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Generation of Cyclopenta[*c*]piperidines and Pyrrolo[3,4-*c*]piperidines—Potential Substance P Antagonists—from Adducts of Cyclic Dienophiles and 5-Chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one

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Abstract—1,1,4,4-Tetrasubstituted cyclopenta[*c*]piperidines and the corresponding 4,4,7,7-pyrrolo[3,4-*c*]piperidines have been synthesised via cycloaddition of 5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one with cyclopentene and 3-pyrroline derivatives, respectively, followed by reductive opening of the lactone-bridged adducts. The axial-equatorial conformational preferences of the substituents in these *cis*-fused bicyclic systems were opposite to those for the monocyclic piperidine analogues. The specific array of functional groups in the bicyclic aminoalcohols was used to accommodate, in stereocontrolled fashion, variable pharmacophoric groups that are of interest for substance P antagonist activity.

Introduction

Substance P acts as a neurotransmitter and is the most abundant neurokinin in the mammalian central nervous system (CNS). Mediated by the NK_1 receptor, substance P is postulated to play an important role in a number of biological processes including pain transmission, anxiety, asthma and neurogenic inflammation.[1] This profile has stimulated a search for highly potent and selective antagonists of the neurokinin-1 (NK_1) receptor; many non-peptide NK_1 antagonists have been developed, notable examples including the quinuclidine-based CP-96, 345 (**I**),[2] aminopiperidine CP-99, 994 (**II**),[3] bis(trifluoromethyl)benzyloxypiperidine (**III**),[4] and the perhydroisoindole-based series related to RPR-100, 893 (IV).[5] However, many of the early non-peptide NK1 antagonists suffered from poor brain penetration, low oral bioavailability, significant ion channel affinity, or poor duration of action.[6] Thus patent activity in the area of NK_1 antagonists remains high, and the emphasis has shifted toward the fine-tuning of in vivo properties.

Structure activity relationship studies[1b,6b,c,7] have established that in many potent NK1 antagonists, common pharmacophoric features are a piperidine ring, and phenyl and 3,5-bis(trifluoromethyl)phenyl groups. As part of an ongoing project aimed at developing novel piperidine-based non-peptide substance P antagonists, we synthesised bicyclic piperidine derivatives **1**–**2** mimicking the model compounds **III** and **IV** (Fig. 1). Specific pharmacophoric groups comprised in target products **1**–**2** are like those for the previously reported monocyclic analogues,[8] but now accommodated in *cis*-fused bicyclic systems. Interestingly, target product **2** incorporates both the 3,5-bis(trifluoromethyl)phenyl substitution favoured in the aminoether series (**III**) and the *o*-methoxyphenylacetyl substituent found in the perhydroisoindole-based series (**IV**). The spatial orientation of substituents in these *cis*-decaline-like fused bicyclic systems was studied by NMR compared to conformational model calculations and was found to be opposite to those reported for the monocyclic tetrasubstituted piperidine analogues[8] and the related model compound **III**.[4]

Results and Discussion

Synthesis of compounds 1 and 2

Recently we described an efficient and general approach to 2,2,5,5-substituted piperidines proceeding via cycloaddition of 3-alkyl or 3-phenyl-2*H*-1,4-oxazin-2-ones with ethene and further conversions of the adducts.[8] This methodology now is extended to cyclic dienophiles. Cycloaddition of cyclopentene with 5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one **3** was carried out in refluxing chloroform, yielding predominantly *endo*-adduct **4** (see below for the structural characterisation of **4** and other adducts derived

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

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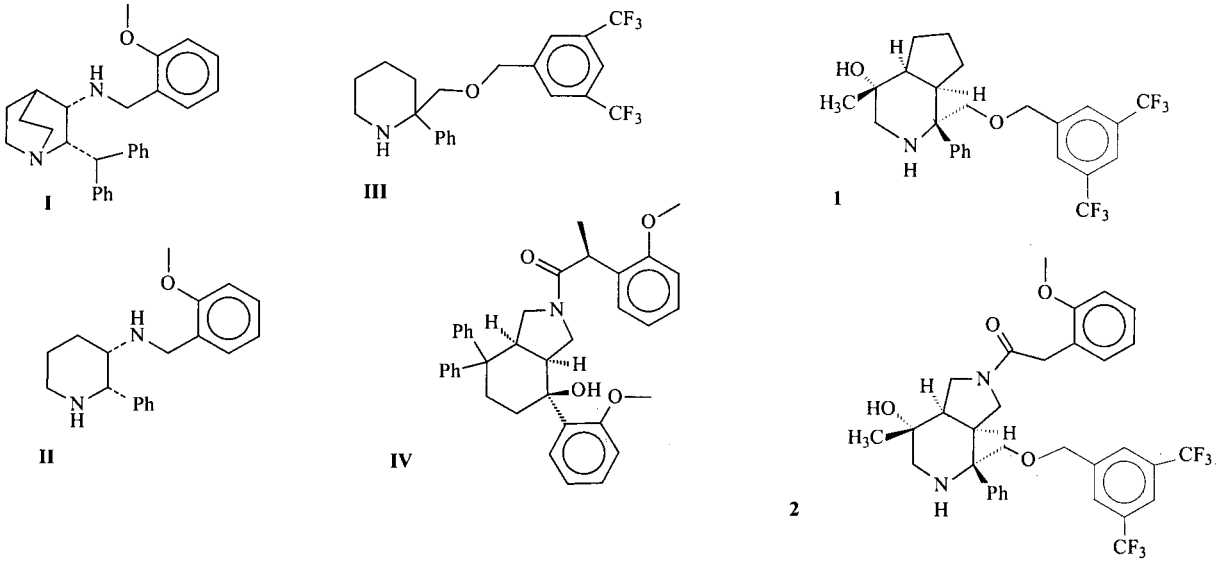
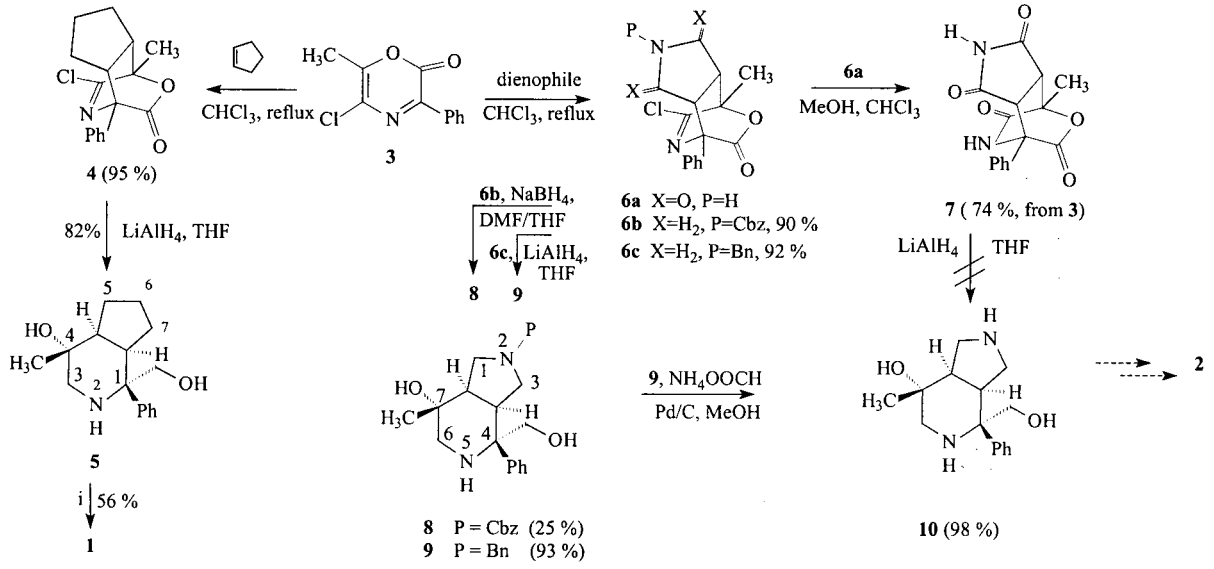


Figure 1.

from **3** and cyclic dienophiles). This adduct was converted to compound **1** in ca. 42% overall yield based on starting oxazinone **3**, by applying the previously described sequence,[8] i.e. reduction of the imidoyl chloride and lactone groups of adduct **4** with lithium aluminium hydride followed by selective *O*-alkylation of the primary alcohol function of aminodiol **5** (Scheme 1).

In our first approach to construct the tetrasubstituted pyrrolo[3,4-*c*]piperidine ring system of compound **2**, cycloaddition of **3** was carried out using maleimide as dienophile to form the *endo*-adduct **6a**. Following conversion of the imidoyl chloride function to a stable lactam group by heating 6a with methanol, the *endo*-configuration of lactam **7** and its precursor was ascertained by NMR analysis (see Fig. 2 and discussion below). Unfortunately, reduction of **7** or **6a** with $LiAlH_4$ gave a complex mixture of products, from which the desired compound **10** could not be isolated.

In a second approach, *N*-carbobenzyloxy(Cbz)-3-pyrroline, prepared from *cis*-1,4-dichloro-2-butene according to the literature procedure,[9] was used as dienophile to give again exclusively the *endo*-adduct **6b**. Not unexpectedly, reduction of the sterically hindered imidoyl chloride and lactone functions of **6b** with $LiAlH_4$ also led to the concurrent conversion of the *N*-Cbz protecting group to a *N*-methyl group. To avoid this unwanted reaction, $NaBH_4$ in DMF/THF was used as a more selective reducing agent, able to reduce ester or lactone carbonyl groups in preference to amide or carbamate functions.[10] Under these conditions, which involved heating at 75°C (oil bath temperature) for 2 days, the desired bicyclic alcohol **8** (P=Cbz) was obtained in low yield only. Finally, the commercially



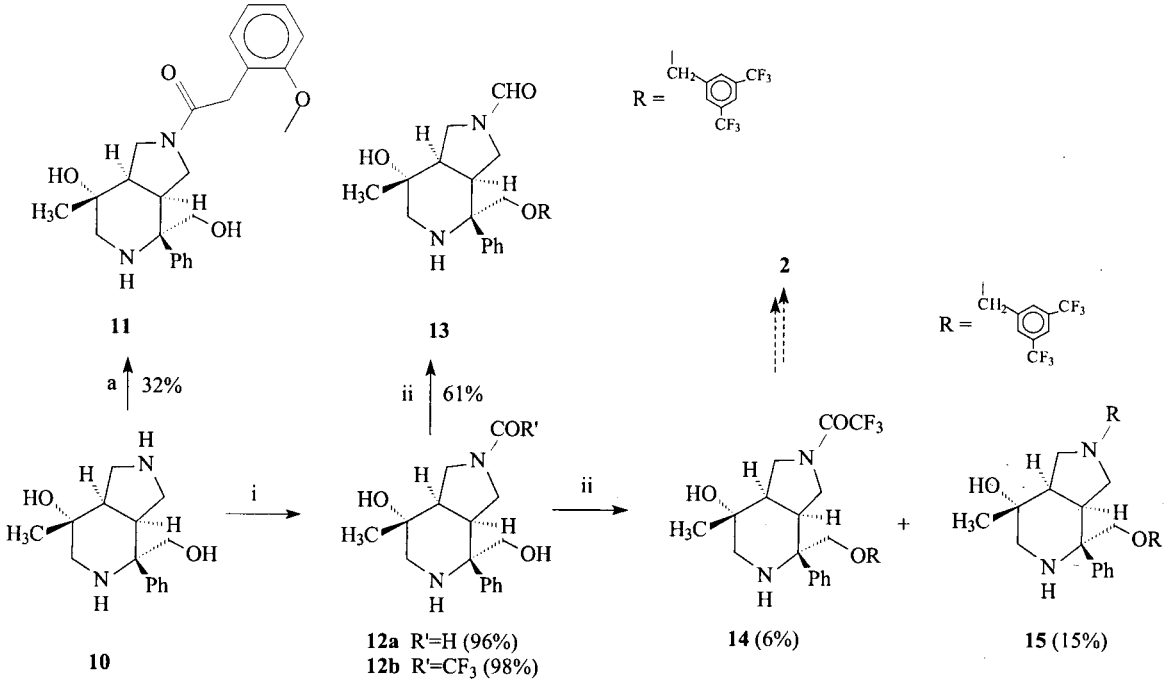
Scheme 1. (i): (1) NaH (2 equiv.), DMF; (2) 3,5-bis(trifluoromethyl)benzylbromide (1.1 equiv.), THF, rt, 1d.

available *N*-benzyl 3-pyrroline was selected as a dienophile for Diels–Alder reaction with oxazinone **3**. The intermediate *endo*-adduct **6c** was isolated (92%) by flash chromatography and reduced with $LiAlH_4$ to give the *N*-benzyl protected pyrrolo[3.4-*c*]piperidinediol **9** in an excellent overall yield.

