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Stereoselective conversion of 2*H*-1,4-oxazin-2-ones into 2,5,5-substituted piperidine-2-carboxamides and 2-methanamines and related octahydro-2*H*-pyrido[1,2-*a*]pyrazines, potential substance P antagonists

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Abstract—4-(Hetero)aryl-2-oxa-5-azabicyclo[2.2.2]octan-3-ones and 3,6-diones, formed via cycloaddition of 2*H*-1,4-oxazin-2-ones and ethene followed by functional group transformation, undergo lactone cleavage by reaction with amines to yield substituted 2-(hetero)aryl-5-hydroxy-2-piperidinecarboxamides. Subsequent reduction affords the corresponding 2-piperidinemethanamines. Both amide and amine compounds are of interest as potential Substance P antagonists. A detailed NMR study, supported by conformational calculations, of an octahydro-2*H*-pyrido[1,2-*a*]pyrazine analogue revealed the existence of a temperature and solvent dependent equilibrium mixture of *transoid* and *cisoid* invertomers.

1. Introduction

Substance P (SP), a neurotransmitter peptide of the tachykinin family, is implicated in pain control and in the pathogenesis of a variety of inflammatory diseases, e.g. migraine, rheumatoid arthritis, emesis and asthma. One of the most potent non-peptide SP antagonists discovered to date is the 2-phenylpiperidine derivative CP 99,994[1] (**I**) (Fig. 1). Some time ago, Merck researchers have claimed SP antagonist activity for the β-hydroxypiperidine derivative

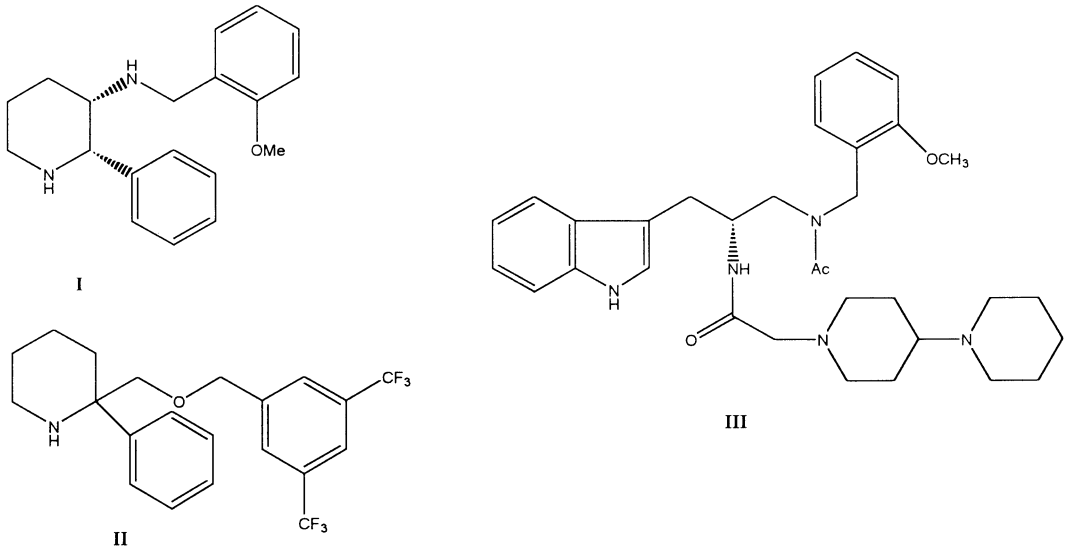

Figure 1.

Keywords: bicyclic heterocyclic compounds; piperidines; Diels–Alder reactions; conformation.
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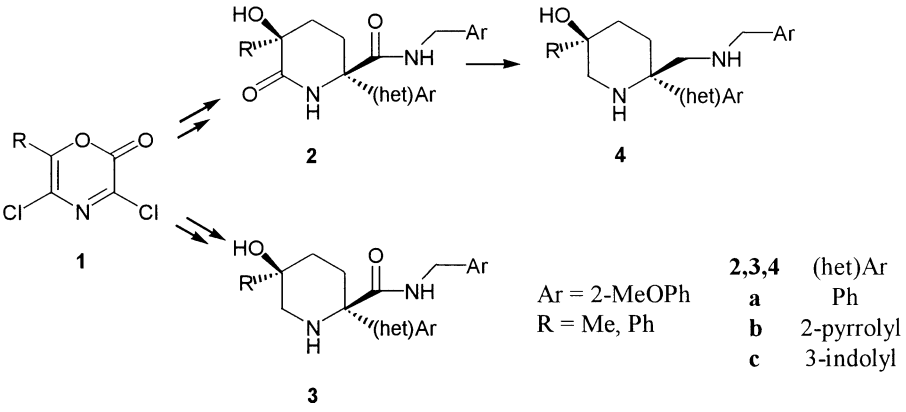


Scheme 1.

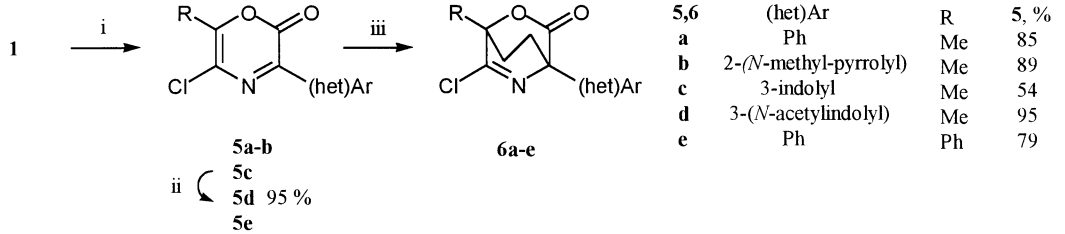
II.[2] Another class of selective SP antagonists identified by Lilly encompass a tryptophan derived structural unit as in LY 303,870 (**III**).[3] We recently described an efficient and general approach leading to 2,5,5-substituted analogues of 2-piperidinemethanol and 2-piperidinecarboxylic acid.[4] In the present paper we report a short and stereoselective route for the synthesis of 2-(hetero)aryl-2-piperidinecarboxamides of type **2** and **3** and the 2-(hetero)aryl-2-piperidinemethanamines **4** (Scheme 1). This involves cycloaddition of the readily accessible 3-(hetero)aryl-2*H*-1,4-oxazin-2-ones with ethene followed by lactone cleavage. Compounds of type **4** can be elaborated further into conformationally constrained bicyclic analogues.

2. Results and discussion

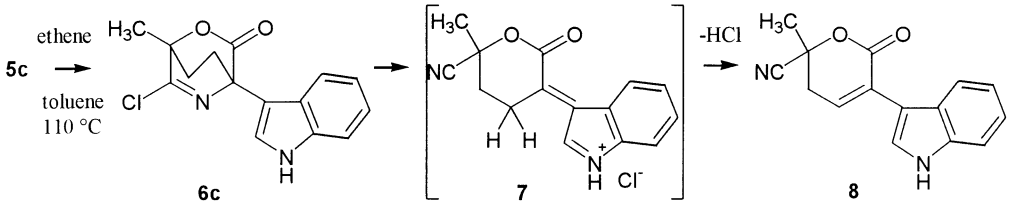
The starting 3,5-dichloro-oxazin-2-one 1 was prepared in a 'one pot' synthesis from the corresponding α-hydroxynitrile.[5] A (hetero)aryl group in position 3 was introduced by reaction of **1** with the corresponding (hetero)aromatic system in the presence of (Lewis) acids (Scheme 2).[6] The 3-(hetero)aryl substituted oxazinones **5** were made to react with ethene at 110°C in toluene in a high pressure vessel (20–40 bar) to produce bicyclic adducts **6**. When exposed to air moisture, the latter compounds are hydrolysed to give the corresponding bridged lactam compounds.

The cycloaddition of the 3-indolyl-oxazinone **5c** with ethene gave not only the expected product **6c** but mainly the 5,6-dihydro-2-oxa-2*H*-pyran-6-carbonitrile **8** (Scheme 3). A similar ring transformation also has been observed in the reaction of olefins with 3-amino-5-chloro-2*H*-1,4-oxazin-2-ones.[7] A plausible mechanism involves conversion of the original adduct **6c** into intermediate **7** (Scheme 3). This may proceed through initial C–N bond cleavage assisted by the strongly electron donating 3-indolyl moiety at the bridgehead position, followed by expulsion of chloride. Further loss of a proton in position 4 provides compound **8**. The ^{1}H NMR ($CDCl_3$) spectrum of 2-carbonitrile **8** shows a dd-absorption at 7.13 ppm for H-4 (^3J=6.3, 3.2 Hz) and two dd-absorptions at 2.90 ppm (^2J=18.3 Hz, ^3J=3.2 Hz) and 2.97 ppm (^2J=18.3 Hz, ^3J=6.3 Hz) for the protons in position 3.

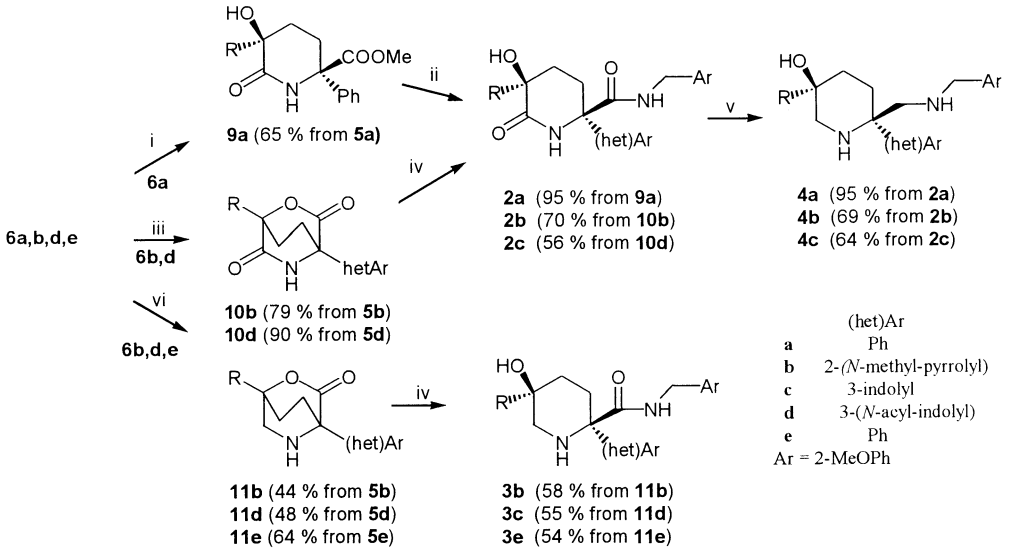
To prevent this rearrangement, the indole ring of compound **5c** was N-acetylated using acetic anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) to produce **5d**



Scheme 2. (i) **5a**, **5e**: 4 equiv. $AlCl_3$, benzene, rt, 12 h; **5b**: EtOAc/HCl, 3 equiv. *N*-methyl pyrrole, rt, 4 h; **5c**: EtOAc/HCl, 3 equiv. indole, rt, 12 h; (ii) $(CH_3CO)_2O$, DMAP, rt, 6 h; (iii) 20–40 bar ethene, toluene, 110°C, 2–4 h.



