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Synthesis of *cis*-fused hexahydro-4a*H*-indeno[1,2-*b*]pyridines via intramolecular Ritter reaction and their conversion into tricyclic analogues of NK-1 and dopamine receptor ligands

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Abstract—Indanol intermediates prepared via Michael addition of 1-indanone β-ketoester and acrylonitrile, followed by Grignard reaction of the ketone group, were submitted to an intramolecular Ritter reaction to produce *cis*-fused methyl 2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylates with 4a,9b-diangular substitution pattern. Further transformation of the bridgehead ester group and the lactam function afforded constrained tricyclic analogues of some monocyclic piperidine NK-1 antagonists and of a bicyclic dopamine receptor ligand.

1. Introduction

Recently, tricyclic piperidinones of type A (Fig. 1) substituted at both bridgehead positions 4a and 9b were made accessible via an intramolecular Ritter reaction.[1] Various R-groups, e.g. Ph, thienyl, Me, and H, are tolerated in the crucial acid-catalysed cyclisation step, resulting in the desired structural variation at the 9b-position. We conceived compounds A as precursors for the construction of conformationally constrained analogues of bioactive molecules containing various arylalkyl(di)amine pharmacophoric units.[2] Thus, in target molecules of type B (Fig. 1, Y=NH), a diamine substructure $Ar_2C(NHR)C(NHR)$ is incorporated into the framework of a tricyclic ring system and the 4a,9b bridgehead substituents. For instance, transforming the ester group of A into a complex benzylamino substituent, e.g. a 2-methoxybenzylamino group, was envisioned as a key step for the generation of constrained analogues of the non-peptide NK-1 antagonist CP-99,994.[3] Similar conversion of the bridgehead ester group into a benzyloxy or benzyloxymethyl group would provide analogues of the 2-phenyl-3-benzyloxypiperidine NK-1 antagonist L-733,060.[4] In this context it should be noticed that not only a C_2, but also a C_3 interconnection (Y=CONH, CH_2O) between the two heteroatoms is of interest for both NK-1[5] and dopamine receptor activity.[6] We also aimed at attaining analogy with 4-phenyl-3-isoquinolones described as NK-1 antagonists by Takeda,[7] via alternative elaboration into amide and urea compounds of type B (Y=NHCO, CONH or NHCONH). Besides these potential substance P antagonists, the 8-OH substituted fenethylamine target compound **1** can be considered as a tricyclic analogue of the bicyclic dopamine receptor ligand **2**, *trans*-2-amino-3-phenyl-2,3-dihydro-1*H*-inden-5-ol, active on both the D_1 and D_2 receptor.[8]

Herein we provide a detailed account on the conversion of tricyclic lactam ester compounds of type A into various target compounds of type B, i.e. the potential dopamine receptor ligand **1** and NK1 antagonists **3**–**5**. Part of this work has appeared in preliminary form.[1,2]

2. Results and discussion

2.1. Preparation of hexahydro-1*H*-indeno[1,2-*b*]pyridine 6

A diastereoselective synthesis of hexahydro-1*H*-indeno-[1,2-*b*]pyridine **6** was readily accomplished via the route outlined in Scheme 1. Treatment of 1-indanone with sodium hydride and dimethyl carbonate[9] gave the corresponding β-keto ester **7** which was subjected to Michael addition with acrylonitrile, using *t*-BuOH as a solvent and *t*-BuOK as a base catalyst. Grignard reaction of the resulting keto nitrile **8** using freshly prepared phenylmagnesium bromide at −78°C yielded the tertiary alcohol **9** as a 3:1 epimeric mixture.

For the major diastereomer of alcohols **9** a *cis*-relationship between the ester and phenyl groups was demonstrated by

Keywords: piperidines; diamines; bicyclic heterocyclic compounds; intramolecular Ritter reaction; Curtius reaction.