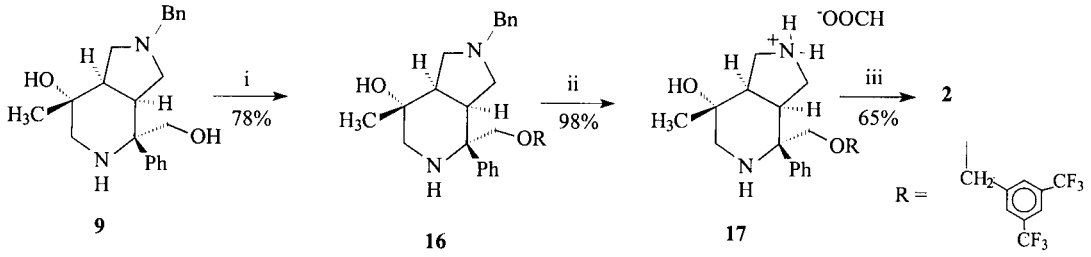
To convert **9** to the end product **2**, two alternative routes can be used starting with: (a) *N*-debenzylation followed by chemoselective acylation of the pyrrolidine *N*-atom; or (b) initial introduction of the desired *O*-benzyl group which then requires selective *N- versus O*-debenzylation. Both sequences may be concluded with a second functionalisation step that allows for a broad variation of pharmacophoric groups on either the hydroxymethyl side chain or the pyrrolidine moiety.

N-Debenzylation of **9** was carried out by catalytic transfer hydrogenation[11] using ammonium formate as the H-transfer agent to produce **10** in excellent yield as the formate salt (Scheme 1). In a preliminary experiment using *o*-methoxyphenylacetyl chloride, a poor selectivity was observed between acylation of the pyrrolidine NH and the primary OH group. When using 1 equiv. of both *o*-methoxyphenylacetic acid and the coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), together with triethylamine to liberate the free amine **10** from its formate salt, **10** was converted to the corresponding *N*-acyl derivative **11** in 32% yield (Scheme 2). With an excess of reagents, the acylation reaction again was not selective. However, the *N*-formyl and *N*-trifluoroacetyl derivatives **12a**, **b** were obtained quantitatively by reaction of the formate salt **10** with methyl formate or ethyl trifluoroacetate in methanol in the presence of triethylamine. Further *O*-benzylation of **12a** yielded the *N*-formylated end product 13. The *N*-trifluoroacetyl compound **12b** in turn was subjected to the same *O*-benzylation conditions, since the expected product **14** could also serve as an intermediate in the synthesis of the end product **2**. Indeed, because of its ready cleavage under variable mild conditions,[12] the *N*-trifluoroacetyl group has been widely used as a protecting function. However, the desired benzyl ether **14** was isolated in small yield only (6%), besides the *N*, *O*-dibenzylated product **15** (15%). Presumably, partial loss of the amide protecting group results from intermolecular (N→O) acyl migration.

In our second approach we started with *O*-benzylation of **9** affording the benzyl ether derivative **16** in good yield (Scheme 3). The next two steps consisted of selective *N*-debenzylation followed by *N*-acylation with *o*-methoxyphenylacetyl chloride. Although *O*-debenzylation normally proceeds more readily than removal of a *N*-benzyl group, Czech and Bartsch[13] reported that hydrogenolysis of the *O*-benzyl group was inhibited when aliphatic amines were added to the hydrogenation medium (Pd/C in ethanol), or even when an aliphatic *N*-benzylamino group was present in the same molecule. This finding was used to develop selective procedures for *N*-debenzylation and hydrogenation of a double bond with retention of the *O*-benzyl group. We further explored conditions for selective *N*-debenzylation by subjecting *N*,*N*-dibenzyl-2-(benzyloxy)-1-ethanamine (DBBEA) to catalytic transfer hydrogenation. Under the conditions already described for *N*-debenzylation of **9**, both *N*-benzyl groups of DBBEA were removed and (benzyloxy)ethylamine was isolated as the formate salt.[14] In a similar way application of this procedure to the *O*-bis(trifluoromethyl)benzyl ether **16** gave the selectively *N*-debenzylated amine **17**, again obtained as the formate salt and characterised by spectral and CHN-analysis. Final



Scheme 2. (a): *o*-methoxyphenylacetic acid (1.0 equiv.), Et_3N (2.2 equiv.), DMAP (0.2 equiv.), EDCI (1.0 equiv.), CH_2Cl_2/DMF, rt, overnight. (i): HCOOMe (for **12a**) (1.5 equiv.) or CF_3COOEt (for **12b**) (1.5 equiv.), Et_3N (1.5 equiv.), MeOH, rt. (ii): (1) NaH (2 equiv.), DMF; (2) 3,5 bis(trifluoromethyl)benzylbromide (1.1 equiv.), THF, rt, 1d.



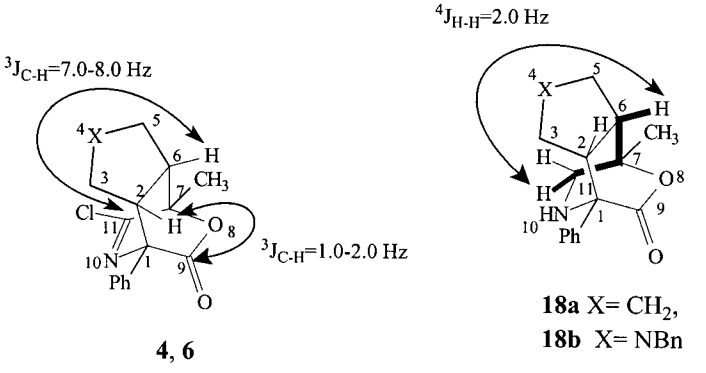
Scheme 3. (i): (1) NaH (2 equiv.), DMF; (2) 3,5 bis(trifluoromethyl)benzylbromide (1.1 equiv.), THF, rt, 1d. (ii): $HCOONH_4$, Pd/C, MeOH, reflux. (iii): (1) *o*-methoxyphenylacetic acid, PPh_3, CCl_4, reflux; (2) pyridine, THF, −15°C.

acylation of the pyrrolidine *N*-atom was effected with *o*-methoxyphenylacetyl chloride and pyridine, affording compound **2** as white crystals; the overall yield for the purified product was ca. 50%, calculated over three steps starting from **9**.

Configuration of cycloadducts 4 and 6 and conformation of the bicyclic piperidine analogues

The stereochemical structure of cycloadducts **4** and **6**, including that of the lactam product **7** derived from **6a**, was assigned on basis of their ^1H coupled ^{13}C NMR spectra (Fig. 2). For compounds **4**, **6b** and **6c**, the *endo* configuration was demonstrated by characteristic coupling constant values of the angular protons H-2 and H-6 with, respectively, the *gauche*-oriented lactone carbon atom C-9 (^3J=ca. 2 Hz) and the *anti*-oriented imidoyl carbon atom C-11 (^3J=ca. 8 Hz). The latter carbon C-11 easily could be distinguished from C-9 by a lower chemical shift value and by the coupling observed with the protons of the bridgehead methyl group. The structure of lactam **7** was attributed in a similar way on basis of ^3J values corresponding to coupling of H-2 and H-6 with, respectively, the lactone and lactam carbon atoms C-9 (^3J=1 Hz) and C-11 (^3J=7 Hz). Further confirmation for the *endo* mode of cycloaddition was obtained from the tricyclic compounds **18**. These were derived from adducts **4** and **6c** via selective reduction of the imidoyl chloride function with $NaCNBH_3$ at pH 5. In the ^1H NMR spectra of the reduced compounds, a clear long range coupling (^4J=2.0 Hz) was observed between the pseudoaxial proton H-11 (**18a** δ=2.98, **18b** δ=3.02) and the *exo* proton H-6, showing the *all-trans* bond connectivity (see W-pattern in Fig. 2). No general explanation can be offered for the exclusive formation of *endo* adducts in the reaction of **3** with cyclic dienophiles. Although similar results have been reported for other dienes,[15] diverse arguments have been invoked: these can be related to a favourable geometry for overlap in the *endo* transition state for cyclopentene adduct **4**,[16] increased electrostatic repulsions in the *exo* transition state for 3-pyrroline adducts **6b**, **c**,[17] or secondary orbital interactions for the maleimide adduct **6a**.[15c]

The well-defined geometry and conformational structure of the novel *cis*-fused bicyclic systems, exemplified by the intermediate aminodiols **5**, **9**, and **10**, and the functionalised products **1** and **2**, offer an excellent opportunity to define more exactly the spatial orientation of the pharmacophoric groups required for bioactivity. From the *endo* mode of cycloaddition, it follows that the *cis*-fused cyclopentane (pyrrolidine) ring and the 1(4)-phenyl and 4(7)-methyl substituents are located at the same side of the piperidine ring. Two conformational structures, $\mathbf{A}_{Pheq}$ and $\mathbf{B}_{Phax}$ having an equatorial and axial orientation of the phenyl group, may apply to these *cis*-decaline-like bicyclic systems (Fig. 3). From model calculations using Hyperchem it was concluded that, in contrast to the analogous monocyclic 2,2,5,5-substituted piperidines which have the 2-phenyl



Adduct	x	^{3}J(C9-H2)	^{3}J (C11-H6)
4	CH_2	2.2Hz	8.0Hz
6b	NCbz	2.0Hz	7.0Hz
6c	NBn	not resolved	8.0Hz
7		1.0Hz	7.0Hz

Figure 2.

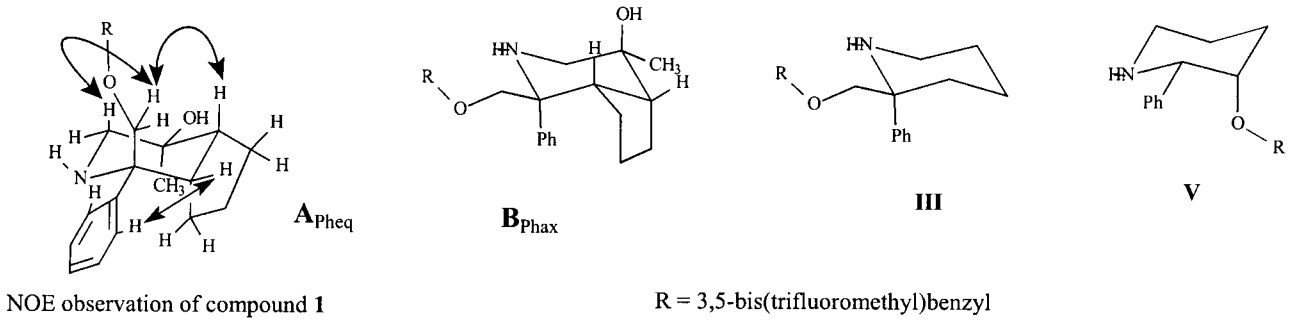


Figure 3.

