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Stereoselective Transformation of 2*H*-1,4-Oxazin-2-ones into 2,(2),5,5-Tri- and Tetrasubstituted Analogues of *cis*-5-Hydroxy-2-piperidinemethanol and *cis*-5-Hydroxy-6-oxo-2-piperidinecarboxylic Acid

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Abstract—2,(2),5,5-Tri- and tetrasubstituted analogues of 5-hydroxy-2-piperidinemethanol and 5-hydroxy-6-oxo-2-piperidinecarboxylic acid have been prepared via Diels–Alder reaction of 3-substituted 2*H*-1,4-oxazin-2-ones with ethene followed by functional group transformation of the resulting imidoyl chloride and lactone groups. Some of the 2-piperidinemethanol products are converted further into potential substance P antagonists.

Introduction

Substituted piperidines exhibit an extensive range of biological activities and are of great interest in the pharmaceutical industry. In particular the structural framework of β-hydroxypiperidines is widely found in naturally occurring piperidine alkaloids, such as (+)-pseudoconhydrine (**I**) (Fig. 1),[1] (−)hydroxysedamine (**II**)[2] and (−)desoxoprosophilline (**III**).[3] These β-hydroxypiperidines can be considered as conformationally constrained cyclic analogues of bioactive β-aminoalcohols showing various activity profiles.[4] Recently, Merck researchers have claimed substance P antagonist activity for the β-hydroxypiperidine derivatives [**IV**][5] and [**V**].[6] Substance P, a neurotransmitter in the central nervous system, is postulated to play an important role in a number of biological processes including pain transmission, asthma and neurogenic inflammation.

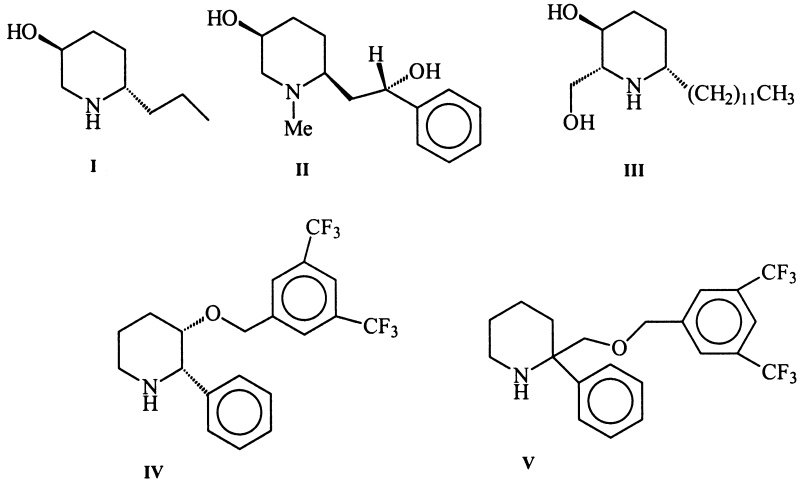

Figure 1.

Keywords: substituted piperidines; 3-piperidinols; substance P antagonists; Diels–Alder reaction.
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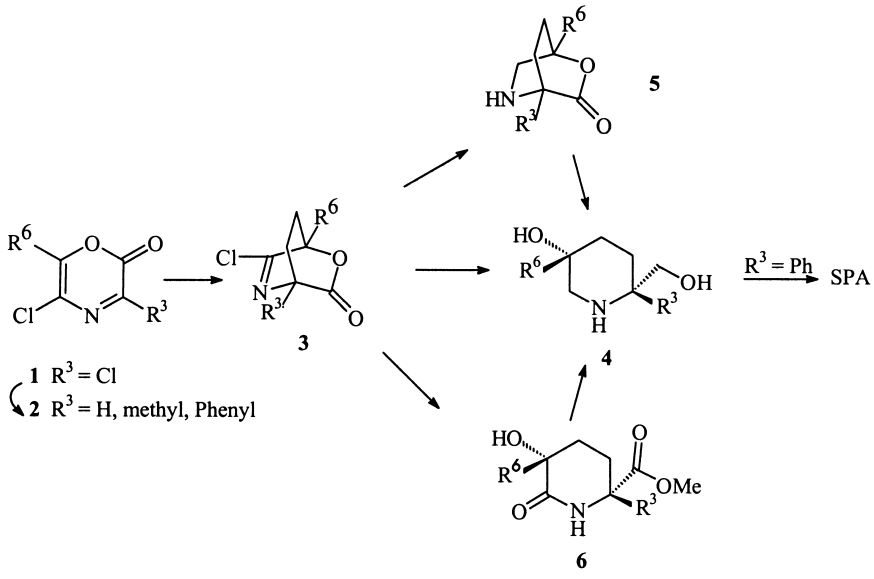


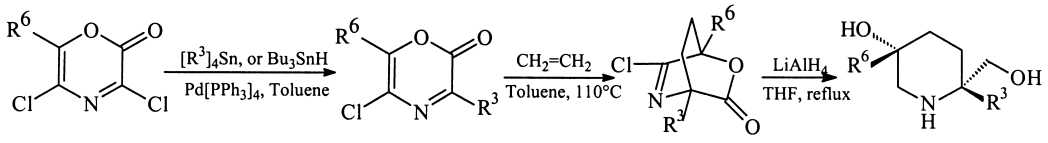
Scheme 1.

Clearly, a short, versatile and stereocontrolled route for the synthesis of substituted piperidines is highly important. Such a route could proceed via Diels–Alder reaction of cyclic 2-azadiene systems. Previously we reported a non-stereoselective synthesis of 2,3,5-substituted piperidines: this involved cycloaddition of 2*H*-1,4-oxazin-2-ones and acetylenic compounds with concomitant elimination of carbon dioxide, followed by catalytic hydrogenation.[7] In contrast to the cycloaddition–elimination reaction observed for acetylenic dienophiles, cycloadducts of 2*H*-1,4-oxazin-2-ones and olefins can be isolated and derivatised.[8] In the present study, we wish to report a short and stereoselective approach to the title compounds, i.e. 2,(2),5,5-tri- and tetra-substituted analogues of 5-hydroxy-6-oxo-2-piperidine-carboxylic acid and 5-hydroxy-2-piperidinemethanol. Our approach involves the cycloaddition of variously substituted oxazinones with ethene, followed by functional group transformation of the resulting lactone and imidoyl chloride groups; some of the β-hydroxypiperidine products were elaborated further into potential substance P antagonists (SPA).

Results and Discussion

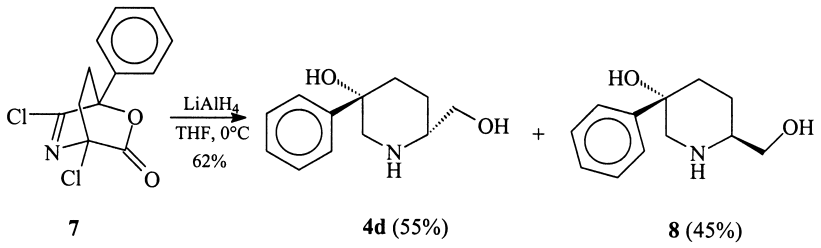
Our synthetic approach is summarised in Scheme 1.

