_{equ}), 3.93–4.02 (m, 1H, 4-H_{ax}), 6.68–7.22 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 20.27, 20.53 ($CH(CH_3)_2$), 27.89 ($CH(CH_3)_2$), 33.58 (C-5), 34.24 (C-3), 40.86 (C-6), 62.47 (C-2), 65.79 (C-4), 115.11, 117.28, 129.16, 150.71 (aromatic C) ppm. Anal. calcd for $C_{14}H_{22}ClNO$ (255.79): C, 65.74; H, 8.67; Cl, 13.86; N, 5.48%. Found: C, 65.71; H, 8.78; Cl, 13.84; N, 5.46%.

3.7.3. (2*RS*,4*SR*)-(±)-1,2-Diphenylpiperidin-4-ol (17a). Yield: 1.70 g (56.0%); mp (HCl): 227°C (ethanol/ethyl acetate); R_f (base)=0.06 (toluene/ethyl acetate=9:1); IR (KBr): $\tilde{\nu}$= 3359 (s), 2520 (s), 1494 (m), 1242 (m), 1081 (s), 762 (s), 699 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.57 (br, 1H, OH), 1.77 (ddd, J=11.6, 11.6, 10.5 Hz, 1H, 3-H_{ax}), 1.85 (dddd, J=11.9, 11.1, 11.1, 4.0 Hz, 1H, 5-H_{ax}), 2.05–2.12 (m, 1H, 5-H_{equ}), 2.18–2.24 (m, 1H, 3-H_{equ}), 2.93 (ddd, J=12.5, 11.9, 2.7 Hz, 1H, 6-H_{ax}), 3.54 (ddd, J=12.5, 4.0, 4.0 Hz, 1H, 6-H_{equ}), 3.83–3.91 (m, 1H, 4-H_{ax}), 4.11 (dd, J=10.5, 3.3 Hz, 1H, 2-H_{ax}), 6.80–7.25 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 35.45 (C-5), 45.18 (C-3), 54.16 (C-6), 62.18 (C-2), 68.89 (C-4), 122.31, 123.10, 126.51, 127.11, 128.23, 128.44, 143.66, 151.74 (aromatic C) ppm. Anal. calcd for $C_{17}H_{20}ClNO+0.3C_2H_5OH$ (303.63): C, 69.62; H, 7.24; Cl, 11.68; N, 4.61%. Found: C, 69.68; H, 7.17; Cl, 11.54; N, 4.50%.

3.7.4. (2*RS*,4*RS*)-(±)-1,2-Diphenylpiperidin-4-ol (17b). Yield: 0.60 g (20.7%); mp (HCl): 169°C (ethanol/ethyl acetate); R_f (base)=0.10 (toluene/ethyl acetate=9:1); IR (KBr): $\tilde{\nu}$= 3447 (m), 2930 (m), 2560 (s), 2315 (s), 1491 (s), 1413 (s), 982 (s), 765 (s), 700 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.68 (dddd, J=12.7, 8.8, 8.8, 4.0 Hz, 1H, 5-H_{ax}), 1.81 (br, 1H, OH), 1.93 (ddd, J=13.6, 8.8, 4.9 Hz, 1H, 3-H_{ax}), 1.96–2.03 (m, 1H, 5-H_{equ}), 2.33–2.40 (m, 1H, 3-H_{equ}), 3.23 (ddd, J=13.2, 9.6, 3.6 Hz, 1H, 6-H_{ax}), 3.65 (ddd, J=13.2, 4.9, 4.9 Hz, 1H, 6-H_{equ}), 3.87–3.93 (m, 1H, 4-H_{ax}), 4.98 (dd, J=4.9, 4.9 Hz, 1H, 2-H_{equ}), 6.72–7.30 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 33.87 (C-5), 39.41 (C-3), 44.37 (C-6), 57.52 (C-2), 64.97 (C-4), 116.80, 118.90, 126.43, 126.91, 128.41, 129.02, 141.88, 150.58 (aromatic C) ppm. Anal. calcd for $C_{17}H_{20}ClNO$ (289.81): C, 70.46; H, 6.96; Cl, 12.23; N, 4.83%. Found: C, 70.37; H, 7.09; Cl, 12.12; N, 4.79%.

3.8. 4-Benzhydryloxy-1-methylpiperidines (20–22)

General procedures. After their preparation according to methods A–D compounds **20**–**22** were purified by CC over silica gel eluting with the solvent mentioned under their R_f values. Their hydrochlorides were afforded by treatment with equivalent amounts of a 1 M solution of hydrogen

chloride in diethylether. The solvent was evaporated and the residues recrystallized.