(alkyl, H) axially oriented,[8] form $\mathbf{A}_{Pheq}$ is largely favoured over $\mathbf{B}_{Phax}$. Apparently, repulsive interactions between the axial phenyl group and both *cis*-disposed methylene groups of the five-membered ring are more severe than those experienced by the axial methyl group in the preferred conformation.

Both ^{1}H coupled ^{13}C NMR spectra and NOE observations confirmed that $\mathbf{A}_{Pheq}$ is the preferred conformer for the bicyclic piperidine derivatives **1**, **2**, **5**, **9**, and **10** and related compounds, as predicted by the conformational calculations. In the ^{1}H coupled ^{13}C NMR spectrum of **1**, the *ipso* carbon of the 1-phenyl group appeared as a quartet with $^{3}J_{C-H}$=6 Hz, which changed to a triplet when decoupled at δ 4.28 ppm. This coupling pattern was verified by 'COLOC' (two dimensional long-range correlation of ^{13}C and ^{1}H, ^{2}J and ^{3}J). In the spectra of compounds **1** and **10**, cross peaks revealed coupling of the Ph-*ipso* carbon with both *meta* protons and one of the hydroxymethylene protons (δ 4.28 for **1**, δ 4.12 for **10**), and of the methyl carbon with two axial protons (δ 2.10/2.80 for **1**, δ 2.05/2.78 for **10**). These observations demonstrate the axial and equatorial orientation of the methyl and Ph-*ipso* carbon, respectively. The latter couples not only with the *meta* protons but also with the *anti* proton from the benzyloxymethyl side chain (δ 4.28), and not with an angular axial proton H-7a, as could be expected for conformation $\mathbf{B}_{Phax}$. On the other hand, a qtd coupling pattern observed in the spectrum of **1** for the methyl carbon at C-4 (^{1}J=125.8 Hz, ^{3}J=5.0, 5.0, 3.5 Hz), indicated coupling with two axial protons H-3ax and H-4a.

NOESY and NOE difference spectra of **1** revealed that the 1-phenyl group is close in space to H-7a (δ 2.05) and that the *anti*-H (δ 4.28) in the benzyloxymethyl sidechain is near to both axial protons H-3ax (δ 2.80) and H-4a (δ 2.10). This is in agreement with the conformation $\mathbf{A}_{Pheq}$, but not $\mathbf{B}_{Phax}$ (Fig. 3). Conformation $\mathbf{A}_{Pheq}$ also was supported by the ^{1}H NMR spectrum as compared to the model analysis. For all bicyclic compounds studied, the *vicinal* coupling between H-4a (for **1** and **5**) or H-7a (for **2**, **9** and related compounds) and one of the two protons H-5 or H-1 was not resolved or the ^{3}J value was less than 1 Hz. This small *vicinal* coupling correlated with a dihedral angle of 86° calculated for the corresponding pair of protons in the model of the preferred conformer. Also in agreement with this model was the upfield shift (<1 ppm) observed for one of the protons H-7 (H-3), which apparently is located in the shielding field of the 1(4)-phenyl group.

As a consequence of the steric constraint imposed by the axial methyl group in the favoured conformation $\mathbf{A}_{Pheq}$, rotation of the amide bond is severely hindered for the *N*-acylated end products **2** and **13**. This resulted in the separation of two rotameric forms on HPLC or TLC. However, reinjection of two fractions of compound **13** separated by HPLC revealed that an equilibrium mixture of the two rotameric forms had been formed again. Reduction of separate HPLC fractions of **13** with $BH_3{\cdot}SMe_2$ gave only one *N*-methyl product, appearing as a single spot on TLC.

The conformational features discussed so far for the bicyclic systems may affect their biological activities. A striking difference, as compared to the monocyclic piperidine analogues, is the inversed orientation of the phenyl and benzyloxymethyl substituents. However, this should not necessarily lead to a decreased activity, as the conformational situation may be compared to that for the analogous 2,3- and 2,2-substituted substance P antagonists **III** and **V**.[18] While a similar high affinity (1 nM) for the NK_1 receptor has been determined for these compounds, an opposite orientation has been established for the phenyl and benzyloxy substituents in their preferred conformations (Fig. 3).

Another important difference between compounds of type **III** and **V** relates to the conformational freedom of the β-aminoether moiety. Model compound **V** necessarily has a *gauche* relationship between the *N*-atom of the piperidine ring and the axial ether *O*-atom, whereas for type **III** compounds including the bicyclic analogues, the heteroatoms of the β-aminoether moiety also might adopt an *anti* orientation. However, from the *anti*-relationship observed for one of the methylene H-atoms and the Ph-*ipso* carbon in the NMR spectra of the bicyclic compounds, it appears that the CH_2 of the oxymethyl sidechain is locked as a single conformer. According to the model calculations, this may correspond to the *O*-atom being *anti*-oriented relative to the largest group, i.e. the angular carbon C-7a, again implying a favoured *gauche* orientation for the *O*- and *N*-heteroatoms as required for **V**.

Conclusion

In this work we have developed an efficient route to *cis*-fused bicyclic systems of type **1** and **2**, which can be substituted with variable pharmacophoric groups of interest for substance P antagonist activity. In our conformational study

of these bicyclic systems, it was established that the phenyl group alpha to the piperidine *N*-atom assumes an equatorial orientation, in contrast to the previously described 2,2,5,5-substituted piperidines. The well-defined geometry and conformational structure of these novel bicyclic systems offer an excellent opportunity to define further the 'bioactive conformation' of these non-peptide substance P antagonists.

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.[1]H 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 preparation and the spectroscopic data of 5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one **3** were described previously.[19]

Model calculations

These were carried out for the *cis*-fused cyclopentene derivative 1 using the molecular mechanics method of HyperChem™: *Release 4.5*, Hypercube, Inc. Two main groups of conformers corresponding to $\mathbf{A}_{Pheq}$ and $\mathbf{B}_{Phax}$ were created by imposing the appropriate torsion angles for the bond sequence Ph_{ipso}C–C1–C7a–C4a. In addition, the torsion angle O–CH_2–C1–N2 was varied to create *anti* and *gauche* conformers. Each of the conformers was then energetically optimised. A difference of ca. 2.3 kcal/mol favouring conformer $\mathbf{A}_{Pheq}$ over $\mathbf{B}_{Phax}$ (both with the favourable *anti*O–CH_2–C1–C7a orientation) was observed. For the $\mathbf{A}_{Pheq}$ conformers a difference of ca. 1.5 kcal/mol favoured the *gauche* O–CH_2–C1–N2 (*anti*O–CH_2–C1–C7a) over the *anti*O–CH_2–C1–N2 orientation.

Synthesis of compound 1 via Diels–Alder reaction of oxazinone 3 with cyclopentene

***endo* 11-Chloro-7-methyl-1-phenyl-8-oxa-10-azatricyclo-[5.2.2.0^{2,6}]undec-10-en-9-one (4).** Cyclopentene (0.8 ml, 9 mmol) was added to a stirred solution of 5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one **3** (663 mg, 3 mmol) in chloroform (15 ml) at room temperature under nitrogen atmosphere. After reaction for one day at reflux temperature the solvent was removed under reduced pressure. The residue was purified by crystallisation to give **4** (824 mg, 95%). Slightly yellow crystals, mp: 152°C (decomposition); IR (KBr) cm^{-1}: 1762 (CO), 1624 (C=N); ^{1}H NMR ($CDCl_3$): 1.24 (m, 2H), 1.40 (m, 1H), 1.42 (m, 1H), 1.65 (m, 1H), 1.94 (m, 1H) [$(CH_2)_3$], 1.73 (s, 3H, CH_3), 2.86 (q, 1H, ^{3}J=8.8 Hz, H-2 or H6), 3.07 (q, 1H, ^{3}J=8.8 Hz, H-6 or H-2), 7.35–7.73 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$): 19.36 (CH_3), 26.8, 27.7, 28.8 [$(CH_2)_3$], 47.1, 50.6 (C-2 and C-6), 73.0 (C-1), 84.9 (C-7), 127.7, 127.8, 128.1 (Ph–C), 135.5 (C-*ipso*), 165.2 (q×d, $^{3}J_{C-H}$=5 Hz, $^{3}J_{C-H}$=8 Hz, C-11), 170.4 (d, $^{3}J_{C-H}$=2.2 Hz, C-9); *m/z* (%): 290 (1, MH^+), 245 (72, $M^{+\cdot}-CO_2$), 210 (100, $M^{+\cdot}-CO_2-Cl$); exact mass for $C_{16}H_{16}O_2N_1$: 289.0869, for $C_{15}H_{16}N_1$: 245.0971; found: 289.0865, 245.0970.

1α-(Hydroxymethyl)-4β-methyl-1β-phenyl-4aα,7aα-octahydro-1*H*-cyclopenta[c]pyridin-4α-ol (5). To a stirred ice-cooled slurry of $LiAlH_4$ (285 mg, 7.5 mmol) in 25 ml dry THF under nitrogen atmosphere was added dropwise a solution of adduct **4** (722 mg, 2.5 mmol) in 25 ml dry THF. The ice bath was removed and the reaction mixture was stirred first at room temperature for 2 h and then at reflux temperature for 8 h. After the reduction was completed, the mixture was cooled down and 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 compound **5**, which was purified by column chromatography (silica gel, 1:9 MeOH/CH_2Cl_2) and crystallisation from dichloromethane/*n*-hexane. Yield: 535 mg, 82%; white crystals, mp: 162.5–165.5°C; IR (KBr) cm^{-1}: 3393, 3341 (OH, NH); ^{1}H NMR (DMSO-d6): 0.76 (m, 1H, H-7), 1.07 (m, 1H, H-7), 1.11 (s, 3H, CH_3), 1.35 (m, 2H, H-6), 1.50 (m, 1H, H-5), 1.81 (m, 1H, H-5), 1.95 (m, 1H, H-7a), 2.04 (t, 1H, ^{3}J=7.0 Hz, H-4a), 2.19 (s, br., 1H, NH), 2.50 (d, 1H, ^{2}J=11.4 Hz, H-3), 2.76 (d, 1H, ^{2}J=11.4 Hz, H-3), 3.60 (dd, 1H, ^{2}J=11.0 Hz, ^{3}J=6.0 Hz, CH_2OH), 4.09 (s, 1H, OH), 4.15 (dd, 1H, ^{2}J=11 Hz, ^{3}J=4.4 Hz, CH_2OH), 4.34 (dd, 1H, ^{3}J=6.0 Hz, ^{3}J=4.4 Hz, CH_2O*H*), 7.13 (td, 1H, ^{3}J=8 Hz, ^{4}J=1.2 Hz, H-*para*), 7.24 (t, 2H, ^{3}J=8 Hz, H-*meta*), 7.43 (dd, 2H, ^{3}J=8 Hz, ^{4}J=1.2 Hz, H-*ortho*); ^{13}C NMR (DMSO-d6): 23.7 (CH_3), 21.2, 26.4, 27.3 (C-5, C-6 and C-7), 45.6, 46.9 (C-4a and C-7a), 52.9 (C-3), 59.3 (C-1), 62.5 (CH_2OH), 68.8 (C-4), 125.2, 126.0, 127.3 (Ph–C), 146.7 (C-*ipso*); *m/z*(%) (CI): 262 (77, MH^+), 244 (100, MH^+-H_2O), 230 (24, MH^+-CH_3OH); exact mass for $C_{16}H_{23}NO_2$: 261.1729; found: 261.1723; anal. calcd for $C_{16}H_{23}NO_2$: C 73.53, H 8.87, N 5.36; found: 73.48, H 8.91, N 5.40.