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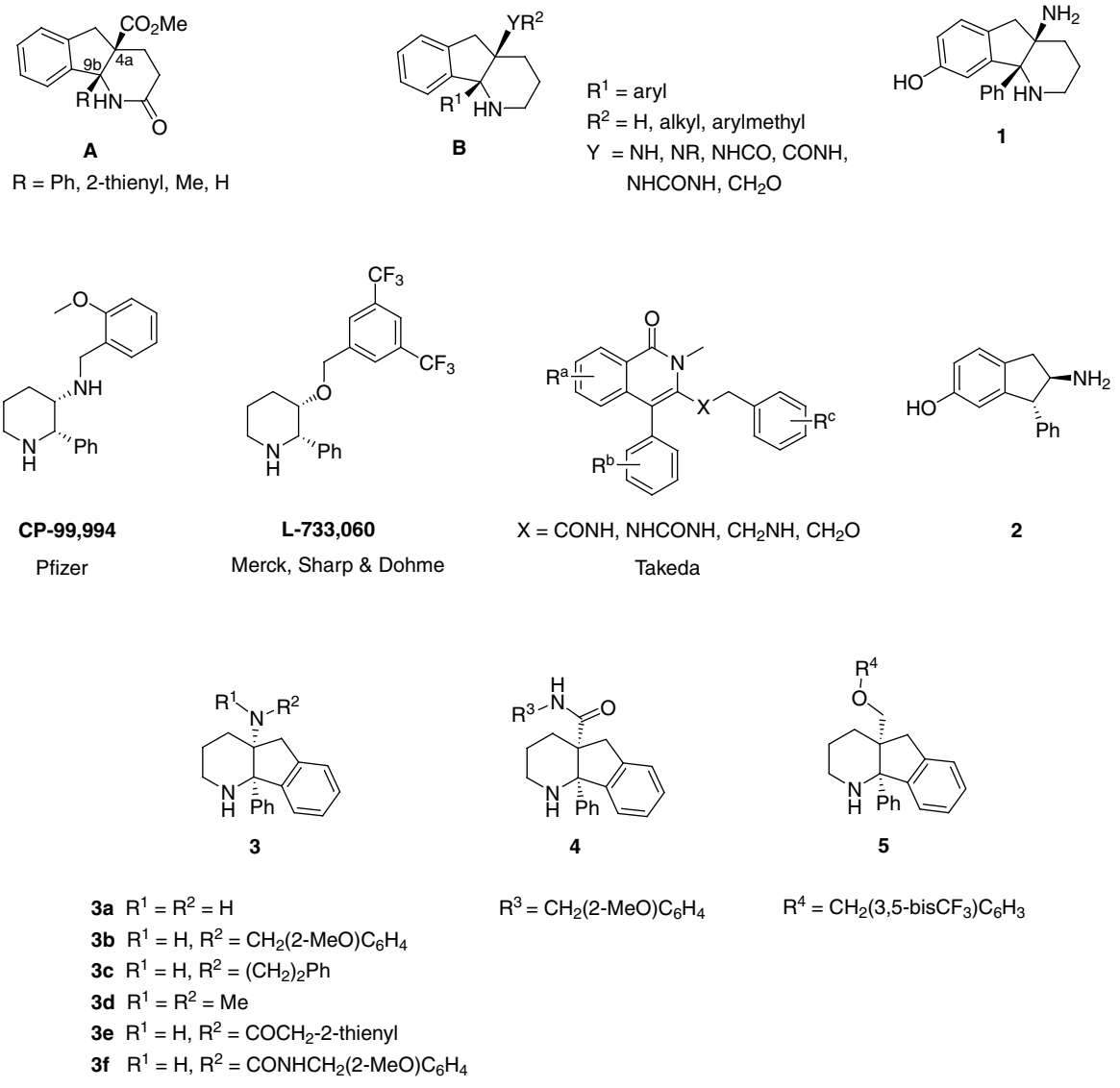
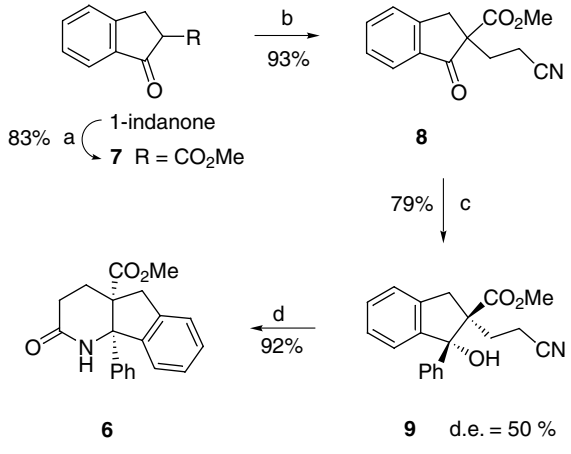