Scheme 3.

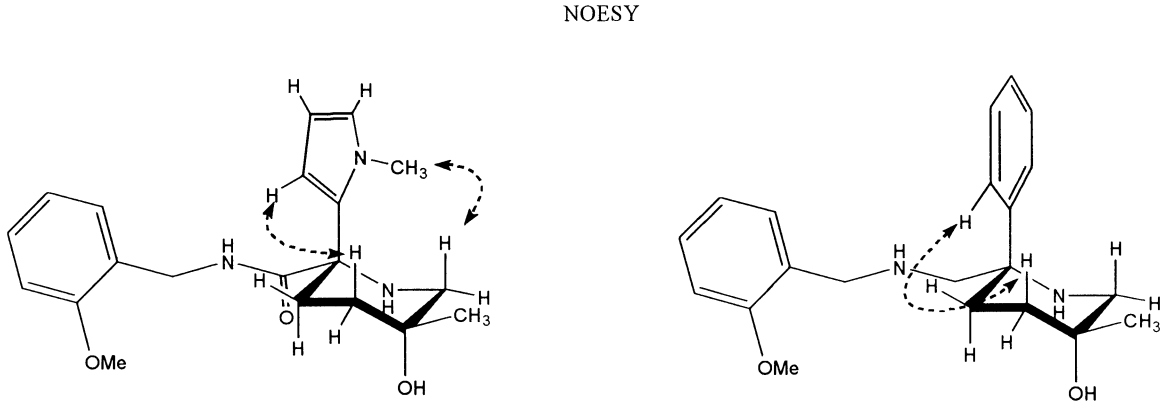


Scheme 4. (i) MeOH, $CHCl_3$, rt; (ii) **2a**: 2-$MeOC_6H_4CH_2NH_2$, MeOH, rt; (iii) **10b**: silica gel; **10d**: wet EtOAc; (iv) **2b**,**c**: THF, 3 equiv. 2-$MeOC_6H_4CH_2NH_2$, reflux; (v) THF, reflux, 4 equiv. $BH_3{\cdot}SMe_2$; (vi) Pd/C, toluene, H_2, DABCO, rt.

in 95% yield (Scheme 2). Subsequent Diels–Alder reaction with ethene gave adduct **6d**, which was used directly in the subsequent hydrolysis step leading to the corresponding dione (see below). It has been shown previously that cycloadducts of 2*H*-1,4-oxazin-2-ones and alkene compounds undergo lactone cleavage by reaction with alcohols.[8] Thus, when the ethene adduct **6a** was treated with MeOH in $CHCl_3$ (1:1) for one day, compound **9a** was isolated in 65% yield calculated on **5a** (Scheme 4). The conversion of the imidoyl chloride function of **6a** into a lactam may proceed via formation of an imino ether followed by a nucleophilic attack of MeOH on the methyl group of the protonated imino ether (HCl-salt). Treatment of the ester **9a** with 2-methoxybenzylamine in methanol at room temperature afforded the amide **2a** in 95% yield.

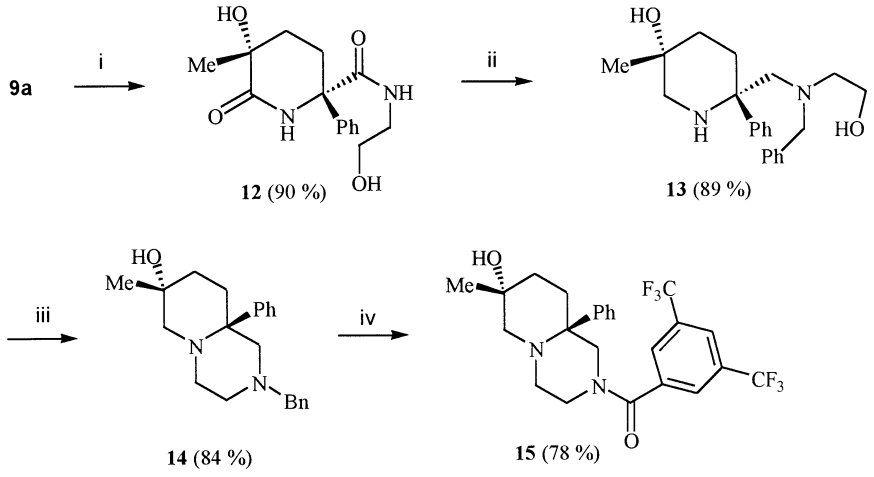
In an alternative sequence the imidoyl chlorides **6b**,**d** were first converted into diones **10b**,**d**, generated by treating **6b**,**d** with wet EtOAc for one day (yield for **10d**: 90% over two steps from **5d**) or by flash chromatography (silica gel; 5% EtOAc/95% CH_2Cl_2; yield for **10b**: 79% over two steps from **5b**). Subsequent lactone cleavage using 3 equiv. of 2-methoxybenzylamine in THF at reflux temperature gave the 2-heteroaryl-2-piperidinecarboxamides **2b** and **2c** in yields of 70 and 56%, respectively. Apparently, aminolysis of **6d** also led to deprotection of the *N*-acetylindole moiety to give **2c**. Compounds **4a**–**c** were prepared by reducing both amide functions of the 6-oxo-2-piperidinecarboxamides **2a**–**c**. The best yields for diamines **4** were obtained when using 4 equiv. of $BH_3{\cdot}SMe_2$ (2 M) in THF.

Compounds **11b**,**d** were obtained by selective hydrogenation of the imidoyl chloride function of **6b** and **6d**. To prevent amide formation by hydrolysis at the air, hydrogenation of the adducts was carried out in situ. Thus, following removal of ethene and addition of palladium on carbon catalyst and 1,4-diazabicyclo[2.2.2]octane (DABCO), the reaction mixture was stirred during 2–4 h under hydrogen (3 bar) to afford **11b** (44% from **5b**) and **11d** (48% from **5d**). The reduction of **6e** was carried out using $NaBH_3CN$ to produce **11e** as described in a previous paper.[4] Aminolysis of lactone compounds **11** using 2-methoxybenzylamine was



3b **4a**

Figure 2.

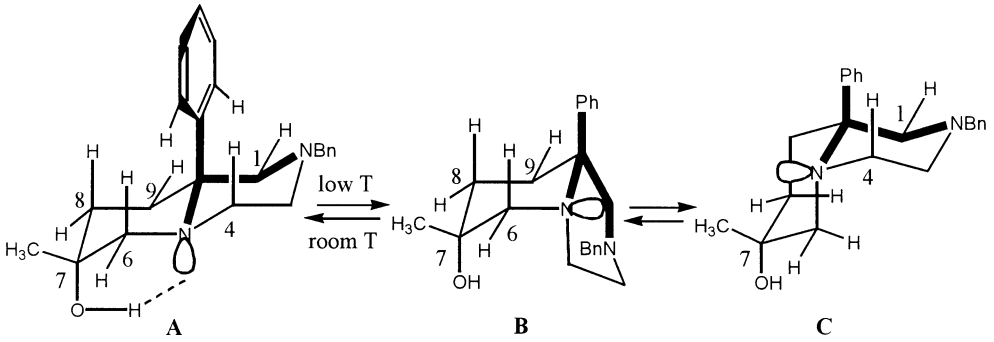


Scheme 5. (i) Ethanolamine, MeOH, rt; (ii) (1) $BH_3{\cdot}SMe_2$, THF (2) BnBr, K_2CO_3, MeOH; (iii) MsCl, TEA, CH_2Cl_2; (iv) (1) $HCOONH_4$, Pd/C, MeOH; (2) 3,5-bis(trifluoromethyl)benzoylchloride, Et_3N, CH_2Cl_2.

effected under the same conditions as for the preparation of diamides 2; however a longer reaction time was required to produce 2-piperidinecarboxamides **3** (3 days). According to a model study, this is due to a higher relief of steric strain when opening the lactone bridge of lactam **10**, i.e. a more severe repulsion is experienced between the bridgehead (hetero)aryl substituent and the planar lactam NH group as compared to the non-planar NH of bridged amine **11**.

Consequent to the generation of compounds **2** and **3** via lactone opening of **10** and **11**, a *cis*-relationship is established between their 5-OH and 2-CONH substituents. The conformational characteristics of compounds **2**–**4** were deduced from NMR spectroscopic data exemplified for **3b** and **4a** in Fig. 2. In the ^1H coupled ^{13}C spectra, the coupling between the 5-methyl group and the protons in 4- or 6-position could not be resolved. These small ^3J coupling values indicate an equatorial orientation of the 5-methyl group. The NOESY spectrum of **3b** revealed the spatial vicinity of H-3 and the *N*-methyl of the pyrrolyl group with H-4ax and H-6ax, respectively. These data indicate a preferred conformational structure with an equatorial 5-CH_3 (or 5-Ph for **3e**) group and axial orientations of 5-OH and the 2-(hetero)aryl group. When comparing the structural and conformational features of compounds **3** and **4** with those of the bioactive models **I** and **II**, a very similar spatial orientation is apparent for the pharmacophoric unit, i.e. the N^2-(2-methoxybenzyl)-1-hetero(aryl)-1,2-ethanediamine moiety. The axial orientation of the 2-(hetero)aryl groups also accords with that reported for model **II**. Apparently, the preferred conformers depicted for **3** and **4** (Fig. 2) are stabilised by the favourable disposition of the equatorial 5-Me or 5-Ph and axial 5-OH substituents. The latter may form an internal H-bridge with the piperidine-*N*-atom as observed earlier with 5-hydroxy-2-piperidinemethanols[4] and other 3-piperidinols (see also below).[9] All of these structural features can enhance the binding affinity to the SP receptor as has been shown in preliminary in vitro experiments carried out for the 2-piperidinemethanol analogues of **3** and **4**, in which the (2-methoxybenzyl)amino group was replaced with the corresponding [3,5-bis(trifluoromethyl)benzyl]oxy moiety.