1α-({[3,5-Bis(trifluoromethyl)benzyl]oxy}-4β-methyl)-1β-phenyl-4aα,7aα-octahydro-1*H*-cyclopenta[*c*] pyridin-4α-ol (1). To a solution of 470 mg (1.8 mmol) of compound **5** in 18 ml DMF was added sodium hydride (91 mg, 3.8 mmol) in a single portion at room temperature. The mixture was stirred for 30 min followed by the addition of 610 mg (2.0 mmol) 3,5 bis(trifluoromethyl)benzyl bromide in 10 ml dry THF during 15 min. The reaction mixture was stirred at rt for one day followed by careful addition of a saturated ammonium chloride solution (up to pH 8.5–9.0), and 40 ml of water. The aqueous layer was extracted with three 40 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 (1:4 EtOAc/CH_2Cl_2) to give 3, 5 bis(trifluoromethyl)benzyl ether **1**.Yield: 490 mg, 56%; colourless oil; IR (NaCl, film) cm^{-1}: 3404 (OH, NH); ^1H NMR($CDCl_3$): 0.98 (m, 1H, H-7), 1.24 (m, 1H, H-7), 1.33 (s, 3H, CH_3), 1.46 (m, 2H, H-6), 1.62 (m, 1H, H-5), 1.84 (m, 1H, H-5), 2.05 (m, 1H, H-7a), 2.10 (t, 1H, ^3J=7.0 Hz, H-4a), 2.80, 2.88 (2×d, 2H, ^2J=11.5 Hz, H-3), 3.68, 4.28 (2×d, 2H, ^2J=9.5 Hz, CH_2OCH_2Ar), 4.42, 4.60 (2×d, 2H, ^2J= 13.2 Hz, CH_2OCH_2Ar), 7.23 (m, 1H), 7.32 (m, 2H), 7.45 (m, 2H), 7.50 (s, 2H), 7.74 (s, 1H) (Ar–H); ^{13}C NMR($CDCl_3$): 21.5 (C-6), 24.1 (CH_3), 26.5, 27.2 (C-5 and C-7), 46.3, 47.9 (C-4a and C-7a), 53.1 (C-3), 59.2 (C-1), 70.6 (C-4), 71.7, 72.4 (CH_2OCH_2), 121.4 (Ar–C), 123.3 (CF_3) 125.5 (Ph–C), 126.2 (Ph–C), 127.2 (Ar–C), 127.9 (Ph–C), 131.4 (q, Ar–C), 141.1 (Ar–C-*ipso*), 145.3 (Ph–C-*ipso*); *m/z* (%) (CI): 488 (65, MH^+), 470 (47, MH^+–H_2O), 468 (39, MH^+–HF), 230 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{25}H_{27}F_6NO_2$: 487.1946; found: 487.1930; anal. calcd for: C25H27F6NO2: C 61.06, H 5.58, N 2.87, found: C 60.79, H5.52, N 2.71.

Generation of adducts 6b–c and conversion of 6a to the corresponding hydrolysed compound 7

***endo* 4-Benzyloxycarbonyl-11-chloro-7-methyl-1-phenyl-8-oxa-4,10-diazatricyclo[5.2.2.0^{2,6}]undec-10-ene-9-one (6b).** 3-Pyrroline prepared from *cis*-1,4-dichloro-2-butene according to the literature procedure[9] was treated with benzyl chloroformate in CH_2Cl_2 in the presence of triethylamine. *N*-Cbz-3-pyrroline was obtained as a colourless oil in 91% yield; *m/z* (%): 203 (3, M^+), 112 (14, M^+−Bn; ^1H NMR ($CDCl_3$): 4.2 (s, 4H, CH_2NCH_2), 5.2 (s, 2H, CH_2Ph), 5.8 (s, 2H, CH═CH), 7.4 (m, 5H, Ph–H). The *N*-Cbz-3-pyrroline (2.38g, 15 mmol) was made to react with 10 mmol oxazinone **3** under the same conditions as described for adduct **4**. Adduct **6b** was purified by flash column chromatography (silica gel, gradient elution: 100% $CHCl_3$ to 5% EtOAc/$CHCl_3$) and/or crystallisation (CH_2Cl_2/Et_2O).Yield: 3.81 g, 90%; slightly yellow crystals; mp: 158°C (decomposition); IR (KBr) cm^{-1}: 1764, 1711 (COO, NCOO), 1618 (C═N); ^1H NMR ($CDCl_3$, 60°C): 1.77 (s, 3H, CH_3), 3.15 (td, 1H, ^3J=^3J=9.0 Hz, ^3J=4.5 Hz, H-6 or H-2), 3.25 (m, 2H, H5), 3.35 (m, 1H, H-2 or H-6), 3.45 (m, 1H, H-3 or H-5), 3.69 (dd, 1H, ^2J=12.7 Hz, ^3J=9.0 Hz, H-5 or H-3), 5.06 (s, 2H, PhCH_2), 7.27–7.69 (m, 10H, 2×Ph); ^{13}C NMR ($CDCl_3$, 35°C): 19.50 (CH_3), 45.7, 46.6, 47.1, 49.4 (C-2, C-3, C-5 and C-6), 67.2 (PhCH_2), 72.3 (C-1), 83.6 (C-7), 127.8–128.5 (Ph–C), 134.4, 136.2 (2×C-*ipso*), 153.8 (NCOO), 165.1 (C-11), 168.8 (C-9, ^3J is not resolved); *m/z* (%) (CI): 425 (52, MH^+), 381 (17, MH^+–CO_2), 345 (7, MH^+–CO_2–HCl), 91 (100, Bn^+); exact mass for $C_{23}H_{21}ClO_4N_2$: 424.1190, found: 424.1191.

***endo* 4-Benzyl-11-chloro-7-methyl-1-phenyl-8-oxa-4, 10-diazatricyclo[5.2.2.0^{2,6}]undec-10-ene-9-one (6c).** Under the conditions described for adduct **4**, *N*-benzyl 3-pyrroline (913 mg, 4.5 mmol) was made to react with 3 mmol oxazinone **3**. Adduct 6c was purified by flash column chromatography (silica gel, gradient elution: 100% $CHCl_3$ to 5% EtOAc/$CHCl_3$) and/or crystallisation (CH_2Cl_2/Et_2O). Yield: 1.05 g, 92%; slightly yellow crystals; mp 166°C (decomposition); IR (KBr) cm^{-1}: 1761 (COO), 1620 (C═N); ^1H NMR ($CDCl_3$): 1.69 (s, 3H, CH_3), 2.39 (m, 2H, H-3 or H-5), 2.47 (dd, 1H, ^3J=4.6 Hz, ^2J=10 Hz, H-5 or H-3), 2.70 (dd, 1H, ^3J=7.6 Hz, ^2J=10 Hz, H-5 or H-3), 3.02 (m, 1H, H-6 or H-2), 3.25 (m, 1H, H-2 or H-6), 3.40, 3.44 (2×d, 2H, ^2J=13.2 Hz, PhCH_2N), 7.22–7.71 (m, 10H, 2×Ph); ^{13}C NMR ($CDCl_3$): 19.50 (CH_3), 45.7, 50.4 (C-2 and C-6), 54.7, 54.8 (C-3 and C-5), 59.4 (PhCH_2N), 72.5 (C-1), 84.1 (C-7), 127.1–128.3 (Ph–C), 135.4, 138.1 (2×C-*ipso*), 165.7 (q×d, $^3J_{C-H}$=5 Hz, $^3J_{C-H}$=8 Hz, C-11), 169.8 (C-9); *m/z* (%): 380 (2, M^+), 336 (18, $M^{+\cdot}$–CO_2), 300 (13, $M^{+\cdot}$–CO_2–HCl), 245 (41, $M^{+\cdot}$–CO_2-Bn), 91 (100, $Bn^{+\cdot}$); exact mass calcd for $C_{22}H_{21}ClO_2N_2$: 380.1292, found: 380.1290.

***endo* 7-Methyl-1-phenyl-8-oxa-4,10-diazatricyclo-[5.2.2.0^{2,6}]-undecane-3,5,9,11-tetraone (7).** Maleimide (582 mg, 6 mmol) was added to a stirred solution of 5-chloro-6-methyl-3-phenyl-2*H*-1,4-oxazin-2-one 3 (442 mg, 2 mmol) in toluene (15 ml) at room temperature under nitrogen atmosphere. After reaction for one day at reflux temperature the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and following addition of methanol (5 ml) the solution was heated at reflux temperature for one day. The solvent was removed and the residue was purified by chromatography (silica gel, 1:1 EtOAc/ CH_2Cl_2) to give pure compound **7**. Yield: 444 mg, 74%; white crystals, mp: 290°C (decomp.); IR (KBr) cm^{-1}: 3187 (NHCO), 1775–1682 (CONH); ^1H NMR (DMSO-d_6): 1.71 (s, 3H, CH_3), 3.38 and 4.39 (2×d, 2H, ^3J=8 Hz, H-2 and H-6), 7.44 (m, 5H, Ph–H), 10.0 (br.s, 1H, NHCO), 11.70 (br.s, 1H, CONHCO); ^{13}C NMR (DMSO-d_6): 16.8 (CH3), 43.0, 51.2 (C-2, C-6), 63.5 (C-1), 81.5 (C-7), 127.7, 128.1 and 128.4 (Ph–C), 131.5 (Ph–C_{ipso}), 167.8 (C-9), 168.1 (C-11), 173.5 and 173.8 (C-3 and C-5); *m/z* (%): 301 (1, MH^+), 256 (48, M^+–CO_2), 185 (16, M^+–CO_2–CONHCO); exact mass for $C_{14}H_{12}N_2O_3$ (M^+–CO_2): 256.0848; found: 256.0849.