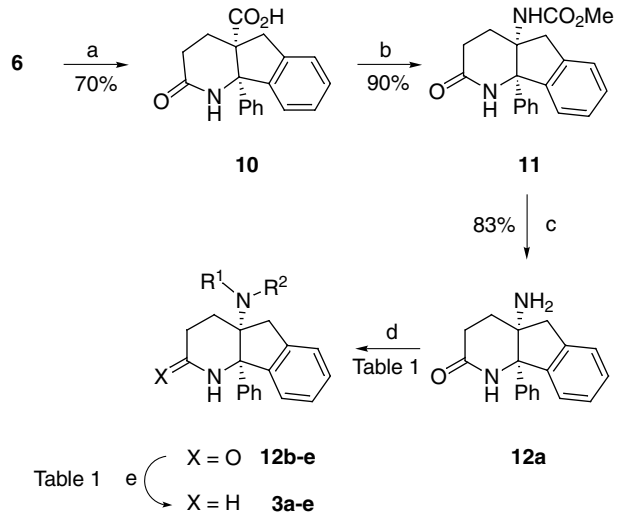
Figure 1. Potential dopamine receptor ligand **1** and NK1 antagonists **3**–**5**, as constrained analogues of some mono- and bicyclic model compounds.



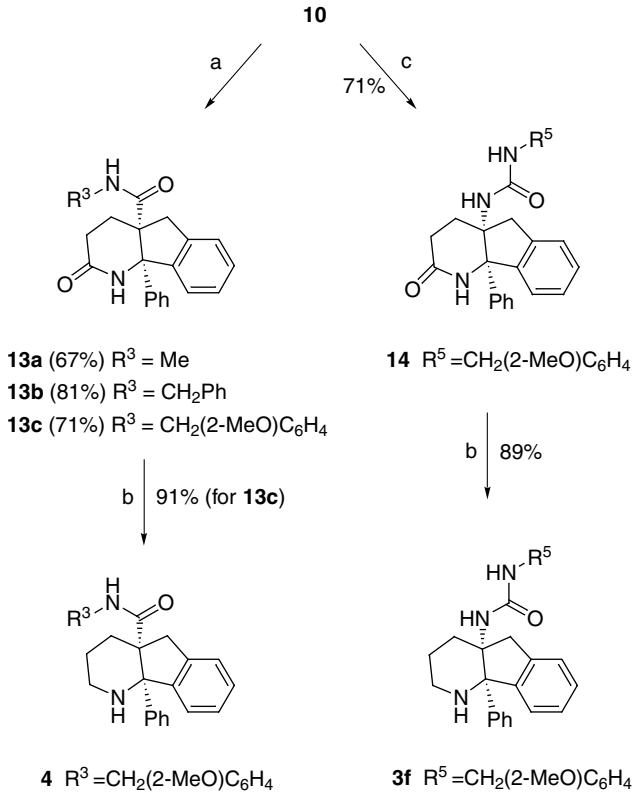
Scheme 1. *Reagents and conditions*: (a) NaH, $(CH_3O)_2CO$, reflux (b) CH_2═CH–CN, *t*-BuOK (cat.), *t*-BuOH (c) PhMgBr, THF, −78°C (d) $MeSO_3H$, rt.

^{1}H NMR analysis. This revealed a NOE correlation between the *ortho*-protons of the Ph group and a downfield 3-methylene proton; the latter proton in turn was shown to be *cis*-disposed relative to the ester group by comparison with the spectrum of ester compound **7**.[1] The diastereoselectivity observed may be explained by the formation of a cyclic Mg^{2+} chelate involving both the ester and ketone carbonyl group. Inspection of a conformationally optimised model of the chelate revealed a nearly flat tricyclic structure with perpendicular orientation for the cyanoethyl side chain. Accordingly, nucleophilic attack will occur preferentially from the sterically less hindered side, resulting in a *cis*-disposition of the ester and Ph group.

Subsequent intramolecular Ritter reaction was accomplished by treatment of the epimeric mixture **9** with methanesulfonic acid at room temperature to produce the tricyclic lactam **6** in 92% yield. Only one stereoisomer was detected by TLC and ^{1}H NMR analysis. Therefore ring closure must proceed diastereoselectively and the original stereochemistry at C-1 of the alcohol epimers **9** apparently is inconsequential, as this centre is transformed into a



Scheme 2. *Reagents and conditions*: a) 20% NaOH–THF (1:1), MeOH, ΔT (b) DPPA, Et_3N, toluene, ΔT, MeOH, ΔT (c) *i*-PrOH–KOH (d) see Table 1 (e) $BH_3{\cdot}Me_2S$, THF, ΔT, yields: see Table 1.