The starting 3,5-dichloro-oxazinones[9] **1a**,**b** were prepared from the corresponding α-hydroxynitriles, and subsequently functionalised (Ph, Me) or dechlorinated at the 3 position (Scheme 2). Due to the lactone function of **1a**,**b**, nucleophilic attack at the reactive 3-position does not proceed selectively when using organolithium or Grignard reagents. However, a convenient alternative for regioselective introduction of the desired C-substituents was provided by palladium-catalysed coupling with organotin reagents. This mild and selective coupling reaction serves to form a C–C bond with vinylic and aromatic halides, with formation of triorganotin halide as a driving force. Thus a mixture of **1a** or **1b** and the tetramethyl- or tetraphenyltin reagent was heated with a catalytic amount of tetrakis(triphenylphosphine)palladium at reflux temperature in degassed toluene under inert atmosphere to produce the 3-methyl and 3-phenyl substituted oxazinones **2a–c** as the sole products in high yield. Similarly **2d** was obtained by using tributyltin hydride at room temperature. When, in the latter reaction, the temperature was raised above 50°C, the 3-butyl and 3-tributylstannyl substituted oxazinones were formed as side products. The 3-substituted oxazinones **2a–d** then were made to react with ethene in toluene at 110°C in a sealed tube. Following cycloaddition and evaporation of the solvent, the crude adducts **3a–d** were used directly in the next step without further purification.



2, 3, 4	R^6	R^3	2, %	4, % (from 2)
a	Me	Ph	85	72
b	Ph	Ph	79	78
c	Me	Me	90	56
d	Ph	H	86	60

Scheme 2.



Scheme 3.

To convert adducts **3** to compounds of type **4**, both the imidoyl chloride and lactone function must be reduced. From examination of various reaction conditions including the use of $NaBH_4$, $LiBH_4$, $BH_3{\cdot}SMe_2$ and $LiAlH_4$, we found the best yields of the desired piperidinols **4** when using $LiAlH_4$ in THF. Thus a solution of the crude adducts **3a–d** in freshly distilled THF was added carefully to an ice-cooled suspension of $LiAlH_4$ in THF under N_2 atmosphere. Following reaction at room temperature for 4–12 h, reduction of both the imidoyl chloride and lactone groups was completed to afford products **4a–d** in 56–78% yield over two steps. Therefore our two-step sequence, consisting of cycloaddition and reduction, allows for the stereoselective synthesis of 2,2,5,5-tetrasubstituted analogues of *cis*-5-hydroxy-2-piperidinemethanol having variable R^3 and R^6 substituents (Scheme 2). Other substituent combinations than those described in the scheme can be accessible via the corresponding oxazinones **1**; however it should be mentioned that compound **1** (R^6=H) could only be obtained in a low yield.[9]

Reduction was also carried out on the adduct **7** formed via cycloaddition of 3,5-dichloro-oxazinone **1b** with ethene (the angular Cl-substituent derives from the 3-Cl-atom in **1b**). The starting material was consumed after reaction at 0°C for 1 h. Following workup and chromatographic separation, two isomeric products were isolated that showed the same molecular ion as that observed in the mass spectrum of compound **4d** described above. The isomers were characterised further as the *cis* and *trans* compounds **4d** and **8** (Scheme 3). Presumably, reduction of the lactone and imidoyl chloride proceeds as described for the conversion **3a–d→4a–d** (see Scheme 2). However, in this case a 2-chloropiperidine is formed as an intermediate which—probably following loss of HCl and generation of an imine—is reduced in a non-stereoselective way.

From a conformational study using NMR spectroscopy, it appears that the 5-hydroxy-2-piperidinemethanol products **4** and **8** uniformly assume the conformational structure indicated in Fig. 2. This conformational preference seems to be governed by the favourable equatorial disposition of the 5-phenyl or 5-methyl group and an equally favourable axial orientation of the 5-hydroxyl group. The latter may form an internal H-bridge with the piperidine-*N*-atom as found in other 3-piperidinols[4a,4e] (see also below). In the preferred conformational structure of compound **8**, both these stabilising factors co-operate to force the large 2-hydroxymethyl substituent in the axial position. In this context it should be noticed that in model compound **V**, the 2-phenyl and 2-benzyloxymethyl groups adopt an axial and equatorial orientation, respectively. In the ^1H coupled ^{13}C NMR spectra of **4a–c**, the 2-methyl carbon or the *ipso* carbon of the 2-phenyl group exhibited a large coupling $^3J_{C-H}$ (6.0–7.0 Hz) with the axial proton in 3-position, while the coupling between the 5-methyl or 5-phenyl *ipso* carbon and the protons in 4- or 6-position could not be resolved. These $^3J_{C-H}$ coupling values conclusively show the axial orientation for the 2-Ph-groups in **4a**,**b** and the 2-Me in **4c**. Similarly, in the ^1H NMR spectrum of **4d**, a large coupling (J=11.6 Hz) was observed between H-2 (δ 2.52) and the axial H-3 (δ 1.55), indicating an axial orientation of H-2. In the ^1H NMR spectrum of **8**, proton H-2 displayed a downfield (δ 3.00) double quartet signal (J=10.0 and 4.5 Hz). By selective decoupling it was shown that the larger coupling value (J=10.0 Hz) corresponds to an *anti*-oriented proton in the hydroxymethyl side chain, whereas the other *vicinal* protons displayed an equal value of 4.5 Hz for the coupling constant with H-2. On the other hand, no coupling could be observed between the 5-phenyl *ipso* carbon and protons H-4 and H-6. On the basis of these observations, the *trans*-5-hydroxy-2-piperidinemethanol configuration was assigned to **8**, with H-2 equatorially oriented.

Besides the direct conversion of adducts **3** to the 5-hydroxy-2-piperidinemethanol products **4**, we also investigated stepwise approaches proceeding via intermediates **5** or **6**. Partial

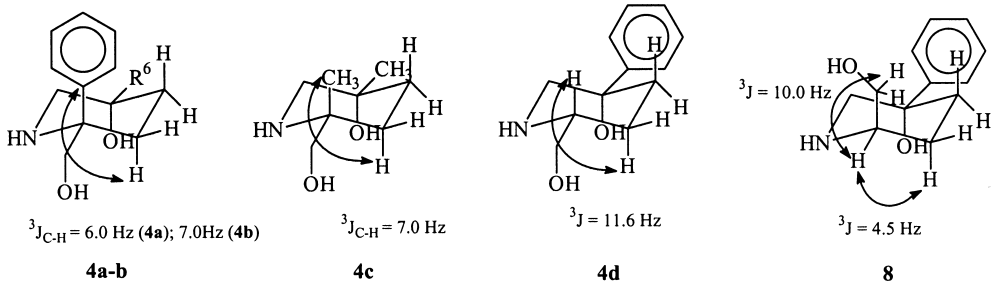
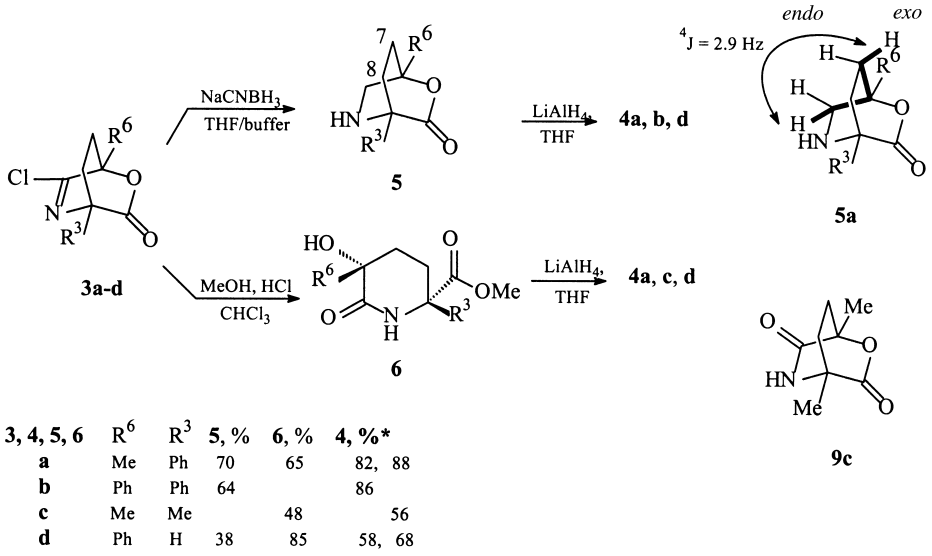


Figure 2.