General method A. The piperidinols **6**, **16** or **17** (0.006 mol), bromodiphenylmethane (0.006 mol) and potassium carbonate (0.003 mol) were stirred on an oil bath at 140°C for 5 h. The mixture was cooled and benzene (30 ml) was added. The inorganic salts were dissolved in water (5 ml). The layers were separated in a separatory funnel. The aqueous layer was extracted once with benzene (10 ml). The combined organic layers were washed twice with water, dried and evaporated.

General method B. To an ice-cooled solution of compounds **6**, **16** or **17** (0.006 mol) in 50 ml of freshly distilled *N*,*N*-dimethylformamide (DMF) was added sodium hydride (0.007 mol of a 60% dispersion in mineral oil). Bromodiphenylmethane (0.007 mol) was dissolved in DMF and added dropwise to the reaction mixture, which was stirred at room temperature for 3 h (longer reaction periods did not cause increase in yield). After addition of ethanol (10 ml), the mixture was poured into ice-water (200 ml). The product was extracted three times with benzene. The workup was identical with method A.

General method C. To a solution of the piperidinols **6**, **16** or **17** (0.002 mol) in 20 ml of dry toluene diphenyldiazomethane (0.0024 mol) was added. The mixture was heated under reflux for 18 h. After cooling to room temperature the organic layer was repeatedly extracted with a 2 M solution of HCl in water. The aqueous phase was made alkaline with dilute caustic soda and extracted with toluene. The organic layer was concentrated in vacuo.

General method D. A solution of the piperidinols **6**, **16** or **17** (0.002 mol), diphenylmethanol (0.0025 mol) and toluene-4-sulfonic acid monohydrate (0.0025 mol) in 100 ml of toluene was refluxed at a water separator for 6 h. After cooling to room temperature the mixture was washed once with a 1 M aqueous solution of caustic soda and twice with water. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo.

3.8.1. (2*RS*,4*SR*)-(±)-4-Benzhydryloxy-2-isopropyl-1-methylpiperidine (20a). Yield (A): 1.65 g (76.4%), (B): 1.11 g (51.4%); mp (HCl): 229°C (acetone/ether); R_f (base)=0.20 (toluene/methanol=9:1); IR (base, KBr): $\tilde{\nu}$=3029 (w), 2957 (s), 2780 (m), 1492 (m), 1455 (s), 1274 (m), 1075 (s), 744 (m), 701 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.84, 0.86 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.31 (ddd, J=11.7, 11.7, 11.7 Hz, 1H, 3-H_{ax}), 1.58–1.68 (m, 2H, 2-H_{ax}, 5-H_{ax}), 1.85–1.92 (m, 1H, 3-H_{equ}), 1.93–2.05 (m, 3H, 5-H_{equ}, 6-H_{ax}, $CH(CH_3)_2$), 2.16 (s, 3H, NCH_3), 2.87 (ddd, J=12.0, 3.5, 3.5 Hz, 1H, 6-H_{equ}), 3.29–3.37 (m, 1H, 4-H_{ax}), 5.56 (s, 1H, OCH), 7.20–7.37 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.89, 19.71 ($CH(CH_3)_2$), 27.77 ($CH(CH_3)_2$), 30.21 (C-3), 31.98 (C-5), 41.70 (NCH_3), 55.73 (C-6), 67.04 (C-2), 74.90 (C-4), 80.08 (OCH), 127.06, 127.08, 127.25, 127.31, 128.28, 128.32, 142.71, 142.91 (aromatic C) ppm. Anal. calcd for $C_{22}H_{30}ClNO$ (359.94): C, 73.41; H, 8.40; Cl, 9.85; N, 3.89%. Found: C, 73.22; H, 8.18; Cl, 9.83; N, 3.91%.