Synthesis of octahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol 10

2-Benzyloxycarbonyl-4α-(hydroxymethyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo[3,4-*c*] pyridin-7α-ol (8). To a stirred solution of 1.70 g (4 mmol) adduct **6b** in 40 ml dry THF was added 1.51 g (40 mmol) $NaBH_4$. After stirring for 15 min. at 0°C 10 ml dry DMF was added slowly via a syringe. The reaction mixture was warmed up slowly to a bath temperature of 75°C and heated for two days. The excess of hydride was decomposed by careful addition of a saturated NH_4Cl solution at 0°C. Following extraction (CH_2Cl_2), drying, filtration, and evaporation, the crude product was purified by column chromatography (silica gel, 1:9 MeOH/CH_2Cl_2) to yield compound **8** (396 mg, 25%). White crystals, mp: 195°C; IR (KBr) cm^{-1}: 3485, 3395 (OH, NH), 1670 (CO); **rotamer a** (55%): ^1H NMR (CD_3OD): 1.20 (s, 3H, CH_3), 2.29 (m, 1H, H-7a), 2.60 (m, 1H, H-3a), 2.70, 2.93 (2d, 2H, ^2J=11.9 Hz, H-6), 2.78 (m, 2H, H-3), 3.33 (m, 1H, H-1), 3.76 (m, 1H, H-1), 3.79, 4.27 (2d, 2H, ^2J=11.4 Hz, CH_2OH), 5.02, 5.08 (2d, 2H, ^2J=12.5 Hz, OCH_2Ph), 7.15–7.52 (m, 10H, Ph–H); ^{13}C NMR (CD_3OD): 22.9 (CH_3), 44.0, 46.8 (C-3a and C-7a), 48.9, 49.2 (C-1 and C-3), 53.0 (C-6) 59.5 (C-4), 63.9 (CH_2OH), 67.9 ($NCOOCH_2Ph$), 70.2 (C-7), 127.0–129.5 (C–Ph), 138.2

(C-*ipso*Ph–Cbz), 145.4 (C-ipso Ph-4), 156.5 (NCO); **rotamer b** (45%): ^{1}H NMR (CD_3OD): 1.19 (s, 3H, CH_3), 2.29 (m, 1H, H-7a), 2.60 (m, 1H, H-3a), 2.70, 2.93 (2d, 2H, ^2J=11.9 Hz, H-6), 2.78 (m, 2H, H-3), 3.33 (m, 1H, H-1), 3.76 (m, 1H, H-1), 3.79, 4.27 (2d, 2H, ^2J=11.4 Hz, CH_2OH), 4.98, 4.99 (2d, 2H, ^2J=12.5 Hz, OCH_2Ph), 7.15–7.52 (m, 10H, Ph–H); ^{13}C NMR (CD_3OD): 22.9 (CH_3), 44.8, 46.1 (C-3a and C-7a), 48.4, 49.5 (C-1 and C-3), 53.0 (C-6) 59.6 (C-4), 64.0 (CH_2OH), 67.7 ($NCOOCH_2Ph$), 70.1 (C-7), 127.0–129.5 (C–Ph), 138.3 (C-*ipso*Ph–Cbz), 145.3 (C-ipso), 156.6 (NCO); *m/z* (%): 397 (0.1, MH^+), 365 (MH^+–CH_2OH, 100), 91 (68, CH_2Ph); exact mass for $C_{23}H_{28}N_2O_4$: 396.2049; for $C_{22}H_{25}N_2O_3$: 365.1865; found: 396.2051, 365.1897; anal. calcd for $C_{23}H_{28}N_2O_4$: C 69.68, H 7.12, N 7.07, found: C 69.77, H 7.13, N 7.10.

2-Benzyl-4α-(hydroxymethyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol (9). Reduction of adduct **6c** (950 mg, 2.5 mmol) was carried out as described for the conversion of **4** to **5**. Compound **9** was purified by column chromatography (silica gel, 90/8/2 AcOEt/MeOH/Et_3N). Yield: 818 mg, 93%; white powder; mp: 118°C; IR (KBr) cm^{-1}: 3412 (OH, NH); ^{1}H NMR (CD_3OD): 1.40 (s, 3H, CH_3), 2.02 (dd, 1H, ^2J=10.0 Hz, ^3J=8.6 Hz, H-3), 2.28 (td, 1H, ^3J=^3J=6.5 Hz, ^3J=0.9 Hz, H-7a), 2.34 (dd, 1H, ^3J=11.0 Hz, ^2J=10.0 Hz, H-3), 2.48 (m, 1H, H-3a), 2.72 (d, 1H, ^2J=12.0 Hz, H-6), 2.78 (dd, 1H, ^3J=6.5 Hz, ^2J=10.0 Hz, H-1), 2.91 (d, 1H, ^2J=12.0 Hz, H-6), 2.98 (dd, 1H, ^2J=10.0 Hz, ^3J=0.9 Hz, H-1), 3.57, 3.58 (2×d, 2H, NCH_2Ph), 3.74, 4.25 (2×d, 2H, ^2J=11 Hz, CH_2OD), 7.1–7.3 (m, 8H, Ph–H), 7.42 (d, 2H, Ph–H*ortho*); ^{13}C NMR (CD_3OD): 24.9 (CH_3), 44.6, 47.9 (C-3a and C-7a), 53.2, 55.9, 61.4 (C-1, C-3 and C-6), 59.4 (C-4), 64.7 (CH_2OD), 70.5 (C-7), 127.1, 127.2, 127.8, 128.8, 129.1, 129.5 (Ph–C), 140.6 (C-ipso of Bn), 146.0 (C-*ipso*); *m/z* (%): 353.3 (2, MH^+), 321 (100, M^+–CH_2OH), 91 (61, $PhCH_2$); exact mass for $C_{22}H_{28}N_2O_2$: 352.2151, found: 352.2151.

4α-Hydroxymethyl-7β-methyl-4β-phenyl-3aα,7aα-octahydro-1H-pyrrolo[3,4-*c*]pyridin-7α-ol (formate salt of 10). To a stirred suspension of compound **9** (1.06 g, 3 mmol) and 530 mg 10% Pd/C in absolute methanol (20 ml) under nitrogen atmosphere was added anhydrous ammonium formate (945 mg, 15 mmol) in a single portion. The reaction mixture was heated to reflux temperature and reaction progress was monitored by TLC. When the reaction was completed, the catalyst was removed by filtration through a celite pad. After washing with 20 ml of chloroform, the combined organic filtrates were evaporated to afford formate salt **10** (814 mg) in a yield of 98%. Slightly yellow crystals; mp: 155°C; IR (KBr) cm^{-1}: 3332 (br., OH, NH); ^{1}H NMR (DMSO-d_6): 1.18 (s, 3H, CH_3), 1.99 (m, 1H, H-3), 2.05 (t, 1H, ^3J=6.0 Hz, H-7a), 2.11–2.16 (m, 2H, H-3 and H-3a), 2.51, 2.78 (2×d, 2H, ^2J=12.0 Hz, H-6), 2.80 (dd, 1H, ^2J=11.0 Hz, ^3J=6.0 Hz, H-1), 2.99 (d, 1H, ^2J=11.0 Hz, H-1), 3.62, 4.12 (2×d, 2H, ^2J=11.0 Hz, CH_2OH), 7.13 (t, 1H, ^3J=7.5 Hz, Ph–H*para*), 7.24 (t, 2H, ^3J=7.4 Hz, Ph–H*meta*), 7.46 (d, 2H, ^3J=7.6 Hz, Ph–H*ortho*), 8.34 (s, 1H, $HCOO^-$); ^{13}C NMR: 23.6 (CH_3), 44.6 (C-3a), 46.6 (C-7a), 47.8, 47.9 (C-1 and C-3), 52.6 (C-6), 58.2 (C-4), 62.6 (CH_2OH), 68.2 (C-7), 125.4, 125.9 and 127.2 (Ph–C), 146.1 (C-*ipso*), 168.9 ($HCOO^-$); *m/z* (%): 231 (100, M^+–CH_2OH); exact mass for $C_{14}H_{19}N_2O$ (M^+–CH_2OH): 231.1497, found: 231.1498.

***N*-Acylation of 10: formation of compounds 11 and 12a–b and conversion of 12a–b into 3,5-bis(trifluoromethyl)-benzyl ethers 13–15**

4α-(Hydroxymethyl)-2-[*o*-methoxyphenylacetyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo[3,4-*c*]-pyridin-7α-ol (11). *o*-Methoxyphenylacetic acid (166 mg, 1.0 mmol), formate salt 10 (308 mg, 1.0 mmol), DMAP (25 mg, 0.2 mmol), and Et_3N (0.30 ml, 2.2 mmol) were dissolved in a mixture of **10** ml of methylene chloride and 2 ml of DMF. The solution was cooled to 0°C and 192 mg (1.0 mmol) EDCI (1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride) was added. After 30 min, the cooling bath was removed and the reaction was allowed to proceed at room temperature overnight. Water (10 ml) was added and the aqueous layer was extracted with methylene chloride (3×10 ml). The combined organic layers were dried and evaporated. Column chromatography (silica gel, 10 MeOH/90 CH_2Cl_2) gave 132 mg (32%) pure compound **11** as a white solid. Mp: 125°C; IR (KBr, cm^{-1}): 3397(OH, NH), 1614, 1445 (CON); **rotamer a** (60%): ^{1}H NMR ($CDCl_3$): 1.12 (s, 3H, CH_3), 1.60- 2.04 (br., 3H, NH, OH), 2.24 (t, 1H, ^3J=6.5 Hz, H-7a), 2.56 (m, 1H, H-3a), 2.72, 2.90 (2×d, 2H, ^2J=11.5 Hz, H-6), 2.76 (m, 1H, H-3), 2.89 (m, 1H, H-3), 3.26 (dd, 1H, ^2J=12.8 Hz, ^3J=6.5 Hz, H-1), 3.30, 3.36 (2d, 2H, ^2J=15 Hz, $NCOCH_2Ar$), 3.52 (s, 3H, CH_3O), 4.0 (d, 1H, ^2J=12.8 Hz, H-1), 3.70, 4.25 (2×d, 2H, ^2J=9.4 Hz, CH_2OH), 6.72 (dd, 1H, ^3J=8.2 Hz, ^4J=1.0 Hz, H-*ortho*), 6.83 (td, 1H, ^3J=7.6 Hz, ^4J=1.0 Hz, H-*para*), 7.09–7.40 (m, 7H, Ph–H, Ar–H); ^{13}C NMR ($CDCl_3$): 22.8 (CH_3), 35.4 ($COCH_2Ar$), 44.0, 44.4 (C-3a and C-7a), 47.6, 47.9 (C-1 and C-3), 52.0 (C-6), 55.1 (OCH3), 58.6 (C-4), 63.9 (CH_2OH), 69.1 (C-7), 110–157 (C–Ar), 170.1 (CO); **rotamer b** (40%): ^{1}H NMR ($CDCl_3$): 1.16 (s, 3H, CH_3), 1.60- 2.04 (br., 3H, , NH, OH), 2.30 (t, 1H, ^3J=6.0 Hz, H-7a), 2.48 (m, 1H, H-3a), 2.72, 2.90 (2×d, 2H, ^2J=12.0 Hz, H-6), 2.88 (m, 1H, H-3), 3.11 (m, 1H, H-3), 3.40 (dd, 1H, ^2J=11.2 Hz, ^3J=6.0 Hz, H-1), 3.50, 3.61 (2d, 2H, ^2J=15 Hz, $NCOCH_2Ar$), 3.79 (s, 3H, CH_3O), 3.75 (d, 1H, ^2J=11.2 Hz, H-1), 3.67, 4.20 (2×d, 2H, ^2J=9.4 Hz, CH_2OH), 6.83 (dd, 1H, ^3J=8.2 Hz, ^4J=1.0 Hz, H-*ortho*), 6.87 (td, 1H, ^3J=7.6 Hz, ^4J=1.0 Hz, H-*para*), 7.09–7.40 (m, 7H, Ph–H, Ar–H); ^{13}C NMR ($CDCl_3$): 22.9 (CH_3), 35.4 ($COCH_2Ar$), 42.4, 46.1 (C-3a and C-7a), 47.3, 48.6 (C-1 and C-3), 55.4 (OCH3), 52.4 (C-6), 58.6 (C-4), 64.2 (CH_2OH), 69.2 (C-7), 110–157 (C-Ar), 169.8 (CO); *m/z* (%): 411 (1, MH^+), 379 (100, MH^+–CH_2OH); exact mass for $C_{24}H_{30}N_2O_4$: 410.2206, found: 410.2208.