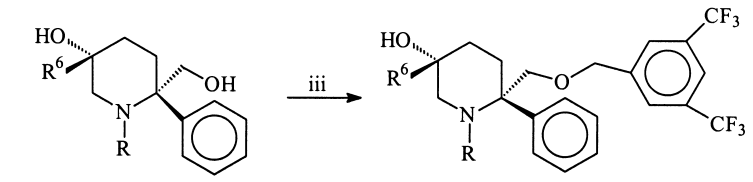


3, 4, 5, 6	R^6	R^3	5, %	6, %	4, %*
a	Me	Ph	70	65	82, 88
b	Ph	Ph	64		86
c	Me	Me		48	56
d	Ph	H	38	85	58, 68

Scheme 4. The yields for **5** and **6** refer to the isolated pure products formed over two steps from **2**; the yields of **4** refer to reduction of **5** and **6** respectively.

reduction of **3** to form the bridged lactone compounds **5** was accomplished using sodium cyanoborohydride ($NaBH_3CN$) in a 4:1 mixture of THF and an aqueous buffer system (1 M NaOAc/HOAc, pH 5.0). It has been reported[10] that $NaBH_3CN$ reduces the imine function with remarkable selectivity in slightly acidic medium. Generally the reduction is performed in a protic solvent, e.g. methanol. However, the HCl produced under these conditions resulted in the autocatalytic solvolysis of the imidoyl chloride while the lactam product was found to be stable to the reducing agent. Hence, the slightly acidic buffer system used may act both as a proton source required for generation and reduction of the intermediate iminium ions, and as a proton acceptor which counteracts hydrolysis by avoiding a severe change in pH of the system. Complete and selective reduction of the imidoyl chloride was effected by heating **3** in the buffered reducing medium, affording the bicyclic aminolactones **5** in moderate to good yields. The relatively low yield of **5d** possibly was due to facilitated hydrolysis of **3d**. The structures of these novel compounds were assigned on the basis of spectral data. The ^1H NMR spectra displayed an AB system for the two H-6 protons, while the pseudoaxial proton H-6_{ax} showed an additional long-range coupling with the *exo* proton H-7 (^4J=2.9 Hz for **5a**) (Scheme 4). In the IR spectra, a strong absorption at 1733 cm^{-1} revealed the presence of the lactone group. Reductive cleavage of the lactone group of compounds **5** was effected by treatment with $LiAlH_4$, offering an alternative route to the 2-piperidinemethanol products **4**.

Solvolysis of the ethene adducts **3** was carried out with methanol in chloroform. This resulted first in hydrolysis of the imidoyl chloride to form the bridged lactam intermediate **9**, and then opening of the lactone group catalysed by the HCl released. This observation is similar to that reported for the ethene adducts of 3,5-dichloro-oxazinone.[11] The yield of the monocyclic ester compounds **6** was found to be dependent on the nature of the substituents R^6 and R^3, being highest (85%) for **6d** and lowest (48%) for **6c**. Presumably, the solvolysis reaction of the imidoyl chloride and especially that of the lactone are slowed down by the steric congestion imposed by the substituents R^3 and R^6, respectively, during conversion of the planar imidoyl and lactone groups into tetrahedral intermediates. Consequently, **6d** was the only product isolated upon treatment of **3d** with acidic methanol, whereas bicyclic lactone **9c** was detected as a major side product. Upon treatment of lactam esters **6** with $LiAlH_4$, complete reduction of both the amide and ester function was achieved, providing a third way for accessing compounds **4**. Apparently the stepwise approaches proceeding



4

a R^6 = Me, R = H
b R^6 = Ph, R = H
e R^6 = Me, R = Me
f R^6 = Me, R = CH_2Ph

ii 82% i 80%

10

a R^6 = Me, R = H (56%)
b R^6 = Ph, R = H (65%)
c R^6 = Me, R = Me (70%)
d R^6 = Me, R = CH_2Ph (87%)

Scheme 5. (i) MeI (1.2 equiv.), K_2CO_3, acetone, reflux, 4 h. (ii) $PhCH_2Br$ (1.2 equiv.), K_2CO_3, acetone, reflux, 3 h. (iii) (1) NaH (2 equiv.), DMF; (2) 3,5 bis(trifluromethyl)benzylbromide (1.1 equiv.), THF, rt, 1 d.

via **5** or **6** are less efficient than the one-step reduction described above. However, compounds **5** and **6** display a stereospecific arrangement of multiple functionalities that may prove useful in further transformations.

In view of the SP potency displayed by compounds **IV** and **V**, we transformed the 2-piperidinemethanol compounds **4a**,**b** into potential SP antagonists **10a**–**d** mimicking the model compounds **IV** and **V**; this involved chemo- and regioselective derivatisation of the amine and/or alcohol functions (Scheme 5). Compounds **10a**,**b** were prepared by selective *O*-benzylation of the primary alcohol group of the 2-phenyl substituted compounds **4a**,**b** following deprotonation with NaH in DMF. The corresponding *N*-substituted derivatives **10c**,**d** were prepared via initial *N*-methylation or *N*-benzylation (MeI or BnBr with K_2CO_3 in acetone/DMF) to form **4e**,**f**, followed by *O*-benzylation of the primary alcohol function.

From the ^{1}H and ^{13}C NMR spectra, compounds **10a**–**d** were shown to adopt the '*2-Ph axial*' conformational structure, in accordance with that reported for the bioactive model **V**. Apparently, as argued above for the alcohol analogues **4a**–**d** and **8**, this conformer is further stabilised by the favourable disposition of the equatorial 5-Me or 5-Ph and axial 5-OH substituents. For compounds **10a**–**c**, the occurrence of intramolecular H-bonding (as discussed above) was demonstrated by the characteristic IR absorption at about 3505 cm^{-1} in dilute solutions of carbon tetrachloride. However, this intramolecular OH···N interaction was largely suppressed for the *N*-benzyl compound **10d**, probably due to distortion of the regular chair conformation. Accordingly, the long range coupling between H-4eq and H-6eq (^4J=1.1–3.0 Hz), which uniformly characterises the chair forms of **10a**–**c** and **4a**–**e**, was no longer observed in the ^{1}H NMR spectrum of **10d**.

Conclusion

Cycloaddition of 3-substituted 5-chloro-2*H*-1,4-oxazinones with ethene followed by transformation of the resultant imidoyl chloride and lactone functions was shown to be a highly efficient route for the synthesis of 2,(2),5,5-tri- and tetrasubstituted analogues of *cis*-5-hydroxy-2-piperidinemethanol and *cis*-5-hydroxy-6-oxo-2-piperidinecarboxylic acid. This approach allows for the stereoselective introduction of variable substituents on the piperidine ring and further elaboration of the 2-piperidinemethanol intermediates into potential substance P antagonists. Extension of this approach including reactions with other olefins is in progress.

Experimental

General methods

Melting points were taken using a Reichert–Jung Thermovar apparatus and an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 297 grating IR spectrophotometer and a Perkin–Elmer 1720 Fourier transform spectrometer. For the determination of OH stretching frequencies corresponding to OH···N intermolecular H-bridge formation, compounds **10a**–**d** were dissolved in CCl_4, using a quartz cell of 0.5 cm optical length, at concentrations of 0.01 M or lower to suppress intermolecular association. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the chromatography, analytical TLC plates (Alugram Sil G/UV_{254}) and 70–230 mesh silica gel 60 (E.M. Merck) were used. Microanalyses were performed by Janssen Pharmaceutica. The spectroscopic data of 2H-1,4-oxazin-2-one **2a**,**b**[12] and the preparation of adducts **3a** and **7**[8] have been described in previous papers.