For biological screening it is also of interest to evaluate conformationally constrained analogues, e.g. bicyclic structures incorporating the required pharmacophoric groups. A bicyclic analogue of **4** was constructed starting from the ester **9a**. This was converted first into N^2-(hydroxyethyl)-2-piperidinecarboxamide **12** by treatment with ethanolamine (90% yield) (Scheme 5). Subsequent reduction of both amide functions and selective N-benzylation using 1 equiv. of benzyl bromide at room temperature afforded compound **13** in 89% yield. Treatment of **13** with methanesulfonyl chloride resulted in the formation of bicyclic compound **14**, which was debenzylated and N-benzoylated to yield target compound **15**.



Scheme 6.

Table 1. Selected ^{1}H NMR data of compound **14**: δ values in ppm relative to TMS (^2J, ^4J in Hz)

	$CDCl_3$, 50°C; *trans* **A**	CD_2Cl_2, −80°C; *cis* **C** 75%	CD_3OD, 40°C; *trans* **A**	CD_3OD, −85°C; *cis* **B** 90%
H1, d	2.60	2.88	2.48	2.44
H1, d	2.28(11.2)	1.75(11)	2.27(11.6)	1.68
H3ax, t	2.55	2.2, t	2.23	2.1, t
H3eq	2.55	2.73, d (9.5)	2.66(10.8)	2.9
H4ax	3.40	3.68, t	3.45	4.22, t
H4eq	3.08(12)	2.6, (9.9)d	3.05(12)	2.8, d
H6, d	3.04(12.6)	3.29(11.6)	2.79	2.74, d
H6, d	2.56(12.6, 2.3)	2.35(11.6)	2.69(13.3, 2)	2.5, d
H8ax	1.36	1.57, t	1.43	1.45, t
H8eq	1.49(13.5, 2.3)	1.70, d(13.5)	1.58(13.7, 2)	1.60, d
H9ax	2.13	0.84, t	2.36	2.9
H9eq	1.83(14)	1.18, d(12.4)	1.70(14)	1.78, d
CH_3	1.06	0.9, d	1.0	0.81
$PhCH_2N$	3.33, 3.45 AB (13.5)	3.53; 3.1 AB (14.4)	3.37 A2	3.58; 3.16 AB (12.4)

At this point it was important to examine in further detail the conformational restrictions imposed on the pharmacophoric moiety by its incorporation into the octahydro-2*H*-pyrido[1,2-*a*]pyrazine bicyclic system with angular 9a-phenyl group. Compounds **14** and **15** can exist as *transoid* or *cisoid* invertomers,[10] corresponding to a unique *trans*-fused structure **A** and the two *cis*-fused conformers **B** and **C**, respectively (Scheme 6). As illustrated by the bold substructures, each of these structures displays a different orientation for the nitrogen lone pair and/or other parts of the pharmacophoric group. Similar inversion of the bridgehead nitrogen was shown to have a marked effect on biological profile for the analogous quinolizidine marine alkaloids halichlorine and pinnaic acid.[11] Extensive NMR and IR analysis of compound **14**, supported by conformational calculations, revealed the existence of an equilibrium mixture of *transoid* (**A**) and *cisoid* (**B**, **C**) forms showing a composition that is strongly dependent on temperature and solvent. At higher temperatures structure **A** is the predominant form stabilised by internal H-bonding. However, at low temperatures this stabilising effect is superseded by intermolecular H-bonding, which favours either **B** or **C** via interaction with, respectively, OH groups of the solvent (CD_3OD) or the equatorial 7-OH group (CD_2Cl_2).

In the IR (KBr) spectrum of compound **14**, a major contribution of *transoid* structure **A** was indicated by a prominent Bohlmann band observed at 2804 cm^{-1}.[12,13] The spectrum further displayed an OH absorption at 3410 cm^{-1} corresponding to intra- and/or intermolecular H-bonding. Upon dissolution of **14** in CCl_4, IR bands due to both free (3610 cm^{-1}, sharp) and intramolecular H-bonded (3520 cm^{-1}, broad) OH groups were detected; the intensity ratio of these bands remained unchanged on further dilution to a concentration below 0.01 M. These IR results are consistent with the co-existence of form **A** exhibiting a permanent internal H-bond as the main component, together with component **B** and/or **C** characterised by intermolecular H-bonding or free OH groups.

In the ^{1}H NMR spectra determined at 25°C in CD_2Cl_2 or at 50°C in $CDCl_3$ (Table 1), characteristic ax, eq-coupling patterns were observed for protons H-6, H-8, and H-9, e.g. a long-range coupling $^4J_{6eq,8eq}$=2.3 Hz, which allowed a clear differentiation between axial and equatorial protons H-6 and H-8. Moreover, an equatorial orientation for the 7-Me group was demonstrated by cross-peaks with each of the vicinal protons H-6 and H-8 in the ^{1}H NOESY spectrum (30°C in CD_2Cl_2). These data suggest one predominant chair form for the piperidine ring, corresponding to either structure **A** or **B**, or to an equilibrium mixture **A**, **B**. Other ^{1}H NOESY cross-peaks, involving the ortho-protons of the 9a-phenyl group, were due to 1,3-diaxial and vicinal interactions with the *cis*-disposed protons H-4ax, H-6ax and H-1eq, H-9eq, respectively. In particular the NOE's with H-4ax and H-6ax strongly support structure **A** as the major form. Since no NOE was observed with H-8ax, the Ph ring apparently is oriented mainly in a plane between H-4ax and H-6ax. The co-existence, besides H-bonded structure **A**, of a component **B** or **C** that lacks an internal H-bond was indicated by a ^{1}H NOESY cross-peak relating the 7-OH and 7-Me protons. According to the ^{1}H coupling data already mentioned, this component is presumed to be **B**. Table 1 also displays selected ^{1}H NMR data for the two *cisoid* conformers **B** and **C** whose structures were assigned on basis of the ^{13}C NMR data and ^{1}H–^{13}C coupling values discussed below. At −85°C in CD_3OD, form **B** was shown to be the main component (ca. 90%), whereas a 1:3 mixture of components **B** and **C** was apparent from the spectra determined at −80°C in CD_2Cl_2. From Table 1 it appears that the ^{1}H chemical shift values determined for each single component **B** and **C** differ markedly from those assigned to form **A** as the main constituent, proving that the high-temperature values are not due to an average spectrum of **B** and **C**. This conclusion was confirmed by ^{13}C characterisation of each component **A**, **B** and **C**.

In the ^{13}C NMR spectrum determined at 25°C in $CDCl_3$, severe broadening was observed for several carbon signals, e.g. C-1, C-6, and C-9. In support of the supposed equilibrium mixture of **A** and **B**, a nearly exclusive equatorial orientation was inferred for the 7-Me group on basis of the low $\sum J$ value measured for coupling of the 7-Me carbon with H-6, H-8 in the ^{1}H-coupled spectrum ($CDCl_3$, 50°C; peak width at half-height: 7.5 Hz). In contrast to the results obtained at higher temperature, **B** and **C** were the only components detected at low temperature. At −85°C in CD_2Cl_2, two series of carbon signals were discerned corresponding to a 3:1 mixture of **C** and **B** (Table 2). Structure **C** was assigned to the major component, based on the large

Table 2. Selected ^{13}C NMR data of compound **14**: δ values in ppm relative to TMS

	$CDCl_3$, 50°C; *trans* **A**	CD_2Cl_2, −85°C; *cis* **B** and **C**		CD_3OD, 40°C; *trans* **A**	CD_3OD, −80°C; *cis* **B**, 90%
		B, 25%	**C**, 75%		
C-1	65.7	67.0	67.1	63.8	68.0
C-3	53.8	(54.3)	54.3	53.7	55.9
C-4	50.3	48.7	49.7	50.7	50.1
C-6	60.3	57.3	60.2	59.9	58.5
C-7	68.2	68.0	66.8	69.6	69.5
C-8	34.3	34.1	33.7	35.5	35.1
C-9	30.0 (br)	19.0	32.4	28.1	20.4
C-9a	59.8	59.0	58.9	61.1	61.2
CH_3	27.2	29.3	25.3	28.3	29.6
$PhCH_2N$	62.7	62.0	61.5	64.0	63.7
C-*ipso*Bn	138.6	138.0	137.4	139.5	138.5
C-*ipso*Ph	143.8	144.0	142.0	146.6	145.4

$\sum J$ value measured for the axial 7-Me carbon atom (peak width at half-height: 16 Hz). An equatorial orientation of the 7-Me group was indicated for the minor component by a low $\sum J$ value (10 Hz). Definite assignment of structure **B** to this component finally rested on the large upfield shift observed for C-9, i.e. δ 19.0 versus 32.4 for **C** and δ 30.0 for a mixture enriched in **A**. This upfield shift can be attributed to a double γ-*gauche* effect exerted by C-4 and N-2, since both atoms exhibit a *syn*-orientation relative to C-9 in structure **B**, opposite to the *anti*-orientation for **A** and **C**. The ^{13}C spectra also reveal a characteristic difference in chemical shift values for an axial and equatorial 7-Me group (δ 25.3 and 29.3).