2-Formyl-4α-(hydroxymethyl)-7β-methyl-4β-phenyl-3aα,7aα-octahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol (12a). To a solution of compound **10** (786 mg, 3 mmol) in methanol was added 456 mg (4.5 mmol) triethylamine and 270 mg (4.5 mmol) methyl formate at room temperature under nitrogen. After stirring overnight the solvent and the excess of reagents were removed under reduced pressure. The residue was purified by crystallisation to give pure *N*-formyl derivative **12a**. Yield: 835 mg, 96%; white

crystals, mp:104°C; IR (KBr) cm^{-1}: 3380 (OH, NH), 1650 (NCHO); **rotamer a** (60%): ^1H NMR (DMSO-d_6): 1.08 (s, 3H, CH_3), 2.23 (m, 1H, H-3a or H-7a), 2.43 (s, 1H, NH or OH), 2.56 (m, 1H, H-7a or H-3a), 2.81 (m, 1H, H-3), 3.07 (m, 1H, H-3), 3.17 (s, 2H, H-6), 3.65 (m, 1H, H-1), 3.82 (m, 1H, H-1), 4.10 (s, br. 1H, OH), 4.48 (s, 2H, CH_2OH), 7.29 - 7.49 (m, 5H, Ph–H), 8.10 (s, 1H, HCON); ^{13}C NMR (DMSO-d_6): 22.8 (CH_3), 41.8, 44.4 (C-3a and C-7a), 45.0, 47.5 (C-1 and C-3), 52.3 (C-6) 58.2 (C-4), 62.3 (CH_2OH), 67.9 (C-7), 125.8–127.6 (C–Ph), 145.2 (C-*ipso*), 160.9 (HCON); **rotamer b** (40%): ^1H NMR (DMSO-d_6): 1.09 (s, 3H, CH_3), 2.23 (m, 1H, H-3a or H-7a), 2.43 (s, 1H, NH or OH), 2.56 (m, 1H, H-7a or H-3a), 2.86 (m, 1H, H-3), 2.83 (s, 2H, H-6), 3.40 (m, 1H, H-3), 3.65 (m, 1H, H-1), 4.10 (s, br., OH), 4.15 (m, 1H, H-1), 4.48 (s, 2H, CH_2OH), 7.29–7.49 (m, 5H, Ph–H), 7.90 (s, 1H, HCON); ^{13}C NMR (DMSO-d_6): 22.7 (CH_3), 42.1, 44.0 (C-3a and C-7a), 45.2, 46.5 (C-1 and C-3), 52.1 (C-6), 58.0 (C-4), 62.2 (CH_2OH) 68.1 (C-7), 125.8–127.6 (Ph–C), 145.1 (C-*ipso*), 161.1 (HCON); *m/z* (%): 259 (100, MH^+–CH_2OH); exact mass for $C_{16}H_{22}N_2O_3$: 290.1630; for $C_{15}H_{19}N_2O_2$: 259.1447; found: 259.1451; anal. calcd for $C_{16}H_{22}N_2O_3.H_2O$: C 62.30, H 7.85, N 9.09; found: C 62.09, H 7.69, N 8.83.

2-Trifluoroacetyl-4α-(hydroxymethyl)-7β-methyl-4β-phenyl-3aα,7aα-octahydro-1*H*-pyrrolo[3,4-*c*]-pyridin-7α-ol (12b). The same procedure was applied as for the preparation of **12a**, using ethyl trifluoroacetate instead of methyl formate for *N*-acylation of compound **10** (1.57 g, 6 mmol). Yield: 2.10 g, 98%; white crystals, mp: 98°C; IR (KBr, cm^{-1}): 3424 (OH, NH), 1681 (NCHO); **rotamer a** (60%): ^1H NMR ($CDCl_3$): 1.24 (s, 3H, CH_3), 1.93 (s, br., 3H, NH, OH), 2.37 (t, 1H, ^3J=6.4 Hz, H-7a), 2.52 (m, 1H, H-3a), 2.78, 2.91 (2d, 2H, ^2J=12.0 Hz, H-6), 2.98 (m, 1H, H-3), 3.10 (m, 1H, H-3), 3.56 (dd, 1H, ^2J=13.0 Hz, ^3J=6.4 Hz, H-1), 3.73, 4.23 (2×d, 2H, ^2J=11.4 Hz, CH_2OH), 4.00 (d, 1H, ^2J=13.0 Hz, H-1), 7.26–7.43 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$): 22.9 (CH_3), 41.6, 45.9 (C-3a and C-7a), 48.7 (C-1 and C-3), 52.2 (C-6) 58.4 (C-4), 63.9 (CH_2OH), 69.0 (C-7), 117.4 (q, CF_3), 125.4–128.8 (C–Ph), 142.2 (C-*ipso*), 155.3 (q, NCO); **rotamer b** (40%): ^1H NMR ($CDCl_3$): 1.23 (s, 3H, CH_3), 1.93 (s, br., 3H, NH, OH), 2.32 (t, 1H, ^3J=6.4 Hz, H-7a), 2.62 (m, 1H, H-3a), 2.78, 2.91 (2d, 2H, ^2J=12.0 Hz, H-6), 2.98 (m, 1H, H-3), 3.10 (m, 1H, H-3), 3.40 (dd, 1H, ^2J=13.0 Hz, ^3J=6.0 Hz, H-1), 3.77, 4.26 (2×d, 2H, ^2J=11.4 Hz, CH_2OH), 4.00 (d, 1H, ^2J=13.0 Hz, H-1), 7.26–7.43 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$): 23.0 (CH_3), 43.5, 44.2 (C-3a and C-7a), 47.3, 49.7 (C-1 and C-3), 52.0 (C-6), 58.5 (C-4), 63.5 (CH_2OH), 69.1 (C-7), 117.4 (q, CF_3), 125.4–128.8 (Ph–C), 142.1 (C-*ipso*), 155.8 (q, NCO); *m/z* (%): 327 (100, MH^+–CH_2OH); exact mass for $C_{17}H_{21}F_3N_2O_3$: 358.1504; for $C_{16}H_{18}F_3N_2O_2$: 327.1320; found: 327.1321; anal. clacd. for $C_{17}H_{21}F_3N_2O_3$: C 56.98, H 5.91, N 7.82, found: C 56.74, H 6.16, N 7.56.

2-Formyl-4α-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo-[3,4-*c*]pyridin-7α-ol (13). *O*-Benzylation of **12a** (777 mg, 3 mmol) was carried out using the same procedure as for the preparation of **1**. Compound **13** was purified by column chromatography (silica gel, 6:94 MeOH/CH_2Cl_2). Yield: 928 mg, 60%; white crystals, mp: 133.0–135°C; IR (KBr) cm^{-1}: 3435 (OH, NH), 1657 (NCHO); **rotamer a** (56%): ^1H NMR ($CDCl_3$): 1.32 (s, 3H, CH_3), 2.21 (s, 1H, OH or NH), 2.16 (br. s, 1H, NH or OH), 2.34 (t, 1H, ^3J=6.2 Hz, H-7a), 2.50 (m, 1H, H-3a), 2.79, 2.94 (2×d, 2H, ^2J=12.0 Hz, H-6), 2.80 (m, 1H, H-3), 3.03 (t, 1H, ^3J=^2J=10.6 Hz, H-3), 3.46 (dd, 1H, ^2J=13.0 Hz, ^3J=6.2 Hz, H-1), 3.72, 4.28 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 3.84 (d, 1H, ^2J=13.0 Hz, H-1), 4.44, 4.58 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.24 -7.46 (m, 5H, Ph–H), 7.48 (s, 2H, Ar–H-*ortho*), 7.75 (s, 1H, Ar–H-*para*), 7.96 (s, 1H, HCON); ^{13}C NMR ($CDCl_3$): 23.3 (CH_3), 43.3, 44.5 (C-3a and C-7a), 45.7, 46.7(C-1 and C-3), 52.4 (C-6) 57.8 (C-4), 69.5 (C-7), 71.2, 71.8 (CH_2OCH_2), 121.6 (Ar–C), 123.2 (q, CF_3)125.1 (Ph–C), 127.1 (Ar–C), 127.2 (Ph–C), 128.4 (Ph–C), 131.4 (q, Ar–C), 140.7 (C-*ipso* Ar), 143.5 (C-*ipso*Ph), 161.2 (HCON); rotamer b (44%): ^1H NMR ($CDCl_3$):1.31 (s, 3H, CH_3), 1.97 (s, 1H, OH or NH), 2.16 (br. s, 1H, NH or OH), 2.29 (t, 1H, ^3J=6.2 Hz, H-7a), 2.46 (m, 1H, H-3a), 2.79, 2.94 (2×d, 2H, ^2J=12.0 Hz, H-6), 2.80 (m, 1H, H-3), 2.84 (m, 1H, H-3), 3.25 (dd, 1H, ^2J=13.0 Hz, ^3J=6.2 Hz, H-1), 3.69, 4.25 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 3.88 (d, 1H, ^2J=13.0 Hz, H-1), 4.42, 4.62 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.24 -7.46 (m, 5H, Ph–H), 7.48 (s, 2H, Ar–H-*ortho*), 7.75 (s, 1H, Ar–H-*para*), 8.12 (s, 1H, HCON); ^{13}C NMR ($CDCl_3$): 23.5 (CH_3), 42.9, 44.8 (C-3a and C-7a), 44.9, 47.9 (C-1 and C-3), 52.8 (C-6), 57.9 (C-4), 69.4 (C-7), 71.2, 71.6 (CH_2OCH_2), 121.6 (Ar–C), 123.2 (q, CF_3)125.1 (Ph–C), 127.1 (Ar–C), 127.2 (Ph–C), 128.5 (Ph–C), 131.4 (q, Ar–C), 140.6 (C-*ipso* Ar), 143.1 (C-*ipso* Ph), 161.0 (HCON); *m/z* (%): 259 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); 227 (22, $^+CH_2C_6H_3(CF_3)_2$); exact mass for $C_{25}H_{26}F_6N_2O_3$: 516.1848; found: 516.1826; anal. calcd for $C_{25}H_{26}F_6N_2O_3$: C 58.14, H 5.07, N 5.42, found: C 57.90, H 5.01, N 5.41.