5-Chloro-3,6-dimethyl-2*H*-1,4-oxazin-2-one (2c). A mixture of 540 mg (3 mmol) 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one, 644 mg (3.6 mmol) tetramethyl tin, and 34 mg (0.03 mmol) Pd[PPh_3]$_4$ in 6 ml dry toluene was heated at 110°C under N_2 atmosphere until completion of the reaction (two days). The mixture was stirred with 2.0 g KF at room temperature for 2 h, then it was filtered and the solids washed with dry toluene. The filtrate was evaporated, the residue dissolved in CH_3CN (50 ml) and washed with pentane (2×30 ml). After evaporation the residue was purified by Kugelrohr distillation or flash chromatography. Yield: 429 mg, 90%; white crystals; mp: 90°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1746 (CO), 1619 (C═N); ^{1}H NMR ($CDCl_3$): 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3); ^{13}C NMR($CDCl_3$): 16.8, 20.2 (2×CH_3), 124.7 (C-5), 147.4 (C-6), 152.1 (C-3), 154.0 (C-2); *m*/*z* (%): 159 (7, M^+), 131 (12, $M^+\surd-CO$), 43 (100, CH_3CO^+); exact mass for $C_6H_6ClNO_2$: 159.0087; found:159.0081.

5-Chloro-6-phenyl-2*H*-1,4-oxazin-2-one (2d). To a solution of 1.210 g (5 mmol) 3,5-dichloro-6-phenyl-2*H*-1,4-oxazin-2-one and 0.05 g tetrakis (Pd[PPh_3]$_4$) (0.05 mmol) in 50 ml dry toluene, 1.60 g *n*-Bu_3SnH (5.5 mmol) was added via a syringe under argon atmosphere. The reaction mixture was stirred at room temperature for one day and then KF (3.0 g) was added. After being stirred for 2 h, the mixture was filtered and the solids washed with dry toluene. The filtrate was concentrated in vacuo, the residue was taken up in 50 ml dry MeCN and the solution washed with two 30 ml portions of pentane. The MeCN layer was evaporated and the residue was purified by Kugelrohr distillation or flash chromatography. Yield: 890 mg, 86%; yellow crystals; mp: 88°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1738 (CO), 1585 (C═N); ^{1}H NMR ($CDCl_3$): 7.48–7.53 (m, 3H, Ph-H), 7.85 (s, 1H, H-3), 7.90–7.93 (m, 2H, Ph-H); ^{13}C NMR: 125.2 (C-5), 128.6, 128.7, 128.8, 131.6 (C-Ph), 142.2 (C-3), 148.7 (C-6), 152.5 (C-2); *m*/*z* (%): 207 (25, $M^{+\cdot}$), 179 (47, $M^{+\cdot}-CO$), 105 (85, $PhCO^+$), 77 (100, Ph^+); exact mass for $C_{10}H_6ClNO_2$: 207.0087; found: 207.0089.

Generation of adducts 3 and their reduction to piperidinols (4). A solution of 2*H*-1,4-oxazin-2-one **2** (5 mmol)

in 10 ml dry toluene was heated at 110°C for 4 h under ethene pressure (20 atm.) in a stainless steel tube. The progress of the cycloaddition was controlled by TLC, which showed the disappearance of the starting oxazinone detected as a typical dark spot under UV light of 366 nm. After evaporation of the solvent, the crude products **3** (e.g. **3b**) were used directly in the next step.

6-Chloro-1,4-diphenyl-2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-one (3b). IR (KBr) cm^{-1}: 1758 (CO), 1678 (C=N); ^1H NMR ($CDCl_3$): 2.10 (m, 1H, $-CH_2CH_2-$), 2.53–2.64 (m, 3H, $-CH_2CH_2-$), 7.40–7.75 (m, 10H, Ph-H); ^{13}C NMR ($CDCl_3$): 29.5 and 30.4 (C-7 and C-8), 70.8 (C-4), 85.6 (C-1), 126.6, 127.4, 128.3, 128.4, 128.6, 129.5 (C-Ph), 134.5, 136.4 (C-*ipso*), 164.6 (C-6), 169.5 (C-3); *m/z* (%) (CI): 312 (1, MH^+), 267 (33, $M^{+\cdot}-CO_2$), 232 (12, $M^{+\cdot}-CO_2-Cl$), 103 (100, $C_6H_5C_2H_2^+$).

To a stirred solution of 570 mg $LiAlH_4$ (15 mmol) in 60 ml dry THF at 0°C under nitrogen atmosphere, a solution of 5 mmol crude adduct **3** in 50 ml dry THF was added dropwise. When the addition was finished, the ice bath was removed and the reaction mixture was stirred for 4–12 h at room temperature. The excess of hydride was decomposed by careful addition of a saturated NH_4Cl solution to form a white granular precipitate. The organic layer was decanted and the precipitate washed three times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford crude compounds **4**, which could be purified by crystallisation from dichloromethane and *n*-hexane. The yields (%) are given in Scheme 2.

1,2,3,4,5,6-Hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (4a). Yield: 796 mg; white crystals; mp: 142°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 3334, 3279 (OH, NH); ^1H NMR (CD_3OD): 0.95 (s, 3H, CH_3), 1.39 (td, 1H, $^2J=^3J_{aa}$=14.0 Hz, $^3J_{ae}$=4.0 Hz, H-4ax), 1.62 (dq, 1H, ^2J=14.0 Hz, $^3J_{ea}=^3J_{ee}$=4.0 Hz, $^4J_{ee}$=2.7 Hz, H-4eq), 2.08 (dt, 1H, ^2J=14.0 Hz, $^3J_{ea}=^3J_{ee}$=4.0 Hz, H-3eq), 2.32 (td, 1H, $^2J=^3J_{aa}$=14.0 Hz, $^3J_{ae}$=4.0 Hz, H-3ax), 2.50 (d, 1H, ^2J=13.7 Hz, H-6ax), 2.58 (dd, 1H, ^2J=13.7 Hz, $^4J_{ee}$=2.7 Hz, H-6eq), 3.34, 3.38 (2×d, 2H, ^2J=11.0 Hz, CH_2OH), 7.25 (tt, 1H, ^3J=7.0 Hz, ^4J=1.2 Hz, H-*para*), 7.35 (t, 2H, H-*meta*), 7.50 (d, 2H, H-*ortho*); ^{13}C NMR (CD_3OD): 26.0 (C-3), 28.1 (CH_3), 34.3 (C-4), 53.1 (C-6), 61.5 (C-2), 67.3 (C-5), 72.6 (CH_2OH), 127.8 (C-*para*), 128.3 (C-*ortho*), 129.5 (C-*meta*), 141.9 (C-*ipso*); *m/z* (%): 190 (100, M^+-CH_2OH), 172 (28, $M^+-CH_2OH-H_2O$); exact mass for $C_{12}H_{16}O_1N_1$ (M^+-CH_2OH): 190.1232; found: 190.1235; anal. calcd for $C_{13}H_{19}O_2N_1$: C 70.56, H 8.65, N 6.33; found: C 70.29, H 8.88, N 6.21.