To examine whether intermolecular H-bonding with a hydroxylic solvent affects the position of the equilibrium between **B** and **C**, ^1H and ^{13}C NMR spectra also were determined in CD_3OD at low-temperature (−85°C) (Tables 1 and 2). Interestingly, under these conditions the equilibrium was shifted nearly exclusively (ca. 90%) towards form **B**, again characterised by the upfield value δ 20.4 for C-9. Overall, the low-temperature results in two different solvents indicate a slow conformational equilibrium between the two *cisoid* conformers **B** and **C** (Scheme 6). At higher temperature (40°C) in CD_3OD, **A** is again found to be the predominant form (Table 2).

Apparently, intra- and intermolecular H-bonding governs the equilibrium between the various forms. At low temperature, structures **B** and **C** may be stabilised by intermolecular association involving H-bonding to the N lone pairs. In methanol, form **B** appears to be favoured by interaction with OH groups of the solvent, whereas in CD_2Cl_2 structure **C** is stabilised via H-bonding with the equatorial OH group. Due to the entropy effect intermolecular associations are disrupted at higher temperature and the equilibrium shifts to *transoid* form **A**, stabilised by an internal H-bridge. To verify the latter assumption, conformational calculations were carried out on the N–Me analogue of **14** representing a simplified, more rigid bicyclic system. Molecular mechanics and semi-empirical calculations using Hyperchem™ (version 4.5; MM+ force-field and semi-empirical AM1 method) disfavoured *transoid* structure **A** relative to **B** and **C** by ca. 2–3 kcal mol^{-1}, due to the additional 1,3-diaxial repulsions experienced by the 9a-phenyl group. *Cisoid* conformer **B** was slightly favoured over **C** (0.3–1.1 kcal mol^{-1}). As the MM+ calculations did not take into account any H-bonding, we applied standard density functional theory (DFT) to calculate the stabilising effect provided by the supposed internal H-bridge (for computational details Section 4). Two MM+ optimised rotamers of the N–Me *transoid* structure **A** with OH bond pointing either to the angular N-5 atom or in between 7-Me and C-8, were submitted to DFT geometry optimisation. This indicated a stabilisation of ca. 3.4 kcal mol^{-1} for the internal H-bridge, whereas the initial energy difference for the two rotamers calculated by MM+ was only ca. 0.1 kcal mol^{-1}. During the DFT optimisation process the OH–N bond distance decreased from 2.51 Å (original MM+ value) to 2.27 Å (DFT), with a C7–O–H bond angle of 105.5°. Owing to the rigid character of the bicyclic system, this effect was found to be lower than that determined for a monocyclic analogue of **A**, 3-methyl-3-piperidinol (stabilising effect ca. 5.3 kcal mol^{-1}; OH–N bond distance 2.02 Å; C3–O–H bond angle 104°). Hence, the energy gained from the internal H-bridge (ca.3.4 kcal mol^{-1}) is able to overcome the increased non-bonded interactions of the axial Ph group in form **A** relative to those in **B** or **C** (ca. 2–3 kcal mol^{-1}). These comparable energy values may further explain why form **A** occurs along with the non H-bonded form **B** at room temperature.

3. Conclusion

Nucleophilic opening of the lactone bridged compounds **10** or **11** (obtained from the reaction of 3-(hetero)aryl-5-chloro-2*H*-1,4-oxazinones **5** and ethene followed by hydrolysis or reduction of the imidoyl chloride function) with amines offers an interesting route for the preparation of stereoselectively substituted 2-(hetero)aryl-5-hydroxy-2-piperidinecarboxamides of type **2** and **3**. Subsequent reduction of compounds **2** afforded the corresponding 2-piperidinemethanamines **4**. Further conversions of **9a** gave the more conformationally constrained bicyclic analogues **14** and **15**. From a detailed NMR study supported by conformational calculations, the latter were shown to exist as a temperature and solvent dependent equilibrium mixture of *transoid* and *cisoid* invertomers **A**–**C**, controlled by intra- and intermolecular H-bonding. These specifically substituted piperidines are of interest as potential SP antagonists.

4. Experimental

4.1. 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. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300, WM 250, and AMX 400 instruments. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane or the deuterated solvent as an internal reference. One- and two-dimensional NMR techniques were used to assign the ^{1}H and ^{13}C chemical shifts. At room temperature and at higher temperatures, assignment of the various protons was carried out by careful spin–spin coupling analysis. One-bond ^{1}H–^{13}C correlated spectroscopy (HMQC) was used to assign carbon atoms and their corresponding pair of diastereotopic protons. The chemical shift values for the main component of compound **14** present in CD_2Cl_2 (**C**) and CD_3OD (**B**) at −80° also were determined by using HMQC. 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 preparations and spectroscopic data of compounds **5a**–**c**,**e**[16], **6a**[17], **9a**[4] and **11e**[4] have been described in previous papers.

4.2. Computational details

Conformational calculations were carried out using Hyperchem™ (version 4.5; MM+ force-field and semi-empirical AM1 method). For the DFT calculations, the B3LYP functional was applied in combination with the split-valence (SV) basis sets from Schäfer,[14] extended with a polarisation function. These DFT calculations were performed with the Turbomole code.[15]

4.2.1. 3-(1-Acetyl-1*H*-indol-3-yl)-5-chloro-6-methyl-2*H*-1,4-oxazin-2-one (5d). To a solution of 3.9 g (15 mmol) 5-chloro-6-methyl-3-(indol-3-yl)-2*H*-1,4-oxazin-2-one (**5c**) in 120 mL acetic acid anhydride was added a small amount of DMAP and the reaction mixture was stirred for 6 h at room temperature. After evaporation the residue was purified by flash chromatography (silica gel; CH_2Cl_2). Yield: 4.3 g, 95%; yellow crystals; mp 233°C; IR (KBr) cm^{-1}: 1600 (C=N), 1710 (OCO), 1743 (NCO);^{1}H NMR (DMSO-d$_6$): 2.39 (s, 3H, CH_3), 2.77 (s, 3H, $COCH_3$), 7.44 and 8.45 (2×m, 2×2H, indH-4,5,6,7), 8.77 (s, 1H, indH-2); ^{13}C NMR (DMSO-d$_6$): 16.8 (CH_3), 23.9 ($CO\mathit{C}H_3$), 114.0 (indC-3), 115.9 (indC-7), 122.3 (indC-4), 124.0 (C-5), 124.6 (indC-5), 126.0 (indC-6), 127.2 (indC-3a), 132.1 (indC-2), 135.2 (indC-7a), 143.1 (C-6), 146.6 (C-3), 152.7 (C-2), 169.8 (NCO); *m/z* CI (%): 303 (MH^+, 100); exact mass for $C_{15}H_{11}ClN_2O_3$: 302.0458; found: 302.0463.

4.3. Generation of compounds 8–11

In a stainless steel tube a solution of 5 mmol 2*H*-1,4-oxazin-2-one **5a**–**e** in 30 mL dry toluene was heated at 110°C for 2 or 4 h under ethene pressure (40 or 20 atm. respectively). After removal of ethene and evaporation of the solvent, the crude product from **5c** was found to be **8** instead of **6c**. It was purified by column chromatography (silica gel; CH_2Cl_2). For the other reactions the crude product **6** was converted into compounds **9**–**11**. Compound **9a** was obtained after treatment of **6a** with MeOH, as described previously.[4] The crude product **6b** was hydrolysed during flash chromatography (silica gel; 5% CH_2Cl_2/95% EtOAc) to provide the pure lactam **10b**. Crude product **6d** was first hydrolysed by treatment with wet EtOAc for one day. After removal of the solvent and crystallisation from a dichloromethane–hexane mixture white crystals of **10d** were obtained. The compounds **11b**–**e** were obtained from in situ hydrogenation of the adducts **6b**–**e**. After removal of ethene, 30% (w/w) Pd/C (10%) and 60% (w/w) DABCO was added and the reaction mixture was stirred for 2–4 h (MS control) under hydrogen pressure (3 atm.). The mixture was filtered over celite and the filtrate was concentrated in vacuo and purified with column chromatography (**11b**: silica gel; 5% EtOAc/95% CH_2Cl_2, **11d**: silica gel; 5% MeOH–95% CH_2Cl_2) and crystallisation from a dichloromethane–hexane mixture.

4.3.1. 5-(1*H*-Indol-3-yl)-2-methyl-6-oxo-3,6-dihydro-2*H*-pyran-2-carbonitrile (8). Yield from **5c**: 806 mg, 64%; Yellow crystals; mp 145°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 2365 (CN), 3250 (NH);^{1}H NMR ($CDCl_3$): 1.94 (s, 3H, CH_3), 2.90 (dd, 1H, ^2J=18.3 Hz, ^3J(H3eq–H4)=3.2 Hz, H3eq), 2.97 (dd, 1H, ^2J=18.3 Hz, ^3J(H3ax–H4)=6.3 Hz, H3ax), 7.00 (td, 1H, indH-5), 7.08 (td, 1H, indH-6), 7.13 (dd, 1H, ^3J(H4–H3ax)=6.3 Hz, ^3J(H4–H3eq)=3.2 Hz, H4), 7.18 (s, 1H, indH-2), 7.33 (d, 1H, indH-7), 7.82 (d, 1H, indH-4); ^{13}C NMR ($CDCl_3$): 26.6 (CH_3), 33.0 (C-3), 73.5 (C-2), 109.5 (indC-3), 110.4 (indC-7), 119.4 (CN), 119.5 (indC-4), 120.5 (indC-5), 122.1 (indC-6), 124.8 (indC-3a), 126.9 (C-5), 129.0 (indC-2), 131.4 (C-4), 136.8 (indC-7a), 161.5 (C-6); *m/z* CI (%): 253 (MH^+, 100), 226 (MH^+−HCN, 28).