2-Trifluoroacetyl-4α-({[3,5-bis(trifluoromethyl)benzyl]-oxy}methyl)-7β-methyl-4β-phenyl-3aα,7aα-octa hydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol (14) and 2-[3,5-bis(trifluoromethyl)benzyl]-4α-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-7β-methyl-4β-phenyl-3aα,7aα-octahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol (15). Compound **12b** (1.79 g, 5 mmol) was subjected to the same procedure as for the conversion of **12a** to **13**, to give a mixture from which compounds **14** and **15** were isolated by column chromatography (silica gel, 6:94 MeOH/CH_2Cl_2). Yield of **14**: 175 mg, 6%; colourless oil; IR (NaCl, film) cm^{-1}: 3445 (OH, NH), 1682 (NCHO); **rotamer a** (56%): ^1H NMR ($CDCl_3$): 1.29 (s, 3H, CH_3), 2.03 (br. s, 1H, NH or OH), 2.20 (s, 1H, OH or NH), 2.36 (t, 1H, ^3J=6.5 Hz, H-7a), 2.50 (m, 1H, H-3a), 2.78, 2.94 (2×d, 2H, ^2J=12.0 Hz, H-6), 3.00 (m, 1H, H-3), 3.03 (t, 1H, ^3J=^2J=11.5 Hz, H-3), 3.55 (dd, 1H, ^2J=13.0 Hz, ^3J=6.5 Hz, H-1), 3.70, 4.24 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 4.03 (d, 1H, ^2J=13.0 Hz, H-1), 4.42, 4.59 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.15 -7.45 (m, 5H, Ph–H), 7.48 (s, 2H, Ar–H-*ortho*), 7.75 (s, 1H, Ar–H-*para*); ^{13}C NMR ($CDCl_3$): 23.1 (CH_3), 41.8, 46.1 (C-3a and C-7a), 48.7, 49.7(C-1 and C-3), 52.6 (C-6) 57.7 (C-4), 69.3 (C-7), 71.5, 71.8 (CH_2OCH_2), 116.2 (q, $COCF_3$), 121.8–128.9 (C–Ar, Ph), 123.1 (CF_3) 131.6 (q, Ar–C), 140.7 (C-*ipso* Ar), 142.9 (C-*ipso*Ph), 155.3 (q, $COCF_3$); **rotamer b** (44%): ^1H NMR ($CDCl_3$): 1.28 (s, 3H, CH_3), 2.18 (br. s, 1H, OH), 2.20 (s, 1H, OH), 2.32 (t, 1H,

^3J=6.2 Hz, H-7a), 2.58 (m, 1H, H-3a), 2.78, 2.94 (2×d, 2H, ^2J=12.0 Hz, H-6), 3.00 (m, 1H, H-3), 3.15 (t, 1H, ^2J=^3J=11.5 Hz, H-3), 3.38 (dd, 1H, ^2J=13.0 Hz, ^3J= 6.2 Hz, H-1), 3.72, 4.28 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 4.02 (d, br. 1H, ^2J=13.0 Hz, H-1), 4.44, 4.62 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.15 -7.45 (m, 5H, Ph–H), 7.48 (s, 2H, Ar–H-*ortho*), 7.75 (s, 1H, Ar–H-*para*); ^{13}C NMR ($CDCl_3$): 23.1 (CH_3), 43.6, 44.4 (C-3a and C-7a), 47.2, 48.7 (C-1 and C-3), 52.3 (C-6), 57.8 (C-4), 69.3 (C-7), 71.1, 71.8 (CH_2OCH_2), 116.0 (q, $COCF_3$), 121.8–128.9 (C–Ar and Ph–C), 123.1 (CF_3), 131.6 (q, Ar–C), 140.6 (Ar–C-*ipso*), 142.8 (Ph–C-*ipso*), 155.7 (q, $COCF_3$); *m/z* (%): 585 (13, MH^+), 259 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); 227 (35, $^+CH_2C_6H_3(CF_3)_2$); exact mass for $C_{26}H_{25}F_8N_2O_3(M^+-F^\cdot)$: 565.1737; found: 565.1706.

Yield of **15**: 556 mg, 15%; colourless oil; IR (NaCl, film) cm^{-1}: 3383 (OH, NH); ^{1}H NMR($CDCl_3$): 1.48 (s, 3H, CH_3), 2.07 (t, 1H, H-3), 2.28 (t, 1H, ^3J=5.6 Hz, H-7a), 2.35 (br. s, 1H, NH, OH), 2.55 (m, 1H, H-3), 2.53 (m, 1H, H-3a), 2.72 (dd, 1H, ^3J=5.6 Hz, ^2J=10.0 Hz, H-1), 2.84, 2.93 (2×d, 2H, ^2J=11.8 Hz, H-6), 2.96 (d, br. 1H, ^2J=10.0 Hz, H-1), 3.70 (s, 2H, NCH_2Ar), 3.68, 4.24 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 4.43, 4.58 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.21–7. 74 (m, 11H, Ph–H, Ar); ^{13}C NMR ($CDCl_3$): 24.8 (CH_3), 43.6, 47.3 (C-3a and C-7a), 52.8 (C-6), 54.8, 55.3 (C-1 and C-3), 58.4 (C-4), 59.5 (NCH_2Ar), 69.9 (C-7), 71.8 (CH_2OCH_2Ar), 72.7 (CH_2OCH_2Ar), 121.4- 128.1 (Ph–C and Ar–C), 140.9, 142.9 (Ar–C-*ipso*), 144.3 (Ph–C-*ipso*); *m/z* (%): 715 (8, MH^+), 457 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{33}H_{30}F_{12}N_2O_2$: 714.2116; found: 714.2109.

Synthesis of compound 2: *O*-benzylation of 9 followed by *N*-debenzylation and *N*-acylation

2-[Benzyl]-4α-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo-[3,4-*c*]pyridin-7α-ol (16). This was prepared from compound **9** (704 mg, 2 mmol) using the same procedure as for **1**. Compound **16** was purified by column chromatography (silica gel, 6:94 MeOH/CH_2Cl_2). Yield: 902 mg, 78%; colourless oil; IR (NaCl, film) cm^{-1}: 3414 (OH, NH); ^{1}H NMR ($CDCl_3$): 1.46 (s, 3H, CH_3), 2.00 (br. s, 1H, NH, OH), 2.08 (t, 1H, H-3), 2.22 (t, 1H, ^3J=6.0 Hz, H-7a), 2.46 (m, 1H, H-3), 2.50 (m, 1H, H-3a), 2.70 (dd, 1H, ^3J=6.0 Hz, ^2J=10.0 Hz, H-1), 2.81, 2.87 (2×d, 2H, ^2J=11.8 Hz, H-6), 2.90 (dd, 1H, ^2J=10.0 Hz, ^3J=0.8 Hz, H-1), 3.59 (s, 2H, CH_2Ph), 3.63, 4.20 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 4.42, 4.56 (2×d, 2H, ^2J=13.2 Hz, CH_2OCH_2Ar), 7.17–7.31 (m, 8H), 7.44 (m, 2H) (Ph–H), 7.48 (s, 2H), 7.74 (s, 1H) (Ar–H); ^{13}C NMR ($CDCl_3$): 25.0 (CH_3), 43.4, 47.2 (C-3a and C-7a), 52.8, 54.7, 55.1, 60.4 (4×CH_2N), 58.4 (C-4), 70.1 (C-7), 71.8, 73.0 (CH_2OCH_2), 121.5 (Ar–C), 125.5, 126.6, 126.7 (Ph–C), 127.2 (Ar–C), 127.9, 131.4 (q, Ar–C), 140.0 (Ar–C-*ipso*), 141.9, 144.5 (Ph–C-*ipso*); *m/z* (%): 579 (1, MH^+), 561 (2, MH^+–H_2O), 559 (1, MH^+–HF), 321 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{31}H_{32}F_6N_2O_2$: 578.2368; found: 578.2360; anal. calcd for $C_{31}H_{32}F_6N_2O_2$:C 64.35, H 5.57, N 4.84, found: C 64.11, H 5.82, N 4.79.

4α-({[3,5-bis(trifluoromethyl)benzyl]oxy}methyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo [3,4-*c*]-pyridin-7α-ol (formate salt of 17). Prepared by *N*-debenzylation of 16 (867 mg, 1.5 mmol) using the same procedure as for **10**. Yield: 786 mg, 98%; white crystals, mp: 82.5–85.0°C; IR (KBr) cm^{-1}: 3394 (OH, NH); ^{1}H NMR ($CDCl_3$)*:*1.33 (s, 3H, CH_3), 2.41 (m, 3H), 2.63 (m, 1H), 2.72, 2.88 (2×d, 2H, ^2J=11.6 Hz, H-6), 3.20 (m, 1H), 3.54 (m, 1H), 3.67, 4.23 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar), 4.40, 4.60 (2×d, 2H, ^2J=13.0 Hz, CH_2OCH_2Ar), 7.24 (t, 1H, ^3J=7.2 Hz, H-*para*), 7.31 (t, 2H, ^3J=7.3 Hz, H-*meta*), 7.39 (d, 2H, ^3J=7.4 Hz, H-*ortho*), 7.46 (s, 2H, H-*ortho*), 7.74 (s, 1H, H-*para*), 8.35 (s, 1H, HCOO); ^{13}C NMR ($CDCl_3$): 23.7 (CH_3), 44.3, 45.9 (2×CH), 45.9, 46.5, 51.9 (3×CH_2N), 57.6 (C-4), 68.6 (C-7), 71.1, 71.8 (CH_2OCH_2), 121.6 (Ar–C), 123.2 (q, CF_3), 125.0 (Ph–C), 127.1 (Ar–C), 127.2 (Ph–C), 128.6 (Ph–C), 131.4 (q, Ar–C), 140.6 (Ar–C-*ipso*), 143.2 (Ph–C-*ipso*), 169.0 (HCOO); *m/z* (%): 489 (1, MH^+), 469 (1, MH^+–HF), 231 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{24}H_{26}F_6N_2O_2$: 488.1898; found: 488.1902; anal. calcd for $C_{24}H_{26}F_6N_2O_2$.-CH_2O_2: C 56.18, H 5.28, N 5.24, found: C 55.94, H 5.23, N 5.15.

2-[*o*-Methoxyphenylacetyl)-4α-({[3,5-bis(trifluoromethyl)-benzyl]oxy}methyl)-7β-methyl-4β-phenyl-3aα, 7aα-octahydro-1*H*-pyrrolo[3,4-*c*]pyridin-7α-ol (2). To a solution of 498 mg (3 mmol) *o*-methoxy-phenylacetic acid in 30 ml CCl_4 was added 943 mg (3.6 mmol) PPh_3 in a single portion. The suspension was stirred at reflux temperature until completion of the reaction (overnight). The mixture was cooled and the white deposit was filtered off. The filtrate was concentrated under reduced pressure to give 496 mg of (*o*-methoxyphenyl)acetyl chloride as a colourless oil (yield, 90%). This acid chloride (256 mg, 1.4 mmol) was added dropwise to a solution of formate salt 17 (641 mg, 1.2 mmol) and pyridine (0.32 ml, 4 mmol) in dry THF at −15°C. After being stirred at this temperature for 2 h the reaction mixture was worked up in the usual way. Purification by chromatography (silica gel, 4:96 MeOH/CH_2Cl_2) and recrystallisation gave pure compound 2. Yield: 496 mg, 65%; white crystals; mp: 175.4–175.8°C; IR (KBr, cm^{-1}): 3403 (shoulder, OH, NH), 1622.8 (s, CON); rotamer a (65%): ^{1}H NMR ($CDCl_3$): 1.18 (s, 3H, CH_3), 2.20 (s, 1H, OH), 2.24 (t, 1H, ^3J=6.5 Hz, H-7a), 2.49 (m, 1H, H-3a), 2.73, 2.90 (2×d, 2H, ^2J=11.5 Hz, H-6), 2.77 (m, 1H, H-3), 2.88 (m, 1H, H-3), 3.26 (dd, 1H, ^2J=12.8 Hz, ^3J= 6.5 Hz, H-1), 3.30, 3.36 (2d, 2H, ^2J=15 Hz, $NCOCH_2Ar$), 3.53 (s, 3H, CH_3O), 4.0 (d, 1H, ^2J=12.8 Hz, H-1), 3.65, 4.25 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar'), 4.40, 4.58 (2×d, 2H, ^2J=13.0 Hz, CH_2OCH_2Ar'), 6.72 (dd, 1H, ^3J=8.2 Hz, ^4J=1.0 Hz, H-*ortho*), 6.82 (td, 1H, ^3J=7.6 Hz, ^4J=1.0 Hz, H-*para*), 7.09 -7.40 (m, 7H, Ph–H, Ar–H), 7.45 (s, 2H, H-ortho Ar′), 7.74 (s, 1H, H-para Ar′); ^{13}C NMR ($CDCl_3$): 23.2 (CH_3), 35.4 ($COCH2Ar$), 44.2, 44.5 (C-3a and C-7a), 47.5, 47.9 (C-1 and C-3), 55.1 (OCH3), 52.3 (C-6), 57.9 (C-4), 69.4 (C-7), 71.4, 71.8 (CH_2OCH_2), 110–157 (C-Ar), 170.1 (CO); rotamer b (35%): ^{1}H NMR ($CDCl_3$): 1.23 (s, 3H, CH_3), 2.32 (s, 1H, OH), 2.27 (t, 1H, ^3J=6.0 Hz, H-7a), 2.40 (m, 1H, H-3a), 2.73, 2.90 (2×d, 2H, ^2J=12.0 Hz, H-6), 3.00 (m, 1H, H-3), 2.88 (m, 1H, H-3), 3.38 (dd, 1H, ^2J=11.2 Hz, ^3J=6.0 Hz, H-1), 3.50, 3.61 (2d, 2H, ^2J=15 Hz, $NCOCH_2Ar$), 3.79 (s, 3H,