1,2,3,4,5,6-Hexahydro-5α-hydroxy-2β,5β-diphenyl-2α-pyridinemethanol (4b). Yield: 1.10 g; white crystals; mp: 179.2–180.5°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 3316, 3199 (OH, NH); ^1H NMR (DMSO-d_6): 1.68 (m, 1H, H-4eq), 1.75 (td, 1H, $^2J=^3J_{aa}$=13.5 Hz, $^3J_{ae}$=3.5 Hz, H-4ax), 2.04 (m, 1H, H-3eq), 2.43 (td, $^2J=^3J_{aa}$=13.5 Hz, $^3J_{ae}$=4.0 Hz, H-3ax), 2.57 (d, 1H, ^2J=14.0 Hz, H-6), 2.59 (d, 1H, ^2J=14.0 Hz, H-6), 2.68 (br.s, 1H, NH), 3.17 (d, 2H, ^3J=5.5 Hz, CH_2OH), 4.98 (s, 1H, OH), 5.02 (t, 1H, ^3J=5.5 Hz, CH_2OH), 7.1–7.3 (m, 6H, Ph-H), 7.36 (t, 2H, *J*=7.4 Hz, H-*meta*), 7.60 (d, 2H, *J*=7.5 Hz, H-*ortho*); ^{13}C NMR (DMSO-d_6): 24.2 (C-3), 32.8 (C-4), 52.7 (C-6), 59.2 (C-2), 69.1 (C-5), 71.4 (CH_2OH), 124.6, 126.0, 126.2, 127.2, 127.7, 128.1 (C-Ph), 142.3(C-$ipso_{at\ C\text{-}2}$), 148.5(C-$ipso_{at\ C\text{-}5}$); *m/z* (%): 284 (0.4, MH^+), 252 (100, M^+-CH_2OH), 234 (44, $M^+-CH_2OH-H_2O$); exact mass for $C_{17}H_{18}NO_1$ (M^+-CH_2OH): 252.1388; found: 252.1391; anal. calcd for $C_{18}H_{21}NO_2$: C 76.30, H 7.47, N 4.94; found: C 75.98, H 7.53, N 4.76.

1,2,3,4,5,6-Hexahydro-5α-hydroxy-2β,5β-dimethyl-2α-pyridinemethanol (4c). Yield: 445 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3324 (OH, NH); ^1H NMR (DMSO-d_6): 0.87 (s, 3H, $CH_{3\ at\ C\text{-}2}$), 0.99 (dt, 1H, ^2J=14.0 Hz, ^3J=4.0 Hz, H-3eq), 1.02 (s, 3H, $CH_{3\ at\ C\text{-}5}$), 1.47 (m, 2H, H-4), 1.72 (ddd, 1H, ^2J=14.0 Hz, ^3J=9.5 Hz, ^3J=6.0 Hz, H-3ax), 2.37 (dd, 1H, ^2J=13.2 Hz, $^4J_{ee}$=1.4 Hz, H-6eq), 2.52 (d, 1H, ^2J=13.2 Hz, H-6ax), 3.10 (br.s, 1H, OH, or NH), 3.12, 3.16 (2×d, 2H, ^2J=9.9 Hz, CH_2OH), 4.10 (br.s, 2H, NH, or OH); ^{13}C NMR (DMSO-d_6): 19.6 ($CH_{3\ at\ C\text{-}2}$), 27.5 ($CH_{3\ at\ C\text{-}5}$), 28.0 (C-3), 33.3 (C-4), 51.7 (C-2), 51.9 (C-6), 65.3 (C-5), 69.2 (CH_2OH); *m/z* (%): 160 (8, MH^+), 128 (100, $M^{+\cdot}-CH_2OH$), 110 (64, $M^{+\cdot}-CH_2OH-H_2O$); exact mass for $C_8H_{18}NO_2$ (MH): 160.1338, found: 160.1338.

1,2,3,4,5,6-Hexahydro-5α-hydroxy-5β-phenyl-2α-pyridinemethanol (4d). Yield: 621 mg; white crystals; mp: 142.5°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3392, 3058 (OH, NH); ^1H NMR (DMSO-d_6): 1.45(m, 1H, H-3eq), 1.55 (qd, 1H, $^2J=^3J_{aa}$=13.0 Hz, $^3J_{aa}$=11.6 Hz, $^3J_{ae}$=4.0 Hz, H-3ax), 1.69 (m, 1H, H-4eq), 1.91 (td, 1H, $^2J=^3J_{aa}$= 13.0 Hz, $^3J_{ae}$= 4.6 Hz, H-4ax), 2.10 (br., 1H, NH), 2.52 (m, 1H, $^3J_{aa}$= 11.6 Hz, $^3J_{ae}$=3.0 Hz, H-2ax), 2.65 (dd, 1H, ^2J=12.8 Hz, $^4J_{ee}$=2.6 Hz, H-6eq), 2.77 (d, 1H, ^2J=12.8 Hz, H-6ax), 3.35 (d, 2H, ^3J=5.0 Hz, CH_2OH), 4.50 (br.s, 1H, CH_2OH), 4.71 (s, 1H, OH), 7.20 (t, 1H, H-*para*), 7.30 (t, 2H, H-*meta*), 7.50 (d, 2H, H-*ortho*); ^{13}C NMR (DMSO): 24.5, 36.1 (C-3, C-4), 56.9 (C-2), 57.2 (C-6), 65.3 (CH_2OH), 69.7 (C-5), 124.8, 126.1, 127.7 (C-Ph), 148.1 (C-*ipso*); *m/z* (%): 208 (1, MH^+), 190 (1, $M^{+\cdot}-H_2O$), 176 (100, $M^{+\cdot}-OCH_3$), 158 (28, $M^{+\cdot}-OCH_3-H_2O$); exact mass for $C_{12}H_{17}NO_2$: 207.1259, found: 207.1251; anal. calcd for $C_{12}H_{17}NO_2$: C 69.54, H 8.27, N 6.76; found: C 69.56, H 8.50, N 6.87.

Preparation of *N*-alkyl piperidinols (4e,f). To a solution of 663 mg **4a** (3 mmol) in 30 ml acetone was added 829 mg (6 mmol) potassium carbonate and then dropwise 3.3 mmol MeI (for **4e**) or $PhCH_2Br$ (for **4f**) at room temperature. The reaction mixture was heated at reflux temperature for one day; after removal of the solvent in vacuo the residue was treated with 30 ml of water. The aqueous suspension was extracted three times with 30-ml of dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give crude products, which were purified by recrystallisation (dichloromethane/*n*-hexane). The yields (%) are given in Scheme 5.

***N*-Methyl-1,2,3,4,5,6-hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (4e).** Yield: 564 mg; white crystals; mp: 109.6°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3747, 3371 (OH); ^1H NMR ($CDCl_3$): 1.15 (s, 3H, CH_3), 1.51 (td, 1H, $^2J=^3J_{aa}$=13.3 Hz, $^3J_{ae}$=4.2 Hz, H-4ax),

1.60 (dtd, 1H, ^2J=13.3 Hz, $^3J_{ae}$=$^3J_{ee}$=4.2 Hz, $^4J_{ee}$=2.3 Hz, H-4eq), 1.86 (dt, 1H, ^2J=14.3 Hz, $^3J_{ae}$=$^3J_{ee}$=4.2 Hz, H-3eq), 2.30 (br., 1H, OH), 2.34 (ddd, 1H, ^2J=14.3 Hz, $^3J_{aa}$=13.3 Hz, $^3J_{ae}$=4.2 Hz, H-3ax), 2.56 (dd, 1H, ^2J=12.3 Hz, $^4J_{ee}$=2.3 Hz, H-6eq), 2.60 (s, 3H, N-CH_3), 2.70 (br., 1H, OH), 2.91 (d, 1H, ^2J=12.3 Hz, H-6ax), 3.67 (d, 1H, ^2J=11.2 Hz, CH_2OH), 3.88 (d, 1H, ^2J=11.2 Hz, CH_2OH), 7.26 (tt, 1H, ^3J=7.2 Hz, ^4J=1.5 Hz, H-*para*), 7.33–7.40 (m, 4H, H-*meta* and H-*ortho*); ^{13}C NMR ($CDCl_3$): 26.8 (CH_3), 28.8, 34.0 (C-3, C-4), 39.3 (N-CH_3), 61.9 (C-6), 62.7 (C-2), 66.8 (CH_2OH), 67.9 (C-5), 124.9, 127.6, 128.3 (C-Ph), 141.1 (C-*ipso*); *m/z* (%) (CI): 236 (100, MH^+), 218 (54, M^+H-H_2O), 204 (26, MH^+-CH_3OH); exact mass for $C_{14}H_{22}NO_2$ (MH^+): 236.1251, found: 236.1646; anal. calcd for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95; found: C 71.60, H 9.11, N 5.83.