4.3.2. 1-Methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxa-5-aza-bicyclo[2.2.2]octane-3,6-dione (10b). Yield: 880 mg, 79% over two steps from **5b**; white crystals; mp 211°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1695 (OCO), 1747 (NCO); ^{1}H NMR ($CDCl_3$): 1.50 (s, 3H, CH_3), 2.05 (ddd, 1H, ^2J=14.5 Hz, ^3J=10.5, 4.2 Hz, H7), 2.24 (m, 1H, H7), 2.41 (m, 2H, H8), 3.52 (s, 3H, NCH_3), 5.98 (dd, 1H, pyrH-4), 6.18 (dd, 1H, pyrH-3), 6.86 (t, 1H, pyrH-5), 9.35 (s broad, 1H, NH); ^{13}C NMR ($CDCl_3$): 18.4 (CH_3), 29.1 (C-7), 29.3 (C-8), 35.2 (NCH_3), 57.4 (C-4), 82.3 (C-1), 106.0 (pyrC-4), 109.5 (pyrC-3), 125.1 (pyrC-2), 125.6 (pyrC-5), 169.5 (C-3), 169.9 (C-6); *m/z* CI (%): 235 (MH^+,100), 207 (MH^+−CO, 13); exact mass for $C_{12}H_{14}N_2O_3$: 234.1004; found: 234.1008; CHN analysis (%): calcd: C 61.53, H 6.02, N 11.96, found: C 61.61, H 5.83, N 11.86.

4.3.3. 4-(1-Acetyl-1*H*-indol-3-yl)-1-methyl-2-oxa-5-aza-bicyclo[2.2.2]octane-3,6-dione (10d). Yield: 1.36 g, 90% over two steps from **5d**; white crystals; mp 223°C

(CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1700 (OCO), 1752 (NCO); ^1H NMR ($CDCl_3$): 1.52 (s, 3H, CH_3), 2.30 (ddd, 1H, ^2J=14.5 Hz, ^3J=10.5, 4.2 Hz, H7), 2.51 (m, 3H, H7,8), 2.67 (s, 3H, $COCH_3$), 7.37 (s, 1H, indH-2), 7.42–7.75 (m, 4H, indH-4,5,6,7); ^{13}C NMR ($CDCl_3$): 19.7 (CH_3), 24.1 ($COCH_3$), 29.7 (C-7), 30.1 (C-8), 57.1 (C-4), 81.8 (C-1), 109.4 (indC-3), 116.7 (indC-7), 117.7 (indC-4), 119.1 (indC-6), 125.3 (indC-5), 127.1 (indC-2),129.9 (indC-3a), 138.8 (indC-7a), 164.3 ($COCH_3$), 169.2 (C-3), 172.2 (C-6); *m*/*z* CI (%): 313 (MH^+,83), 269 (MH^+−[*N*-acetyl-indole], 100); exact mass for $C_{17}H_{16}N_2O_4$: 312.1110; found: 312.1124

4.3.4. 1-Methyl-4-(1-methyl-1*H*-pyrrol-2-yl)-2-oxa-5-azabicyclo[2.2.2]octan-3-one (11b). Yield: 44% over two steps from **5b**; white crystals; mp 136°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1747 (OCO); ^1H NMR ($CDCl_3$): 1.19 (s broad, 1H, NH), 1.42 (s, 3H, CH_3), 1.99 (m, 2H, H7), 2.36 (m, 2H, H8), 3.14 (s, 2H, H6), 3.70 (s, 3H, NCH_3), 6.03 (dd, 1H, pyrH-4), 6.10 (dd, 1H, pyrH-3), 6.63 (t, 1H, pyrH-5); ^{13}C NMR ($CDCl_3$): 23.0 (CH_3), 35.9 (NCH_3), 51.1 (C-6), 54.9 (C-4), 80.3 (C-1), 106.2 (pyrC-4), 108.0 (pyrC-3), 125.0 (pyrC-5), 129.0 (pyrC-2), 172.8 (C-3); *m*/*z* (%): 220 ($M^{+\cdot}$, 6), 176 ($M^{+\cdot}-CO_2$, 100); exact mass for $C_{12}H_{16}N_2O_2$: 220.1212; found: 220.1212.; CHN analysis (%): calcd: C 65.43, H 7.32, N 12.72, found: C 65.40, H 7.49, N 12.62.

4.3.5. 4-(1-Acetyl-1*H*-indol-3-yl)-1-methyl-2-oxa-5-azabicyclo[2.2.2]octan-3-one (11d). Yield: 48% over two steps from **5d**; white crystals; mp 153°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1698 (OCO), 1747 (NCO); ^1H NMR ($CDCl_3$): 1.44 (s, 3H, CH_3), 1.57 (s broad, 1H, NH), 2.02 (m, 2H, H7), 2.37 (m, 2H, H8), 2.57 (s, 3H, $COCH_3$), 3.11 (s, 2H, H6), 7.25 (s, 1H, indH-2), 7.32–7.52 (m, 4H, indH-4,5,6,7); ^{13}C NMR ($CDCl_3$): 21.2 (CH_3), 24.3 ($COCH_3$), 30.2 (C-7), 30.3 (C-8), 50.8 (C-6), 55.4 (C-4), 73.4 (C-1), 115.1 (indC-3), 115.7 (indC-7), 117.3 (indC-4), 118.2 (indC-6), 123.2 (indC-2), 124.8 (indC-5), 130.2 (indC-3a), 140.0 (indC-7a), 164.4 ($COCH_3$), 171.9 (C-3); *m*/*z* CI (%): 299 (MH^+, 65), 255 (MH^+-CO_2, 100); exact mass for $C_{17}H_{18}N_2O_3$: 298.1317; found: 298.1315

4.4. Conversion of compound 9a into 2a

4.4.1. 5α-Hydroxy-N^2-(2-methoxybenzyl)-5β-methyl-6-oxo-2β-phenyl-2α-piperidinecarboxamide (2a) from 9a. To a stirred solution of 565 mg methyl 2-piperidinecarboxylate **9a**[4] (2.15 mmol) in 28 mL absolute methanol was added 588 mg (2 equiv.) 2-methoxybenzylamine. The resulting solution was stirred at room temperature for one day. After evaporation of the solvent, the crude product was purified by column chromatography (silica gel; 5% MeOH–95% CH_2Cl_2) and crystallisation (CH_2Cl_2/Et_2O). Yield: 751 mg, 95%; white crystals; mp 147°C (CH_2Cl_2/*n*-Et_2O); IR (KBr) cm^{-1}: 1656 (NCO), 3401, 3191 (OH, NH); ^1H NMR ($CDCl_3$): 1.35 (s, 3H, CH_3), 1.80 (m, 1H, H4eq), 1.94–2.05 (m, 2H, H3ax and H4ax), 2.82 (m, 1H, H3eq), 3.29 (s, 1H, OH), 3.71 (s, 3H, OCH_3), 4.42 (d, ^{2}J=14.0 Hz, ^{3}J=6.2 Hz, 1H, $NHCH_2$), 4.46 (d, ^{2}J=14.0 Hz, ^{3}J=6.2 Hz, 1H, $NHCH_2$), 6.80 (d, 1H, ArH-3), 6.85 (t, 1H, ArH-5), 6.94 (t, 1H, ^{3}J=5.1 Hz, CH_2NHCO), 7.16 (d, 1H, ArH-6), 7.21 (t, 1H, ArH-4), 7.29 (s broad, 1H, NHCO), 7.30–7.39 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 27.4 (CH_3), 31.2 (C-3), 32.2 (C-4), 40.4 ($NHCH_2$), 55.2 (OCH_3), 66.9, 69.8 (C-2 and C-5), 110.4 (ArC-3), 120.6 (ArC-5), 125.1–129.6 (PhC and ArC), 141.0 (PhC-1), 157.5 (ArC-2), 171.0 (CONH), 177.0 (C-6); *m*/*z* CI (%): 369 (MH^+, 100), 204 (MH^+−[$HCONHCH_2Ar$], 13); CHN analysis (%): calcd: C 68.46, H 6.57, N 7.60, found: C 68.59, H 6.66, N 7.66.

4.5. General procedure for the conversions of compounds 10 and 11 into target compounds 2 and 3

4 mmol 2-oxa-5-azabicyclo[2.2.2]octane-3 one or 3,6-dione (**10** or **11**) was dissolved in 20 mL THF and 3 equiv. 2-methoxybenzylamine were added. The reaction mixture was refluxed until all starting material had disappeared (24 h). After evaporation of the solvent the residue was diluted with 15 mL CH_2Cl_2 and extracted with 3×10 mL 2N HCl solution. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (silica gel; 5% MeOH–95% CH_2Cl_2) or crystallisation (dichloromethane/*n*-hexane).

4.5.1. 5α-Hydroxy-N^2-(2-methoxybenzyl)-5β-methyl-2β-(1-methyl-1*H*-pyrrol-2-yl)-6-oxo-2α-piperidinecarboxamide (2b). Yield from **10b**: 70%; white crystals; mp 147°C (CH_2Cl_2/*n*-C_6H_{14}); IR (KBr) cm^{-1}: 1660, 1662 (NCO), 3380 (OH, NH);^1H NMR ($CDCl_3$): 1.33 (s, 3H, CH_3), 2.06 and 2.38 (2×m, 2×2H, H3 and H4), 1.63 (s broad, 1H, OH), 3.25 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3), 4.34 (dd, 1H, ^2J=14.3 Hz, ^3J=6.0 Hz, $NHCH_2$), 4.40 (dd, 1H, ^2J=14.3 Hz, ^3J=6.0 Hz, $NHCH_2$), 6.06 (dd, 1H, pyrH-4), 6.21 (dd, 1H, pyrH-3), 6.27 (t broad, 1H, CH_2NHCO), 6.43 (s broad, 1H, NHCO), 6.52 (t, 1H, pyrH-5), 6.80 (d, 1H, ArH-3), 6.87 (t, 1H, ArH-5), 7.17 (dd, 1H, ArH-6), 7.24 (td, 1H, ArH-4); ^{13}C NMR ($CDCl_3$): 28.0 (CH_3), 29.7 (C-3), 32.2 (C-4), 34.9 (NCH_3), 40.8 ($NHCH_2$), 55.1 (OCH_3), 62.4 (C-5), 69.6 (C-2), 107.1 (pyrH-4), 108.9 (pyrH-3), 110.1 (ArC-3), 120.6 (ArC-5), 125.5 (ArC-1), 125.5 (pyrH-5), 129.2 (ArC-6), 129.9 (ArC-4), 130.3 (pyrH-2), 157.4 (ArC-2), 171.2 (CONH), 176.7 (C-6); *m*/*z* CI (%): 372 (MH^+, 100), 291 (MH^+−[*N*-Me-pyrrole], 77), 207 (MH^+−[*o*-$MeOC_6H_4CH_2NH_2$], 31); exact mass for $C_{20}H_{25}N_3O_4$: 371.1845; found: 371.1847; CHN analysis (%): calcd: C 64.67, H 6.78, N 11.31, found: C 64.31, H 6.84, N 11.21.