CH_3O), 3.75 (d, 1H, ^2J=11.2 Hz, H-1), 3.67, 4.20 (2×d, 2H, ^2J=9.4 Hz, CH_2OCH_2Ar'), 4.42, 4.54 (2×d, 2H, ^2J=13.0 Hz, CH_2OCH_2Ar'), 6.83 (dd, 1H, ^3J=8.2 Hz, ^4J=1.0 Hz, H-*ortho*), 6.87 (td, 1H, ^3J=7.6 Hz, ^4J=1.0 Hz, H-*para*), 7.09 -7.40 (m, 7H, Ph–H, Ar–H), 7.48 (s, 2H, H-ortho Ar′), 7.74 (s, 1H, H-para Ar′); ^{13}C NMR ($CDCl_3$): 23.3 (CH_3), 35.4 ($COCH2Ar$), 42.6, 46.2 (C-3a and C-7a), 47.2, 48.7 (C-1 and C-3), 55.4 (OCH3), 52.8 (C-6), 57.9 (C-4), 69.7 (C-7), 71.4, 71.8 (CH_2OCH_2), 110–157 (C-Ar), 169.8 (CO); *m/z* (%): 637 (1, MH^+), 617 (2, MH^+–HF), 379 (100, MH^+–$CH_2OCH_2C_6H_3(CF_3)_2$); exact mass for $C_{33}H_{34}N_2O_4F_6$: 636.2423, found: 636.2427; anal. calcd for $C_{33}H_{34}N_2O_4F_6$: C 62.26, H 5.38, N 4.40, found: C 62.31, H5.29, N 4.33.

General procedure for reduction of adducts 4 and 6c with $NaCNBH_3$ to give tricyclic lactones 18

To a clear solution of 502 mg $NaCNBH_3$ (8 mmol) in a mixture of 16 ml of THF and 4 ml acetate buffer (1 M NaOAc/HOAc, pH=5.0) was added 2 mmol of adduct **4** or **6c**. The reaction mixture was heated at a bath temperature of 75°C for one day. After concentration in vacuo 10 ml of saturated $NaHCO_3$ solution was added. 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 **18**. Further purification was carried out by chromatography (silica gel, 4:96 MeOH/CH_2Cl_2) and crystallisation.

***endo* 7-Methyl-1-phenyl-8-oxa-4,10-diazatricyclo-[5.2.2.0^{2,6}]-undecan-9-one (18a).** Yield: 431 mg, 84%; slightly yellow powder; mp: 123.0–124.5°C; IR (KBr) cm^{-1}: 3290 (NH), 1738 (CO); ^{1}H NMR($CDCl_3$): 1.36 (s, 3H, CH_3), 1.1–1.5, 1.65–1.95 (7H, $CH_2CH_2CH_2$+NH), 2.48 (dtd, 1H, ^3J=12.0 Hz, ^3J=^3J=8.0 Hz, ^4J=2.0 Hz, H-6), 2.60 (dt, 1H, ^3J=12.0 Hz, ^3J=^3J=8.0 Hz, H-2), 2.98 (dd, 1H, ^2J=12.0 Hz, ^4J=2.0 Hz, H-11ax), 3.34 (d, 1H, ^2J=12.0 Hz, H-11eq), 7.27–7.49 (m, 5H, Ph–H); ^{13}C NMR ($CDCl_3$): 21.9 (CH_3), 25.6, 27.3, 28.4 (3×CH_2), 45.8 and 47.2 (C-2 and C-6), 46.9 (C-11), 59.9 (C-1), 82.4 (C-7), 126.6, 127.3, 127.8 (Ph–C), 137.7 (C-*ipso*), 174.2 (C-9); *m/z* (%): 258 (15, MH^+), 213 (100, $M^{+\cdot}$–CO_2); exact mass for $C_{16}H_{20}N_1O_2$: 258.1494, found: 358.1494.

***endo* 4-Benzyloxycarbonyl-7-methyl-1-phenyl-8-oxa-4, 10-diazatricyclo[5.2.2.0^{2,6}]undecan-9-one (18b).** Yield: 633 mg, 91%; slightly yellow powder; mp: 142–145°C (decomp.); IR (KBr) cm^{-1}: 3290 (NH), 1728 (CO); ^{1}H NMR($CDCl_3$): 1.35 (s, 3H, CH_3), 2.17 (br. S, 1H, NH), 2.31 (dd, 1H, ^2J=10.0 Hz, ^3J=8.0 Hz, H-3), 2.51 (dd, 1H, ^2J=10.0 Hz, ^3J=4.0 Hz, H-5), 261 (dd, 1H, ^2J=10.0 Hz, ^3J=8.0 Hz, H-5), 2.68 (m, 1H, H-6), 2.72 (dd, 1H, ^2J=10.0 Hz, ^3J=4.0 Hz, H-3), 2.94 (ddd, 1H, ^3J=4.3 Hz, ^3J=8.0 Hz, ^3J=10.0 Hz, H-2), 3.02 (dd, 1H, ^2J=11.6 Hz, ^4J=2.0 Hz, H-11ax), 3.50 (d, 1H, ^2J=11.6 Hz, H-11eq), 3.49, 3.61 (2×d, 2×1H, ^2J=13.0 Hz, NCH_2Ph), 7.27–7.49 (m, 10H, Ph–H); ^{13}C NMR ($CDCl_3$): 22.3 (CH_3), 45.0 and 45.1 (C-2 and C-6), 48.1, 54.0, 55.4, 59.9 (4×CH_2), 60.2 (C-1), 82.0 (C-7), 127.0, 127.1, 127.6, 128.0, and 128.4 (Ph–C), 137.6, 138.6 (2×C-*ipso*), 173.5 (C-9); *m/z* (%):304 (33, $M^{+\cdot}$–CO_2), 91 (78; Bn^+); exact mass for $C_{22}H_{24}N_2O_2$: 348.1838, found: 348.1836.

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References

1. (a) Regoli, D.; Boudon, A.; Fauchere, J. L. *Pharmacol. Rev.* **1994**, *46*, 551–556. (b) Swain, C. *Exp. Opin. Ther. Patents* **1996**, *6*, 367–378 and references cited therein. (c) Kramer, M. S.; Cutler, N. et al. *Science* **1998**, *281*, 1640–1645.
2. Snider, R. M.; Constantine, J. W.; Lowe, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozdda, S. E.; Desai, M. C.; Vinck, F. J.; Spencer, R. W.; Hess, H. *Science* **1991**, *251*, 435–437.
3. Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911–4913.
4. Harrison, T.; Williams, B. J.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2733–2734.
5. Tabart, M.; Peyronel, J. F. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 673–676.
6. (a) Elliott, J.; Seward, E. M. *Exp. Opin. Ther. Patents* **1997**, *7*, 43–54 and references therein. (b) Stevenson, G. I.; Huscroft, I. et al. *J. Med. Chem.* **1998**, *41*, 4623–4635 and references therein. (c) Hale, J. J.; Mills, S. G. et al. *J. Med. Chem.* **1998**, *41*, 4607–4614 and references therein. (d) Ward, P.; Armour, D. R. et al. *J. Med. Chem.* **1995**, *38*, 4985–4992.
7. (a) Seward, E. M.; Swain, C. J.; Merchant, K. J.; Owen, S. N.; Sabin, V.; Cascier, M. A.; Sadowski, S.; Strader, C.; Baker, R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1361–1364. (b) Stevenson, G. I.; Macleod, A. M.; Huscroft, I.; Gascieri, M. A.; Sadowski, S.; Baker, R. *J. Med. Chem.* **1995**, *38*, 1264–1271.
8. Wu, X.; Dubois, K.; Rogiers, J.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 3043–3051.
9. Warmus, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 270–271.
10. Volpin, M.; Dvolaitzky, M.; Levitin, I. *Bull. Soc. Chim. Fr.* **1970**, 1526–1528.
11. (a) Anwer, M. K.; Spatola, A. F. *Synthesis* **1980**, 929–932. (b) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515–516.
12. (a) Newman, H. *J. Org. Chem.* **1964**, *30*, 1287–1288. (b) Bergeron, R. J.; McManis, J. S. *J. Org. Chem.* **1988**, *53*, 3108–3111. (c) Curphey, T. *J. Org. Chem.* **1979**, *44*, 2805–2807.
13. Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076–4076.
14. Commercially available 2-(benzylamino)-1-ethanol (BAE) was converted to *N*,*N*-dibenzyl-2-(benzyloxy)-1-ethanamine (DBBEA) by *N*,*O*-dibenzylation using NaH and benzyl bromide in THF; ^{1}H NMR (DMSO-d_6): 2.57 (t, 2H, $Bn_2NCH_2CH_2OBn$), 3.51 (t, 2H, $Bn_2NCH_2CH_2OBn$), 3.60 (s, 4H, $[PhCH_2]_2N$), 4.40 (s, 2H, $OCH2Ph$), 7.18–7.35 (m, 15H, Ph–H); *m/z* (%): 332 (100, MH^+), 210 (18, MH^+–HCH_2OBn). The pure DBBEA compound was subjected to catalytic transfer hydrogenation under the conditions described for the conversion of **9** to **10**. On removal of catalyst, excess of reagent, and solvent, (benzyloxy)ethylamine was isolated as the formate salt; ^{1}H NMR (DMSO-d_6): 2.84 (br. t, NH_2), 2.99 (t, 2H, CH_2NH_2), 3.61 (t, 2H, CH_2CH_2OBn), 4.48 (s,

2H, OCH_2Ph), 7.24–7.34 (m, 5H, Ph–H), 8.43 (s, 1H, $HCOO^-$); *m*/*z* (%): 152 (100, MH^+), 91 (30, Bn^+).
15. (a) Fannes, C.; Meerpoel, L.; Toppet, S.; Hoornaert, G. J. *Synthesis* **1992**, 705–709. (b) Cristol, S. J.; Seifert, W. K.; Soloway, S. B. *J. Am. Chem. Soc.* **1960**, *82*, 2351–2352. (c) Houk, K. N. *Tetrahedron Lett*. **1970**, 2621–2624.
16. (a) Wassermann, A. *Diels–Alder Reactions*, Elsevier, Amsterdam, 1965. (b) Herndo, W. C.; Hall, L. H. *Tetrahedron Lett.* **1967**, 3095–3100.
17. (a) Kakushima, M.; Scott, D. *J. Can. Chem.* **1979**, *57*, 1399–1401. (b) Kakushima, M.; Scott, D. *J. Can. Chem.* **1979**, *57*, 2564–2568.
18. Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545–2550.
19. Van Aken, K. J.; Lux, G. M.; Deroover, G. G.; Meerpoel, L.; Hoornaert, G. *Tetrahedron* **1994**, *50*, 5211–5224.