3.8.2. (2*RS*,4*RS*)-(±)-4-Benzhydryloxy-2-isopropyl-1-methylpiperidine (20b). Yield (A): 1.43 g (65.2%), (B): 1.15 g (52.5%); mp (HCl): 215°C (acetone/ether); R_f (base)=0.10 (toluene/methanol=9:1); IR (base, KBr): $\tilde{\nu}$=3029 (w), 2957 (s), 2932 (m), 2796 (m), 1492 (m), 1456 (s), 1266 (m), 1065 (s), 746 (m), 701 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.82, 0.84 (2d, J=7.0 Hz, 6H, $CH(CH_3)_2$), 1.32 (ddd, J=14.0, 11.3, 2.7 Hz, 1H, 3-H_{ax}), 1.67–1.87 (m, 3H, 3-H_{equ}, 5-H_{ax}, 5-H_{equ}), 2.06–2.17 (m, 1H, $CH(CH_3)_2$), 2.27 (s, 3H, NCH_3), 2.23–2.33 (m, 1H, 2-H_{ax}), 2.64 (ddd, J=11.8, 11.8, 2.8 Hz, 1H, 6-H_{ax}), 2.66–2.74 (m, 1H, 6-H_{equ}), 3.75–3.78 (m, 1H, 4-H_{equ}), 5.45 (s, 1H, OCH), 7.23–7.37 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.95, 19.82 ($CH(CH_3)_2$), 27.02 ($CH(CH_3)_2$), 27.41 (C-3), 29.34 (C-5), 41.92 (NCH_3), 52.45 (C-6), 63.40 (C-2), 69.40 (C-4), 80.47 (OCH), 126.90, 127.10, 127.30, 127.36, 128.28, 128.31, 142.70, 142.80 (aromatic C) ppm. Anal. calcd for $C_{22}H_{30}ClNO+0.3H_2O$ (365.34): C, 72.33; H, 8.44; Cl, 9.70; N, 3.83%. Found: C, 72.32; H, 8.43; Cl, 9.77; N, 3.84%.

3.8.3. (2*RS*,4*SR*)-(±)-4-Benzhydryloxy-2-isopropyl-1-phenylpiperidine (21a). Yield (A): 1.08 g (42.7%), (B): 0.77 g (30.4%), (C): 0.55 g (65.2%), (D): 0.75 g (88.9%); mp (HCl): 219°C (ethanol/ethyl acetate); R_f (base)=0.25 (cyclohexane/ethyl acetate=19:1); IR (KBr): $\tilde{\nu}$=2969 (m), 2271 (s), 1599 (m), 1492 (s), 1485 (s), 1411 (s), 1092 (s), 709 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.83, 0.89 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.67–1.94 (m, 4H, 3-H, 5-H), 2.11–2.23 (m, 1H, $CH(CH_3)_2$), 3.00 (ddd, J=13.0, 8.6, 4.3 Hz, 1H, 6-H), 3.08–3.14 (m, 1H, 2-H), 3.29 (ddd, J=13.0, 7.8, 3.6 Hz, 1H, 6-H), 3.57–3.63 (m, 1H, 4-H), 5.53 (s, 1H, OCH), 6.82–7.38 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.65, 20.23 ($CH(CH_3)_2$), 28.72 ($CH(CH_3)_2$), 29.84 (C-3), 30.03 (C-5), 46.86 (C-6), 62.03 (C-2), 72.92 (C-4), 80.63 (OCH), 119.85, 120.40, 126.78, 126.95, 127.19, 127.29, 128.28, 128.31, 128.99, 142.80, 143.13, 151.49 (aromatic C) ppm. Anal. calcd for $C_{27}H_{32}ClNO$ (422.01): C, 76.85; H, 7.64; Cl, 8.40; N, 3.32%. Found: C, 76.91; H, 7.77; Cl, 8.30; N, 3.33%.

3.8.4. (2*RS*,4*RS*)-(±)-4-Benzhydryloxy-2-isopropyl-1-phenylpiperidine (21b). Yield (A): 0.92 g (35.6%), (D): 0.67 g (77.7%); mp (HCl): 182°C (ethanol/ethyl acetate); R_f (base)=0.26 (cyclohexane/ethyl acetate=19:1); IR (KBr): $\tilde{\nu}$=2969 (m), 2490 (s), 1596 (m), 1492 (s), 1069 (s), 1048 (s), 760 (m), 700 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.82, 0.84 (2d, J=7.0 Hz, 6H, $CH(CH_3)_2$), 1.56 (ddd, J=11.7, 11.1, 5.0 Hz, 1H, 3-H_{ax}), 1.66 (dddd, J=12.3, 12.3, 10.5, 4.5 Hz, 1H, 5-H_{ax}), 1.86–1.95 (m, 2H, 5-H_{equ}, $CH(CH_3)_2$), 2.07–2.13 (m, 1H, 3-H_{equ}), 2.99 (ddd, J=14.3, 12.3, 2.7 Hz, 1H, 6-H_{ax}), 3.46–3.52 (m, 1H, 2-H_{equ}), 3.59–3.66 (m, 1H, 6-H_{equ}), 3.69–3.78 (m, 1H, 4-H_{ax}), 5.55 (s, 1H, OCH), 6.67–7.34 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 19.95, 20.55 ($CH(CH_3)_2$), 27.73 ($CH(CH_3)_2$), 30.72 (C-5), 31.28 (C-3), 41.23 (C-6), 62.54 (C-2), 70.87 (C-4), 80.19 (OCH), 115.38, 117.33, 127.02, 127.09, 127.34, 128.30, 128.32, 129.10, 142.74, 142.77, 150.91 (aromatic C) ppm. Anal. calcd for $C_{27}H_{32}ClNO+0.2\ C_2H_5OH$ (431.22): C, 76.32; H, 7.76; Cl, 8.22; N, 3.25%. Found: C, 76.18; H, 7.78; Cl, 8.20; N, 3.28%.