4.5.2. 5α-Hydroxy-2β-(1*H*-indol-3-yl)-N^2-(2-methoxybenzyl)-5β-methyl-6-oxo-2α-piperidinecarboxamide (2c). Yield from **10d**: 56%; white crystals; mp 127°C; IR (KBr) cm^{-1}: 1665 (NCO), 3374 (OH, NH);^1H NMR ($CDCl_3$): 1.49 (s, 3H, CH_3), 1.90 (ddd, 1H, ^2J=13.8 Hz, ^3J(H4eq–H3eq)=6.5 Hz, ^3J(H4eq–H3ax)=3.0 Hz, H4eq), 2.00 (ddd, 1H, ^2J=13.8 Hz, ^3J(H4ax–H3ax)=11.4 Hz, ^3J(H4ax–H3eq)=3.0 Hz, H4ax), 2.42 (ddd, 1H, ^2J=13.8 Hz, ^3J(H3ax–H4ax)=11.4 Hz, ^3J(H3ax–H4eq)=3.0 Hz, H3ax), 2.73 (ddd, 1H, ^2J=13.8 Hz, ^3J(H3eq–H4eq)=6.5 Hz, ^3J(H3eq–H4ax)=3.0 Hz, H3eq), 3.59 (s, 3H, OCH_3), 4.38 (d, 1H, $NHCH_2$), 4.45 (d, 1H, $NHCH_2$), 6.77 (d, 1H, indH-7), 6.80 (d, 1H, ArH-3), 6.97 (t, 1H, ArH-5), 7.13 (d, 1H, ArH-6), 7.15 (m, 2H, ArH-4 and indH-5), 7.20 (s, 2H, indH-2), 7.41 (m, 2H, indH-4,6), 8.72 (s broad, 1H, indH-1); ^{13}C NMR ($CDCl_3$): 28.4 (CH_3), 31.8 (C-3), 35.5 (C-4), 41.9 ($NHCH_2$), 56.8 (OCH_3), 66.1 (C-5), 72.2 (C-2), 112.5 (ArC-3), 114.0 (indC-7), 117.7 (indC-3), 121.3 (ArC-5), 122.4 (indC-4), 124.1 (indC-5), 125.4 (indC-6), 126.7 (ArC-6), 126.7

(ArC-1), 128.0 (indC-3a), 130.9 (indC-2), 131.2 (ArC-4), 139.8 (indC-7a) 159.9 (ArC-2) 175.5 (CONH), 178.9 (C-6); *m/z* CI (%): 408 (MH^+, 100), 291 (MH^+−indole, 37), 271 (MH^+−[*o*-$MeOC_6H_4CH_2NH_2$], 18); exact mass for $C_{20}H_{29}N_2O_3$: 407.1845; found: 407.1845.

4.5.3. 5α-Hydroxy-N^2-(2-methoxybenzyl)-5β-methyl-2β-(1-methyl-1*H*-pyrrol-2-yl)-2α-piperidinecarboxamide (3b). Yield from **11b**: 58%; white crystals; mp 148°C; IR (KBr) cm^{-1}: 1649 (NCO), 3407 (OH, NH);^{1}H NMR ($CDCl_3$): 1.05 (s, 3H, CH_3), 1.69 (dq, 1H, ^2J=^3J(H4eq–H3ax)=^3J(H4eq–H3eq)=6.3 Hz, ^4J(H4eq–H6eq)=2.7 Hz, H4eq), 1.94 (m, 1H, H4ax), 2.07 (m, 2H, H3ax and H3eq), 2.33 (d, 1H, ^2J=14.0 Hz, H6ax), 2.45 (s broad, 2H, NH and OH), 2.60 (dd, 1H, ^2J=14.0 Hz, ^4J(H6eq–H4eq)=2.7 Hz, H6eq), 3.44 (s, 3H, NCH_3), 3.68 (s, 3H, OCH_3), 4.28 (dd, 1H, ^2J=14.0 Hz, ^3J=5.6 Hz, NHCH_2Ar), 4.39 (dd, 1H, ^2J=14.0 Hz, ^3J=5.6 Hz, NHCH_2Ar), 6.06 (dd, 1H, pyrH-4), 6.08 (t, 1H, ^3J=5.6 Hz, CONHCH_2Ar), 6.20 (dd, 1H, pyrH-3), 6.55 (t, 1H, pyrH-5), 6.77 (d, 1H, ArH-3), 6.85 (t, 1H, ArH-5), 7.15 (dd, 1H, ArH-6), 7.21 (td, 1H, ArH-4); ^{13}C NMR ($CDCl_3$): 27.5 (CH_3), 29.8 (C-3), 34.4 (C-4), 35.5 (NCH_3), 39.8 ($NHCH_2$), 52.0 (C-6), 55.0 (OCH_3), 60.6, 65.9 (C-2 and C-5), 106.2 (pyrC-4), 109.9 (pyrC-3), 110.9 (ArC-3), 120.5 (ArC-5), 124.7 (pyrC-5), 128.9 (pyrC-2), 126.1 (ArC-1), 128.7 (ArC-6), 129.4 (ArC-4), 157.4 (ArC-2), 174.5 (CONH); *m/z* CI (%): 358 (MH^+, 82), 340 (MH^+-H_2O, 18), 277 (MH^+−[*N*-Me-pyrrole], 100), 193 (MH^+−[*o*-$MeOC_6H_4CH_2NH_2$], 66); exact mass for $C_{20}H_{27}N_3O_3$: 357.2052; found: 357.2048.

4.5.4. 5α-Hydroxy-2β-(1*H*-indol-3-yl)-N^2-(2-methoxybenzyl)-5β-methyl-2α-piperidinecarboxamide (3c). Yield from **11d**: 55%; white crystals; mp 119°C; IR (KBr) cm^{-1}: 1655 (NCO), 3295, 3405 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.05 (s, 3H, CH_3), 1.69 and 2.32 (2×m, 2×2H, H3 and H4), 2.55 (d, 1H, ^2J=13.6 Hz, H6ax), 2.63 (d, 1H, ^2J=13.6 Hz, H6eq), 4.35 (dd, 1H,^2J=14.5 Hz, ^3J=6.0 Hz, NHCH_2Ar), 4.39 (dd, 1H,^2J=14.5 Hz, ^3J=6.0 Hz, NHCH_2Ar), 6.77 (m, 2H, ArH-3,4), 7.00 (s, 1H, indH-2), 7.01–7.26 (m, 4H, ArH-5,6 and indH-5,6), 7.33 (d, 1H, indH-7), 7.38 (t, ^3J=6.0 Hz, CONHCH_2), 7.77 (d, 1H, indH-4), 8.97 (s broad, 1H, indH-1); ^{13}C NMR ($CDCl_3$): 26.6 (CH_3), 29.5 (C-3), 34.5 (C-4), 39.6 ($NHCH_2$), 52.8 (C-6), 55.0 (OCH_3), 61.7, 66.7 (C-2 and C-5), 110.1 (indC-7), 111.6 (ArC-3), 113.8 (indC-3), 119.6 (indC-6), 120.5 (indC-5), 120.6 (ArC-5), 121.9 (indC-4), 124.6 (ArC-6), 125.5 (ArC-1), 126.1 (indC-3a), 128.6 (indC-2), 129.4 (ArC-4), 136.9 (indC-7a) 157.4 (ArC-2) 174.7 (CONH); *m/z* CI (%): 394 (MH^+, 100), 376 (MH^+-H_2O, 23), 277 (MH^+−indole, 46), 299 (MH^+−[*o*-$MeOC_6H_4CH_2NH_2$], 90); exact mass for $C_{23}H_{27}N_3O_3$: 393.2052; found: 393.2043.

4.5.5. 5α-Hydroxy-N^2-(2-methoxybenzyl)-2β,5β-diphenyl-2α-piperidinecarboxamide (3e). Yield from **11e**: 54%; oil; IR (KBr) cm^{-1}: 1654 (NCO), 3406 (OH, NH);^{1}H NMR ($CDCl_3$): 1.84 (m, 1H, H4eq), 2.08 (td, 1H, ^2J=14.0 Hz, ^3J(H4ax–H3ax)=14.0 Hz, ^3J(H4ax–H3eq)=4.0 Hz, H4ax), 2.45 (m, 1H, H3ax), 2.60 (dt, 1H, ^2J=14.0 Hz, ^3J(H3eq–H4ax)=^3J(H3eq–H4eq)=4.0 Hz, H3eq), 2.80 (dd, 1H, ^2J=14.0 Hz, ^4J(H6eq–H4eq)=2.5 Hz, H6eq), 2.92 (d, 1H, ^2J=14.0 Hz, H6ax), 3.74 (s, 3H, OMe), 4.32, 4.33 (2d, 2H, NHCH_2Ar), 6.82 (td, 2H, ^3J=7.5 Hz, ^4J=1.0 Hz, ArH-3,5), 6.98 (t broad, 1H, ^3J=5.4 Hz, CONHCH_2), 7.04 (1H, dd, ^3J=7.3 Hz, ^4J=1.4 Hz, ArH-6), 7.17–7.62 (m, 11H, ArH-4, PhH); ^{13}C NMR ($CDCl_3$): 27.8 (C-3), 33.4 (C-4), 39.4 (CH_2Ar), 52.6 (C-6), 55.2 (OCH_3), 63.4, 70.4 (C-2 and C-5), 110.2 (ArC-3), 120.5–129.3, 138.9, (ArC, PhC), 145.7 (PhC-1), 157.4 (ArC-2), 173.9 (CONH); *m/z* CI (%): 417 (MH^+, 100), 399 (MH^+-H_2O, 45).