***N*-Benzyl-1,2,3,4,5,6-hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (4f).** Yield: 765 mg; white crystals; mp: 125.4°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3419 (OH); ^{1}H NMR ($CDCl_3$): 1.13 (s, 3H, CH_3), 1.51 (m, 1H, H-4ax), 1.62 (m, 1H, H-4eq), 1.91 (br., 1H, CH_2OH), 1.94 (m, 1H, H-3eq), 2.30 (m, 1H, H-3ax), 2.40 (br. s, 1H, OH), 2.61 (dd, 1H, ^2J=12.0 Hz, $^4J_{ee}$=1.7 Hz, H-6eq), 2.83 (d, 1H, ^2J=12.0 Hz, H-6ax), 3.77 (d, 1H, ^2J=14.0 Hz, CH_2Ph), 4.20 (d, 1H, ^2J=14.0 Hz, CH_2Ph), 3.89 (d, 1H, ^2J=11.0 Hz, CH_2OH), 4.01 (d, 1H, ^2J=11.0 Hz, CH_2OH), 7.22–7.50 (m, 10H, Ph-H); ^{13}C NMR($CDCl_3$): 26.4 (CH_3), 30.6 (C-3), 34.2 (C-4), 54.9 (PhCH_2N), 58.5 (C-6), 64.2 (C-2), 66.3 (CH_2OH), 68.1 (C-5), 126.9, 127.0, 127.6, 127.9, 128.6, 128.7 (C-Ph), 140.6, 142.4 (C-*ipso*); *m/z* (%): 312 (1, MH^+), 280 (100, M^+-CH_2OH), 91 (88, Bn^+); exact mass for $C_{19}H_{22}NO_1$ (M^+-CH_2OH): 280.1701, found, 280.1701; anal. calcd for $C_{20}H_{25}NO_2$: C 77.14, H 8.09, N 4.50; found: C 77.04, H 8.21, N 4.53.

General procedure for $NaCNBH_3$ reduction of adducts 3 to yield lactones (5). To a clear solution of 502 mg $NaCNBH_3$ (8 mmol) in a mixture of 16 ml of THF and 4 ml buffered solution (1 M NaOAc/HOAc, pH=5.0) was added 4 mmol crude adduct **3**. The reaction mixture was heated at 75°C for one day; after removal of solvent in vacuo the residue was treated with 10 ml saturated $NaHCO_3$ solution. The aqueous suspension was extracted with three 20-ml portions of dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give the crude product **5**. Further purification was carried out by chromatography and crystallisation. The conversion of **5** to **4** was carried out by treatment with $LiAlH_4$ in THF at room temperature for 3–8 h. The yields (%) are given in Scheme 5.

1-Methyl-4-phenyl-2-oxa-5-azabicyclo [2.2.2]octan-3-one (5a). Yield: 608 mg; white crystals; mp: 113.5–115.2°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 3290 (NH), 1733 (CO); ^{1}H NMR($CDCl_3$): 1.45 (s, 3H, CH_3), 1.92 (m, 1H, H-7*endo*), 1.97 (m, 1H, H-7*exo*), 2.10 (br. s, 1H, NH), 2.21 (m, 2H, H-8), 3.16 (dd, 1H, ^2J=11.3 Hz, ^4J=2.9 Hz, H-6ax), 3.20 (d, 1H, ^2J=11.3 Hz, H-6eq), 7.30–7.39 (m, 3H, Ph-H), 7.51–7.54 (m, 2H, Ph-H); ^{13}C NMR ($CDCl_3$): 23.0 (CH_3), 31.5 and 33.0 (C-7 and C-8), 51.7 (C-6), 57.4 (C-4), 79.8 (C-1), 126.6, 127.7, 128.0 (C-Ph), 138.5 (C-*ipso*), 173.8 (CO); *m/z* (%): 218 (17, MH^+), 188 (31, $M^{+\cdot}-CH_2$=NH), 173 (100, $M^{+\cdot}-CO_2$); exact mass for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1104.

1,4-Diphenyl-2-oxa-5-azabicyclo [2.2.2]octan-3-one (5b). Yield: 716 mg; white crystals; mp: 157°C (CH_2Cl_2/Et_2O); IR (KBr) cm^{-1}: 3294 (NH), 1741 (CO); ^{1}H NMR ($CDCl_3$): 2.22 (m, 1H, H-7*exo*), 2.15 (br. s, 1H, NH), 2.30–2.42 (m, 3H, H-8, and H-7*endo*), 3.35 (dd, 1H, ^2J=11.6 Hz, ^4J=3.2 Hz, H-6ax), 3.75 (d, 1H, ^2J=11.6 Hz, H-6eq), 7.30–7.60 (m, 10H, Ph-H); ^{13}C NMR ($CDCl_3$): 31.9, 33.2 (C-7 and C-8), 52.5 (C-6), 58.0 (C-4), 82.1 (C-1), 124.6, 126.6, 127.8, 128.1, 128.2, 128.6 (C-Ph), 138.4 and 139.6 (C-*ipso*), 173.4 (C-3); *m/z* (%): 235 (100, $M^{+\cdot}-CO_2$); exact mass for $C_{18}H_{18}NO_2$ (MH^+): 280.1338, found: 280.1333; anal. calcd for $C_{18}H_{17}O_2N_1$: C 77.40, H 6.13, N 5.01; found: C 77.19, H 6.12, N 4.97.

1-Phenyl-2-oxa-5-azabicyclo [2.2.2]octan-3-one (5d). Yield: 308 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3327 (NH), 1755 (CO); ^{1}H NMR ($CDCl_3$): 2.02–2.05 (m, 2H, H-7), 2.25–2.29 (m, 2H, H-8), 2.30 (s, 1H, NH), 3.16 (dd, 1H, ^2J=11.6 Hz, ^4J=2.6 Hz, H-6ax), 3.38 (d, 1H, ^2J=11.6 Hz, H-6eq), 3.57 (m, 1H, H-4), 7.31–7.44 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 24.4, 30.7 (C-7, C-8), 50.2 (C-4), 51.9 (C-6), 82.7 (C-1), 124.5, 127.9, 128.6 (C-Ph), 139.5 (C-*ipso*), 173.8 (C-3); *m/z* (%), 204 (4, MH^+), 176 (10, MH^+-CO), 159 (100, $M^{+\cdot}-CO_2$); exact mass for $C_{12}H_{13}NO_2$, 203.0946, found: 203.0948.

General procedure for the generation of methyl 6-oxo-5α-hydroxy-2α-piperidinecarboxylates (6). Methanol (5 ml) was added to the crude cycloadduct **3** (5 mmol) dissolved in $CHCl_3$ (10 ml). The mixture was stirred at room temperature for one day. After evaporation of the solvent, purification was done by chromatography (silica gel, eluent: MeOH/CH_2Cl_2). The conversion of **6** to **4** was carried out with $LiALH_4$ in THF at reflux for 8–14 h. The yields are given in Scheme 5. The yield of **6c** was rather low and **9c** was isolated as major side product.