3.8.5. (2*RS*,4*SR*)-(±)-4-Benzhydryloxy-1,2-diphenylpiperidine (22a). Yield (A): 0.77 g (28.1%), (D): 0.78 g (85.5%); mp (HCl): 195°C (ethanol/ethyl acetate); R_f (base)=0.30 (toluene); IR (KBr): $\tilde{\nu}$=3050 (m), 2358 (s), 1599 (m), 1493 (s), 1449 (m), 1081 (s), 755 (s), 699 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.92 (ddd, J=12.7, 10.5, 10.5 Hz, 1H, 3-H_{ax}), 1.97 (dddd, J=11.9, 11.1, 11.1, 4.1 Hz, 1H, 5-H_{ax}), 2.10–2.18 (m, 1H, 5-H_{equ}), 2.27–2.35 (m, 1H, 3-H_{equ}), 2.87 (ddd, J=11.9, 11.9, 2.8 Hz, 1H, 6-H_{ax}), 3.54 (ddd, J=11.9, 4.1, 4.1 Hz, 1H, 6-H_{equ}), 3.58–3.66 (m, 1H, 4-H_{ax}), 4.05 (dd, J=10.5, 3.3 Hz, 1H, 2-H_{ax}), 5.56 (s, 1H, OCH), 6.78–7.33 (m, 20H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 32.55 (C-5), 41.93 (C-3), 53.86 (C-6), 62.16 (C-2), 73.32 (C-4), 80.13 (OCH), 122.05, 122.84, 126.42, 126.99, 127.04, 127.15, 127.33, 127.34, 128.18, 128.31, 128.34, 128.41, 142.66, 143.90, 151.81 (aromatic C) ppm. Anal. calcd for $C_{30}H_{30}ClNO$ (456.03): C, 79.01; H, 6.63; Cl, 7.77; N, 3.07%. Found: C, 78.73; H, 6.75; Cl, 7.48; N, 3.00%.

3.8.6. (2*RS*,4*RS*)-(±)-4-Benzhydryloxy-1,2-diphenylpiperidine (22b). Yield (A): 0.81 g (29.6%), (D): 0.76 g (83.3%); mp (HCl): 191°C (ethanol/ethyl acetate); R_f (base)=0.46 (toluene); IR (KBr): $\tilde{\nu}$=3056 (m), 2364 (s), 2338 (s), 1598 (m), 1489 (s), 1061 (s), 757 (s), 706 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.84–2.01 (m, 2H, 5-H), 2.06 (ddd, J=13.2, 8.2, 5.1 Hz, 1H, 3-H), 2.23–2.30 (m, 1H, 3-H), 3.16 (ddd, J=12.8, 8.6, 4.0 Hz, 1H, 6-H), 3.60 (ddd, J=12.8, 7.0, 4.0 Hz, 1H, 6-H), 3.68–3.74 (m, 1H, 4-H), 4.88 (dd, J=5.1, 5.1 Hz, 1H, 2-H), 5.52 (s, 1H, OCH), 6.75–7.39 (m, 20H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.04 (C-5), 37.02 (C-3), 45.75 (C-6), 57.96 (C-2), 70.37 (C-4), 80.64 (OCH), 117.95, 119.36, 126.33, 126.89, 127.05, 127.14, 127.32, 127.38, 128.29, 128.32, 128.33, 128.91, 142.46, 142.79, 151.16 (aromatic C) ppm. Anal. calcd for $C_{30}H_{30}ClNO$ (456.03): C, 79.01; H, 6.63; Cl, 7.77; N, 3.07%. Found: C, 78.80; H, 6.72; Cl, 7.68; N, 3.03%.

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