4.6. General procedure for the BH_3·SMe_2 reduction of amides 2 to yield amines 4

Four equivalents BH_3·SMe_2 (2 M in THF) were added dropwise to a solution of **2** (0.6 mmol) in 15 mL dry THF at reflux temperature. The reaction mixture was refluxed for one night; after removal of solvent in vacuo the residue was treated with 15 mL saturated HCl–MeOH solution and refluxed for 30 min. The solvent was evaporated, 15 mL MeOH was added and subsequently removed under reduced pressure. The residue was further treated with 15 mL water and slightly neutralised with K_2CO_3. The aqueous suspension was extracted with three portions of 15 mL dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated to give the crude product **4**. Further purification was carried out by chromatography (silica gel; 5% MeOH/95% CH_2Cl_2→20% MeOH/80% CH_2Cl_2).

4.6.1. 2α-{[(2-Methoxybenzyl)amino]methyl}-5β-methyl-2β-phenyl-5α-piperidinol (4a). Yield from **2a**: 80%; oil; IR (NaCl) cm^{-1}: 3349 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.01 (s, 3H, CH_3), 1.24 (td, 1H, ^2J=^3J(H4ax–H3ax)=14.0 Hz, ^3J(H4ax–H3eq)=4.0 Hz, H4ax), 1.50 (m, 1H, H4eq), 1.93 (td, 1H, ^2J=^3J(H3ax–H4ax)=14.0 Hz, ^3J(H3ax–H4eq)=4.0 Hz, H3ax), 2.18 (dt, 1H, ^2J=14.0 Hz, ^3J(H3eq–H4ax)=4.0 Hz, ^3J(H3eq–H4eq)=4.0 Hz, H3eq), 2.54 (s, 2H, H6), 2.56 (d, 1H, ^2J=11.4 Hz, C2CH_2NH), 2.60 (d, 1H, ^2J=11.4 Hz, C2CH_2NH), 3.59 (s, 3H, OCH_3), 3.62 (d, 1H, ^2J=13.8 Hz, CH_2Ar), 3.66 (d, 1H, ^2J=13.8 Hz, CH_2Ar), 6.74 (d, 1H, ^3J=8.0 Hz, ArH-3), 6.85 (td, 1H, ^3J=8.0 Hz, ^4J=1.0 Hz, ArH-5), 7.08 (dd, 1H, ^3J=8.0 Hz, ^4J=1.0 Hz, ArH-6), 7.18 (td, 1H, ^3J=8.0 Hz, ^4J=1.0 Hz, ArH-4), 7.26–7.36 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 26.2 (CH_3), 29.0 (C-3), 33.8 (C-4), 49.9 (NHCH_2Ar), 52.9 (C-6), 54.9 (OCH_3), 62.3 (C2CH_2NH), 58.8, 67.0 (C-2 and C-5), 110.4 (ArC-3), 120.2 (ArC-5), 126.3, 128.4 (ArC), 127.9, 128.3, 129.5 (PhC), 141.6 (PhC-1), 157.5 (ArC-2); *m/z* CI (%): 341 (MH^+, 100), 323 (MH^+-H_2O, 23), 190 (MH^+−[*o*-$MeOC_6H_4CH_2NHMe$], 29); exact mass for $C_{12}H_{16}N_1O_1$ ($M^+-CH_2NHCH_2Ar$): 190.1232 found: 190.1238; CHN analysis (%): calcd: C 74.08, H 8.29, N 8.23, found: C 73.81, H 8.06, N 7.90.

4.6.2. 2α-{[(2-Methoxybenzyl)amino]methyl}-2β-(1-methyl-1*H*-pyrrol-2-yl)-5β-methyl-5α-piperidinol (4b). Yield from **2b**: 69%; oil; IR (NaCl) cm^{-1}: 3389 (OH, NH);^{1}H NMR ($CDCl_3$): 1.03 (s, 3H, CH_3), 1.68 (m, 2H, H4eq and H4ax), 2.06 (m, 2H, H3ax and H3eq), 2.42 (d, 1H, ^2J=12.6 Hz, H6ax), 2.62 (dd, 1H, ^2J=12.6 Hz, ^4J(H6eq–H4eq)=2.4 Hz, H6eq), 2.74 (d, 1H, ^2J=12.0 Hz, C2CH_2NH), 3.00 (d, 1H, ^2J=12.0 Hz, C2CH_2NH), 3.56 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 3.89 (d, 1H, ^2J=14.0 Hz, NHCH_2Ar), 4.07 (d, 1H, ^2J=14.0 Hz, NHCH_2Ar), 6.02 (dd, 1H, pyrH-4), 6.06 (dd, 1H, pyrH-3), 6.46 (t, 1H, pyrH-5),

6.80 (d, 1H, ArH-3), 6.91 (t, 1H, ArH-5), 7.27 (m, 2H, ArH-4,6); ^{13}C NMR ($CDCl_3$): 27.0 (CH_3), 29.8 (C-3), 34.4 (C-4), 36.3 (CH_3N), 48.4 ($NHCH_2Ar$), 52.6 (C2CH_2NH), 55.4 (OCH_3), 55.6 (C-6), 56.6 (C-2), 66.6 (C-5), 106.3 (pyrC-4), 110.3 (pyrC-3), 111.2 (ArC-3), 120.7 (ArC-5), 125.1 (pyrC-5), 129.3 (pyrC-2), 129.8 (ArC-6), 129.9 (ArC-1), 131.1 (ArC-4), 157.6 (ArC-2); *m/z* CI (%): 344 (MH^+, 91), 326 (MH^+-H_2O, 30), 263 (MH^+-[*N*-Me-pyrrole], 100), 193 (MH^+-[*o*-$MeOC_6H_4CH_2NHMe$], 74); exact mass for $C_{20}H_{29}N_3O_2$: 343.2260; found: 343.2258.

4.6.3. 2β-(1*H*-Indol-3-yl)-2α-{[(2-methoxybenzyl)amino]-methyl}-5β-methyl-5α-piperidinol (4c). Yield from **2c**: 64%; yellow crystals; mp 164°C; IR (KBr) cm^{-1}: 2930, 3288 (NH, OH); ^{1}H NMR ($CDCl_3$): 1.02 (s, 3H, CH_3), 1.47 (td, 1H, $^2J=^3J$(H4ax–H3ax)=14.0 Hz, ^3J(H4ax–H3eq)=3.6 Hz, H4ax), 1.55 (m, 1H, H4eq), 1.98 (td, 1H, $^2J=^3J$(H3ax–H4ax)=14.0 Hz, ^3J(H3ax–H4eq)=4.2 Hz, H3ax), 2.24 (dt, 1H, ^2J=14.0 Hz, ^3J(H3eq–H4ax)=^3J(H3eq–H4eq)=3.6 Hz, H3eq), 2.56 (dd, 1H, ^2J=12.0 Hz, ^4J(H6eq–H4eq)=2.0 Hz, H6eq), 2.71 (d, 1H, ^2J=12.0 Hz, H6ax), 2.75 (s broad, 3H, OH and 2xNH), 2.79 (d, 1H, ^2J=10.7 Hz, C2CH_2NH), 2.87 (d, 1H, ^2J=10.7 Hz, C2CH_2NH), 3.35 (s, 3H, OCH_3), 3.64 (d, 1H,^2J=13.9 Hz, NHCH_2Ar), 3.72 (d, 1H, ^2J=13.9 Hz, NHCH_2Ar), 6.63 (d, 1H, ArH-3), 6.81 (t, 1H, ArH-5), 7.00–7.07 (m, 2H, ArH-6 and indH-6), 7.08 (s, 1H, indH-2), 7.13–7.18 (m, 2H, ArH-4 and indH-5), 7.37 (d, 1H, indH-7), 7.66 (d, 1H, indH-4), 8.50 (s broad, 1H, indH-1); ^{13}C NMR ($CDCl_3$): 26.3 (CH_3), 29.9 (C-3), 34.0 (C-4), 49.7 ($NHCH_2Ar$), 52.9 (C2CH_2NH), 54.6 (OCH_3), 56.9 (C-2), 60.6 (C-6), 67.0 (C-5), 110.0 (ArC-3), 111.3 (indC-7), 115.8 (indC-3), 119.4 (indC-6), 120.2 (ArC-5), 120.5 (indC-4), 121.7 (indC-5), 124.0 (indC-2), 125.9 (ArC-1), 127.6 (indC-3a), 128.0 (ArC-4), 129.6 (ArC-6), 137.1 (indC-7a) 157.4 (ArC-2); *m/z* CI (%): 380 (MH^+, 73), 362 (MH^+-H_2O, 8), 263 (MH^+-indole, 100), 245 (MH^+-indole-H_2O, 45); exact mass for $C_{23}H_{29}N_3O_2$: 379.2260; found: 379.2259.

4.7. Conversion of compound 9a into a bicyclic analogue of 4

4.7.1. 5α-Hydroxy-N^2-(hydroxyethyl)-5β-methyl-6-oxo-2β-phenyl-2α-piperidinecarboxamide (12). To a stirred solution of methyl 6-oxo-5-hydroxy-5-methyl-2-phenyl-2-piperidinecarboxylate **9a** (1.40 mg, 5.32 mmol) in absolute methanol (28 mL) was added 5 equiv. (1.60 mL) 2-aminoethanol. After stirring at room temperature for 24 h, the solvent was evaporated, the residue dissolved in water (20 mL) and extracted with dichloromethane (3×25 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by crystallisation (CH_2Cl_2/Et_2O) to give 1.38 g amide **12**. Yield: 90%; white crystals; mp 142°C; IR (KBr) cm^{-1}: 1531, 1654 (NCO), 3327, 3476 (OH, NH); ^{1}H NMR (DMSO-d_6) (25°C): 1.25 (s, 3H, CH_3), 1.51 (ddd, 1H, ^2J=13.5 Hz, ^3J=7.7, 2.8 Hz, Heq), 1.70 (ddd, 1H, ^2J=13.5 Hz, ^3J=10.6, 2.8 Hz, Hax), 1.90 (ddd, 1H, ^2J=13.5 Hz, ^3J=10.6, 2.8 Hz, Hax), 2.60 (ddd, 1H, ^2J=13.5 Hz, ^3J=7.7, 2.8 Hz, Heq), 3.20 (m, 2H, CONHC$H_2$$CH_2$OH), 3.41 (m, 2H, CONHC$H_2CH_2$OH), 4.70 (s, 1H, CH_2CH_2*OH*), 5.15 (s, 1H, OH), 7.27–7.37 (m, 5H, Ph-H), 7.84 (t, 1H, CON*H*C$H_2$$CH_2$OH), 7.87 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6): 26.6 (CH_3), 30.3, 33.1 (C-3 and C-4), 42.2 (NH*C*$H_2$$CH_2$OH), 59.5 (NHC$H_2$*C*$H_2$OH), 65.9 (C-2), 68.5 (C-5), 125.0 (PhC_{ortho}), 127.4 (PhC_{para}), 128.4 (PhC_{meta}), 142.8 (PhC_{ipso}), 171.6 (CONH),174.6 (C-6); *m/z* (%): 293 (1, MH^+), 204 (100, $M^{+\cdot}-$CONHC$H_2$$CH_2$OH), 186 (35, $M^{+\cdot}-$CONHC$H_2$$CH_2$OH–$H_2O$), 176 (34, $M^{+\cdot}-$CONHC$H_2$$CH_2$OH–CO); exact mass for $C_{15}H_{20}N_2O_4$: 292.1423; found: 292.1417.