Methyl 5α-hydroxy-5β-methyl-6-oxo-2β-phenyl-2α-piperidinecarboxylate (6a). Yield: 855 mg; white crystals; mp: 150°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 3351, 3210 (OH, NHCO), 1740 (COOMe), 1663 (CONH); ^{1}H NMR ($CDCl_3$): 1.50 (s, 3H, CH_3), 1.74 (ddd, 1H, ^2J=14.0 Hz, ^3J=8.0 Hz, ^3J=3.0 Hz, H-4eq), 1.95 (ddd, 1H, ^2J=14.0 Hz, ^3J=10.0 Hz, ^3J=3.0 Hz, H-3ax), 2.17 (ddd, 1H, ^2J=14.0 Hz, ^3J=10.0 Hz, ^3J=3.0 Hz, H-4ax), 2.76 (dddd, 1H, ^2J=14.0 Hz, ^3J=8.0 Hz, ^3J=3.0 Hz, $^4J_{ee}$=1 Hz, H-3eq), 3.45 (s, 1H, OH), 3.77 (s, 3H, COOMe), 6.69 (br., 1H, HNCO), 7.32–7.42 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$): 27.3 (CH_3), 31.0 (C-3), 32.0 (C-4), 53.2 (OMe), 66.3 (C-2), 69.6 (C-5), 124.6 (C-*meta*), 128.4 (C-*para*), 129.0 (C-*ortho*), 140.2 (C-*ipso*), 171.5 (C-6), 176.2 (*C*OOMe); *m/z* (%): 204 (100, $M^{+\cdot}-COOCH_3$), 186 (44, $M^{+\cdot}-COOCH_3$-H_2O), 176 (54, $M^{+\cdot}-COOMe-CO$); exact mass for $C_{12}H_{14}NO_2$ ($M^{+\cdot}-COOCH_3$): 204.1025; found: 204.1032.

Methyl 5α-hydroxy-5β-methyl-2β-methyl-6-oxo-2α-piperidinecarboxylate (6c). Yield: 482 mg; white crystals; mp: 146–148°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3344, 3211 (OH, NHCO), 1739 (COOMe), 1659 (CONH); ^{1}H NMR

($CDCl_3$): 1.44 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.81–1.90 (m, 3H), 2.45 (m, 1H) (CH_2CH_2), 3.60 (s, 1H, OH), 3.76 (s, 3H, COOMe), 6.33 (br.s, 1H, HNCO); ^{13}C NMR ($CDCl_3$): 27.2 (CH_3), 27.6 (CH_3), 30.5, 32.3 (C-3, C-4), 52.9 (OMe), 60.5 (C-2), 69.6 (C-5), 174.0 (C-6), 176.6 (*C*OOMe); *m/z* (%): 202 (6, MH^+), 142 (100, $M^+-COOMe$), 124 (39, $M^+-COOMe-H_2O$), 114 (93, $M^+-COOMe-CO$); exact mass for $C_9H_{16}NO_4$ (MH^+): 202.1079, found: 202.1084; anal. calcd for $C_9H_{15}O_4N_1$: C 53.72, H 7.51, N 6.96; found: C 53.87, H 7.56, N 6.88.

1,4-Dimethyl-2-oxa-5-azabicyclo[2.2.2]octane-3,6-dione (9c). Yield: 45%, 380 mg; white powder; mp: 96–97°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3212 (NHCO), 1769 (COO), 1715, 1672 (CONH); ^{1}H NMR ($CDCl_3$): 1.54 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.93–2.02 (m, 3H, CH_2CH_2), 2.18 (m, 1H, CH_2CH_2), 7.84 (s, 1H, NHCO); ^{13}C NMR (DMSO): 17.8 (CH_3), 18.4 (CH_3), 29.5, 30.8 (C-7 and C-8), 55.3 (C-4), 82.1 (C-1), 170.0, 171.9 (C-3 and C-6); *m/z* (%): 170 (1, MH^+), 125 (60, $M^{+\cdot}-CO_2$), 97 (100, $M^{+\cdot}-CO_2-CO$), exact mass for $C_8H_{11}NO_3$: 169.0739, found: 169.0742.

Methyl 5α-hydroxy-6-oxo-5β-phenyl-2α-piperidinecarboxylate (6d). Yield: 1058 mg; white crystals; mp: 158–161°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3274 (OH, NHCO), 1760 (COOMe), 1660 (CONH); ^{1}H NMR (DMSO-d_6): 1.81–1.95 (m, 4H, CH_2CH_2), 3.70 (s, 3H, COOMe), 4.19 (m, 1H, H-2), 7.25–7.38 (m, 5H, Ph-H), 7.94 (br. s, 1H, NHCO); ^{13}C NMR (DMSO): 21.9, 34.7 (C-3, C-4), 52.1 (OMe), 54.0 (C-2), 74.1 (C-5), 125.8, 126.9, 127.6 (C-Ph), 145.3 (C-*ipso*), 172.4, 172.6 (C-6, *C*OOMe); *m/z* (%): 250 (3, MH^+), 249 (3, M^+), 232 (7, MH^+-H_2O), 221 (18, M^+-CO), 204 (40, MH^+-H_2O-CO), 162 (100, $M^{+\cdot}-CO-COOMe$); exact mass for $C_{13}H_{15}NO_4$: 249.1001, found: 249.1004; anal. calcd for $C_{13}H_{15}O_4N_1$: C 62.64, H 6.07, N 5.62; found: C 62.46, H 6.08, N 5.54.

1,2,3,4,5,6-Hexahydro-5α-hydroxy-5β-phenyl-2β-pyridinemethanol (8). Preparation of compound **8** from **7** (5 mmol) was carried out using the same procedure as for compounds **4a–d**, except that the reaction time was 1 h (Scheme 3). Yield: 288 mg; white crystals; mp: 98°C (MeOH/Et_2O); IR (KBr) cm^{-1}: 3294 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.36 (m, 1H, H-3eq), 1.75 (m, 1H, H-4eq), 1.98 (m, 1H, H-3ax), 2.15 (m, 1H, H-4ax), 2.62 (br., 3H, NH, OH), 2.72 (dd, 1H, ^2J=13.0 Hz, $^4J_{ee}$=1.8 Hz, H-6eq), 2.99 (dq, 1H, $^3J_{anti}$= 10.0 Hz, $^3J_{syn}=^3J_{ee}=^3J_{ea}$=4.5 Hz, H-2eq), 3.22 (d, 1H, ^2J=13.0 Hz, H-6ax), 3.46 (dd, 1H, ^2J=10.6 Hz, ^3J= 4.5 Hz, CH_2OH), 3.70 (dd, 1H, ^2J=10.6 Hz, ^3J=10.0 Hz, CH_2OH), 7.26 (t, 1H, H-*para*), 7.34 (t, 2H, H-*meta*), 7.55 (d, 2H, H-*ortho*); ^{13}C NMR ($CDCl_3$): 23.4, 34.0 (C-3, C-4), 52.2 (C-6), 53.2 (C-2), 61.4 (CH_2OH), 70.6 (C-5), 125.2, 127.1, 128.2 (C-Ph), 145.7 (C-*ipso*); *m/z* (%) (CI): 208 (100, MH^+), 190 (42, MH^+-H_2O), 176 (6, M^+-CH_3OH); exact mass for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1251.

General procedure for the preparation of 3,5-bis(trifluromethyl)benzyl ethers (10). To a solution of 1 mmol of piperidinol **4** in 10 ml DMF was added 50.4 mg (2.1 mmol) sodium hydride in a single portion at room temperature. The mixture was stirred for 30 min. followed by the addition of 338 mg (1.1 mmol) 3,5-bis(trifluromethyl)benzyl bromide in 5 ml dry THF over a 15 min period. The resulting mixture was stirred for one day followed by careful addition of a saturated ammonium chloride solution to pH 8.5–9.0, and 20 ml of water. The aqueous layer was extracted with three 20 ml portions of dichloromethane, and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil was chromatographed over silica gel (dichloromethane–ethyl acetate, 4:1) to give 3,5 bis(trifluromethyl)benzyl ether **10**. The yields (%) are given in Scheme 5.