4.7.2. 2α-{[Benzyl(hydroxyethyl)amino)]methyl}-5β-methyl-2β-phenyl-5α-piperidinol (13). To a stirred solution of amide **12** (1.27 g, 4.20 mmol) in dry THF (40 mL) under argon atomsphere at reflux were added dropwise 5 equiv. BH_3·SMe_2 (10 M in THF). After 8 hours, the reaction mixture was cooled to room temperature and 10 mL HCl saturated methanol was added. After 1 h, the solvent was evaporated; the residue was neutralized with 1N NaOH and extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$, filtered and evaporated under vacuum. The white solid obtained (1.30 g) was dissolved in 30 mL absolute methanol, 520 mg (1.0 equiv.) potassium carbonate and 0.45 mL (1.0 equiv.) benzyl bromide were added. The resulting mixture was stirred for 4 h. After work-up, the crude product was purified by chromatography (EtOAc/MeOH/Et_3N 90:8:2) to give 1.32 g white crystals Yield: 89%; mp 150°C; IR (KBr) cm^{-1}: 3267, 3339 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.01 (s, 3H, CH_3), 1.36 (ddd, 1H, ^2J=13.8 Hz, ^3J(H4ax–H3ax)=11.2 Hz, ^3J(H4eq–H3eq)=6.4 Hz, H4ax), 1.55 (dq, 1H, ^2J=13.8 Hz, ^3J(H4eq–H3eq)=^3J(H4eq–H3ax)=^4J(H4eq–H6eq)=2.5 Hz, H4eq), 2.11 (m, 2H, H3), 2.35 (broad s, 1H, NH), 2.55 (m, 2H, NC$H_2$$CH_2$OH), 2.59 (d, 1H, ^2J=13.0 Hz, H6ax), 2.62 (dd, 1H, ^2J=13.0 Hz, ^4J(H6eq–H4eq)=2.5 Hz, H6eq), 2.71 (d, 1H, ^2J=14.2 Hz, C2CH_2N), 2.78 (d, 1H, ^2J=14.2 Hz, C2CH_2N), 3.44 (d, 1H, ^2J=14.0 Hz, NCH_2Ph), 3.50 (d, 1H, ^2J=14.0 Hz, NCH_2Ph), 3.46–3.53 (m, 2H, CH_2OH), 7.18–7.44 (m, 10H, 2xPh), ^{13}C NMR ($CDCl_3$): 27.3 (CH_3), 28.2(C-3), 33.8 (C-4), 52.5 (C-6), 58.0 (N*C*$H_2$$CH_2$OH), 60.2 (C-2), 61.9 (NCH_2*C*H_2OH), 62.4 (N*C*H_2Ph), 67.0 (C-5), 69.6 (C2*C*H_2N), 126.6, 126.9, 128.3, 128.6 (Ph–C), 139.4, 141.9 (Ph–C_{ipso}); *m/z* (%): 355 (MH^+, 2), 190 (M^+-CH_2N (CH_2Ph)CH_2CH_2OH, 100); exact mass for $C_{22}H_{31}N_2O_2$(MH^+): 355.2385, found: 355.2381; CHN analysis (%): calcd: C 74.54, H 8.53, N 7.90; found: C 74.24, H 8.66, N 7.76.

4.7.3. 2-Benzyl-7α-methyl-9aαphenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazin-7β-ol (14). To a stirred solution of alcohol **13** (0.95 g, 2.68 mmol) and TEA in dry dichloromethane (30 mL) at −15°C was added methanesulfonyl chloride (1.2 equiv., 0.30 mL) via syringe. After reacting for 30 min at this temperature, the reaction mixture was treated with 20 mL saturated aqueous $NaHCO_3$ solution and 20 mL water. The aqueous layer was extracted with 3×30 mL CH_2Cl_2 and the organic layers were dried with $MgSO_4$. After purification via chromatography 0.76 g colorless oil **14** was obtained. Yield: 84%; oil; IR (KBr) cm^{-1}: 3413 (OH); ^{1}H NMR (55°C, $CDCl_3$): 1.06 (s, 3H, CH_3), 1.36 (td, 1H, $^2J=^3J$(H8ax–H9ax)=13.8 Hz, ^3J(H8ax–H9eq)=4.2 Hz, H8ax), 1.49 (dtd, 1H, ^2J=13.8 Hz, ^3J(H8eq–H9ax)=^3J(H8eq–H9eq)=4.2 Hz, ^4J(H8eq–H6eq)=2.3 Hz, H8eq), 1.83 (dt, 1H, ^2J=13.8 Hz, ^3J(H9eq–H8ax)=^3J(H9eq–H8eq)=4.2 Hz, H9eq), 2.13 (td, 1H, ^2J=

^3J(H9ax–H8ax)=13.8 Hz, ^3J(H9ax–H8eq)=4.0 Hz, H9ax), 2.28 (d, 1H, ^2J=11.2 Hz, H1ax), 2.42 (s broad, 1H, OH), 2.55 (m, 2H, 3-CH_2), 2.56 (dd, ^2J=12.6 Hz, ^4J(H6eq–H8eq)=2.3 Hz, H6eq), 2.60 (d, 1H, ^2J=11.2 Hz, H1eq), 3.04 (d, ^2J=12.6 Hz, H6ax), 3.08 (m, 1H, H4eq), 3.33 (d, 1H, ^2J=13.4 Hz, CH_2Ph), 3.45 (d, 1H, ^2J= 13.4 Hz, CH_2Ph), 3.40 (m, 1H, H4ax), 7.07 (dd, 2H, Ph–H*ortho*$_{Bn}$), 7.10 (m, 4H, Ph–H), 7.25 (t, 2H, Ph–H), 7.38 (d, 2H, Ph–H*ortho*$_{9a\text{-}Ph}$); ^{13}C NMR ($CDCl_3$): 27.0 (CH_3), 30.2 (C-9), 34.1 (C-8), 50.2 (C-4), 53.8 (C-3), 59.6 (C-9a), 60.2 (C-6), 62.6 (CH_2Ph), 65.8 (C-1), 68.1 (C-7), 125.9, 126.7, 127.8, 127.9, 128.5 (Ph–C), 138.4, 143.8 (Ph–C$_{ipso}$); *m/z* (%): 337 (MH^+, 2); 318 (M^+-H_2O, 100); 245 (M^+-CH_2Ph, 100); exact mass for $C_{22}H_{28}N_2O$ (M^+-H_2O): 318.2096, found: 318.2099.

4.7.4. 2-[Bis(trifluorobenzoyl)]-7α-methyl-9aα-phenyl-octahydro-2*H*-pyrido[1,2-*a*]pyrazin-7β-ol (15). To a solution of 530 mg (1.58 mmol) benzyl protected bicyclic piperazine **14** in absolute methanol (10 mL) was added 0.26 g 10% Pd/C and 1.00 g $HCOONH_4$ (10 equiv.). The resulting mixture was stirred and heated at reflux temperature for 30 min. After cooling, the mixture was filtered over celite and washed with small amounts of methanol. After evaporation of the solvent, 0.46 g of crude product was obtained.

To a mixture of this crude deprotected piperazine (0.46 g) and potassium carbonate (0.436 g, 2 equiv.) in THF (50 mL) was added 0.315 mL (1.1 equiv.) 3,5-bis(trifluoromethyl)-benzoyl chloride at −15°C. After stirring at this temperature for 2 h, the reaction mixture was worked up and crystallised from dichloromethane/hexane. A white pure crystalline product was obtained in 78% yield (0.60 g). Yield: 78%; white crystals; mp 182°C (decompd.); IR (KBr) cm^{-1}: 1628 (NCO), 3402 (OH);^{1}H NMR ($CDCl_3$): 1.07 (s, 3H, CH_3), 1.29 (m, 1H), 1.52 (m, 1H), 1.92 (m, 2H), 2.00–2.55 (br, 1H), 2.60 (d, 1H), 3.06 (d, 1H), 3.14 (m, 1H), 3.42 (m, 2H), 3.50–4.80 (br, 2H), 7.25 (m, 7H), 7.82 (s, 1H); ^{13}C NMR (55°C, $CDCl_3$): 27.0 (CH_3), 31.1 (C-9), 33.6 (C-8), 43.2 (C-4), 49.1 (C-3), 60.5, 60.8 (C-1, C-6), 67.4, 68.7 (C-9a, C-7), 121.4, 123.2, 124.1, 126.8, 128.1, 128.6 (Ph–C, Ar–C), 131.4 (q, CF_3), 137.2, 139.8 (C $_{ipso}$), 167.3 (CO); *m/z* CI (%):486 (M^+, 75); 485 (M^+-H, 100); 467 (M^+-F, 16); exact mass for $C_{24}H_{24}N_2O_2F_6$: 486.1742; found: 486.1742; CHN analysis (%): calcd: C 59.26, H 4.97, N 5.76; found: C 59.08, H 4.76, N 5.72.

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