***O*-[3,5-Bis(trifluoromethyl)benzyl]-1,2,3,4,5,6-hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (10a).** Yield: 250 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3383 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.03 (s, 3H, CH_3), 1.37 (td, 1H, $^2J=^3J_{aa}$=13.6 Hz, $^3J_{ae}$=4.0 Hz, H-4ax), 1.59 (dddd, 1H, ^2J=13.6 Hz, $^3J_{ea}$=4.0, $^3J_{ee}$=3.5 Hz, $^4J_{ee}$=2.2 Hz, H-4eq), 2.08 (td, 1H, $^2J=^3J_{aa}$=13.6 Hz, $^3J_{ea}$=4.0 Hz, H-3ax), 2.17 (ddd, 1H, ^2J=13.6 Hz, $^3J_{ae}$=4.0 Hz, $^3J_{ee}$= 3.5 Hz, H-3eq), 2.54 (d, 1H, ^2J=12.5 Hz, H-6ax), 2.59 (dd, 1H, ^2J=12.5 Hz, $^4J_{ee}$=2.2 Hz, H-6eq), 2.80 (br., s, 2H, OH and NH), 3.39 (d, 1H, ^2J=8.7 Hz, $CH_2OCH_2C_6H_3(CF_3)_2$), 3.47 (d, 1H, ^2J=8.7 Hz, CH_2O $CH_2C_6H_3(CF_3)_2$), 4.43 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 4.50 (d, 1H, ^2J= 13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 7.29–7.50 (m, 5H, H-Ph), 7.57 (s, 2H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$): 26.6 (C-3), 26.7 (CH_3), 33.4 (C-4), 52.6 (C-6), 58.9 (C-2), 66.8 (C-5), 71.7 ($CH_2OCH_2C_6H_3(CF_3)_2$), 81.8 ($CH_2OCH_2C_6H_3(CF_3)_2$), 121.2–128.4 (C-Ar), 131.5 (CF_3), 140.3 (C-*ipso*), 141.0 (C-*ipso*); *m/z* (%) (CI): 448 (30, MH^+), 428 (20, MH^+-HF), 190 (25, $MH^+-CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{22}H_{23}O_2N_1F_5$ (MH^+-HF): 428.1649; found: 428.1640; anal. calcd for $C_{22}H_{23}O_2N_1F_6$: C 59.04, H 5.18, N 3.13; found: C 58.96, H 5.16, N 3.10.

***O*-[3,5-Bis(trifluoromethyl)benzyl]-1,2,3,4,5,6-hexahydro-5α-hydroxy-2β,5β-diphenyl-2α-pyridinemethanol (10b).** Yield: 331 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3377 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.78 (m, 1H, H-4eq), 1.93 (m, 1H, H-4ax), 2.31 (m, 2H, H-3), 2.75 (dd, 1H, ^2J=12.8 Hz, $^4J_{ee}$=2.6 Hz, H-6eq), 2.90 (d, 1H, ^2J=12.8 Hz, H-6ax), 3.43 (d, 1H, ^2J=8.7 Hz, $CH_2OCH_2C_6H_3(CF_3)_2$), 3.52 (d, 1H, ^2J=8.7 Hz, $CH_2OCH_2C_6H_3(CF_3)_2$), 4.47 (d, 1H, ^2J= 13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 4.53 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 7.18–7.54(m, 10H, 2×Ph), 7.60 (s, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$): 26.5 (C-3), 33.0 (C-4), 52.8 (C-6), 58.9 (C-2), 70.5 (C-5), 71.7 ($CH_2OCH_2C_6H_3(CF_3)_2$), 81.1 ($CH_2OCH_2C_6H_3(CF_3)_2$), 125.0 (CF_3), 124.6, 126.0, 126.9, 127.0, 127.2, 128.1, 128.5 (C-Ph), 131.4, 131.7 (*C*-CF_3), 140.0 (C-*ipso*$_{ax}$), 140.9(C-*ipso*Ar), 145.8 (C-*ipso*$_{eq}$); *m/z* (%) (CI): 510 (100, MH^+), 490 (49, MH^+-HF), 252 (56, $MH^+-CH_2OCH_2Ar$); exact mass for $C_{27}H_{25}O_2N_1F_6$: 509.1789; found: 509.1790; anal. calcd for $C_{27}H_{25}O_2N_1F_6$: C 63.65, H 4.95, N 2.75, found: C 63.40, H 5.14, N 2.50.

***N*-Methyl-*O*-[3,5-bis(trifluoromethyl)benzyl]-1,2,3,4,5,6-hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (10c).** Yield: 323 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3413 (OH); ^{1}H NMR ($CDCl_3$): 1.23 (s, 3H, CH_3), 1.56 (m, 2H, CH_2), 1.90 (m, 1H, CH_2), 2.14 (m, 1H, CH_2), 2.53 (s, 3H, N-CH_3), 2.56 (d, 1H, ^2J=12.0 Hz, H-6ax), 2.76 (d, 1H, ^2J=12.0 Hz, $^4J_{ee}$=1.2 Hz, H-6eq), 3.82

(s, 2H, $CH_2OCH_2C_6H_3(CF_3)_2$), 4.59 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 4.61 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 7.24–7.49 (m, 5H, Ph), 7.69 (s, 2H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$): 26.3 (CH_3), 30.6 (C-3), 34.8 (C-4), 40.1 (CH_3), 61.9 (C-6), 62.3 (C-2), 68.4 (C-5), 71.9, 73.8 ($CH_2OCH_2C_6H_3(CF_3)_2$), 124.6 (CF_3), 121.4, 126.7, 127.1, 127.5, 128.1, 131.5, 131.8, 140.1, 143.1 (C-Ph, Ar); *m/z* (%) (CI): 462 (100, MH^+), 444 (55, M^+H-H_2O), 442 (82, MH^+-HF); exact mass for $C_{23}H_{25}N_1O_2F_6$: 461.1789, found: 461.1786; anal. calcd for $C_{23}H_{25}N_1O_2F_6$: C 59.87, H 5.46, N 3.04; found: C 59.82, H 5.52, N 3.05.

***N*-Benzyl-*O*-[3,5-bis(trifluoromethyl)benzyl]-1,2,3,4,5,6-hexahydro-5α-hydroxy-5β-methyl-2β-phenyl-2α-pyridinemethanol (10d).** Yield: 468 mg; colourless oil; IR (NaCl, film) cm^{-1}: 3413 (OH); ^{1}H NMR ($CDCl_3$): 1.22 (s, 3H, CH_3), 1.60 (m, 2H, CH_2CH_2), 1.98 (m, 1H, CH_2CH_2), 2.22 (m, 1H, CH_2CH_2), 2.10 (br., 1H, OH), 2.49 (d, 1H, ^2J=12.0 Hz, H-6), 2.67 (d, 1H, ^2J=12.0 Hz, H-6), 3.80 (d, 1H, ^2J=14.0 Hz, $PhCH_2N$), 3.84 (d, 1H, ^2J=14.0 Hz, $PhCH_2N$), 3.98 (d, 1H, ^2J=10.0 Hz, $CH_2OCH_2C_6H_3(CF_3)_2$), 4.01 (d, 1H, ^2J=10.0 Hz, $CH_2OCH_2C_6H_3(CF_3)_2$), 4.62 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 4.64 (d, 1H, ^2J=13.0 Hz, $OCH_2C_6H_3(CF_3)_2$), 7.19–7.36 (m, 8H, Ph), 7.60–7.62 (m, 2H, Ph), 7.74 (s, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$): 25.9 (CH_3), 32.4 (C-3), 35.0 (C-4), 55.2 (C-6), 57.6 ($PhCH_2N$), 63.4 (C-2), 68.4 (C-5), 71.9, 72.3 ($CH_2OCH_2C_6H_3(CF_3)_2$), 124.6 (CF_3), 121.5, 126.8, 127.1, 131.5, 140.7, 140.9, 144.1 (C-Ph, Ar); *m/z* (%): 538 (100, MH^+), 520 (31, M^+H-H_2O), 518 (41, MH^+-HF); exact mass for $C_{29}H_{29}N_1O_2F_6$: 537.2102, found: 537.2091; anal. calcd for $C_{29}H_{29}N_1O_2F_6$: C 64.80, H 5.44, N 2.61; found: C 64.70, H 5.41, N 2.56.

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