Scheme 3. *Reagents and conditions*: (a) DPPA, Et_3N, DMF, 0°C, 2 h, then alternatively aq. $MeNH_2$, $BnNH_2$ or (2-MeO)$C_6H_4CH_2NH_2$ (b) $BH_3{\cdot}Me_2S$, THF, ΔT (c) DPPA, Et_3N, toluene, ΔT, (2-MeO)$C_6H_4CH_2NH_2$, ΔT.

common carbocation intermediate upon acidolysis of the alcohol function. An X-ray analysis of **6** unambiguously confirmed the *cis*-annelation that was anticipated from the more probable *syn* attack of the nitrile on the planar dibenzylic cation.[1] Consequently, we established the requisite *cis* relation between the transformable ester function and the aryl substituent in the 9b position, in accordance with target structures **3**–**5** and with the 2,3-*cis* substitution pattern characteristic of the model compounds CP-99,994 and L-733,060.

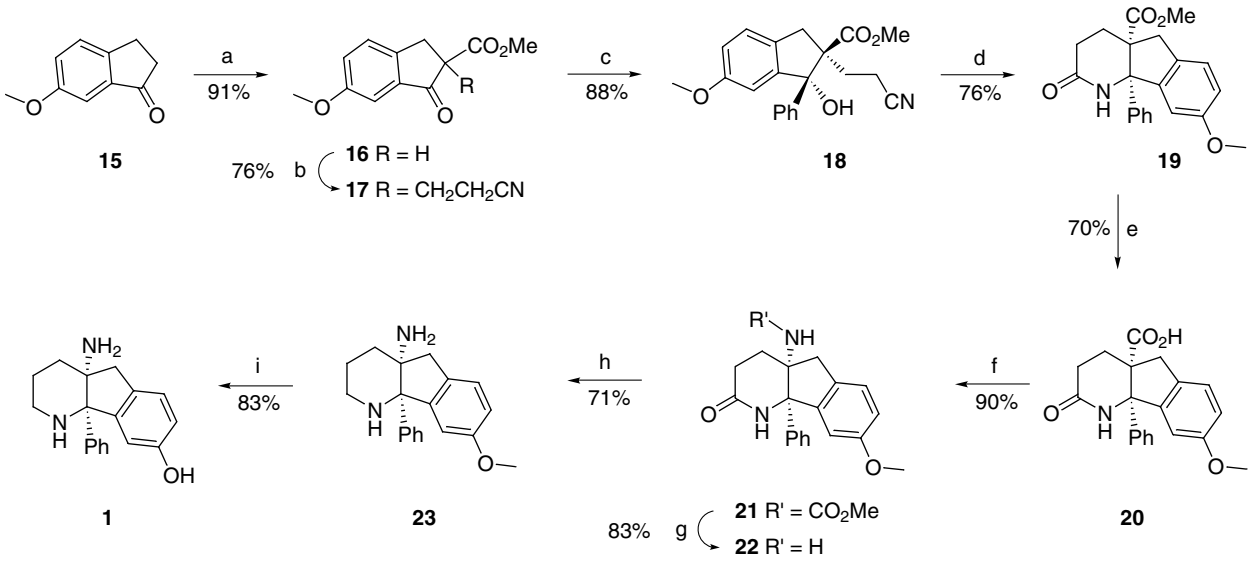
2.2. Preparation of the 4a-amino compounds 3a–e

To convert lactam ester **6** into amine and amide target compounds **3** and **4**, we envisaged saponification of the ester function followed by appropriate activation of the corresponding acid, e.g. as the acyl azide (Scheme 2). Subsequent Curtius reaction of the acyl azide or direct nucleophilic substitution with an amine then would provide suitable precursors of target compounds **3** and **4**, respectively. Drastic reaction conditions were required to hydrolyse the sterically hindered ester function. When using LiOH, MeOH–H_2O (3:1) or Me_3SiOK no conversion of starting material was observed.[10] Finally, hydrolysis was achieved using a 20% aq. NaOH–THF (1:1) solution in MeOH under reflux conditions.[11] Acid **10** was isolated in 70% yield. Subsequent Curtius reaction, when carried out under the usual conditions ($SOCl_2$, toluene; NaN_3), only resulted in recovery of starting acid. However, under modified conditions[12] using diphenylphosphoryl azide and Et_3N in toluene at reflux temperature followed by reaction with MeOH, the methyl carbamate **11** was obtained in 90% yield. Final treatment with *i*-PrOH–KOH under reflux conditions afforded the amine **12a** as a white solid (83%).

Obviously, bridgehead amine **12a** can be used for further functionalisation. Combined with the primary pharmacophore already present, i.e. the 1-phenyl-1,2-diaminoethane moiety, such derivatisation allows to incorporate structural elements characteristic of already known non-peptide Substance P antagonists (Fig. 1: target compounds **3a**–**f**). Starting from amine **12a** and 2-methoxybenzaldehyde, reductive amination was effected using sodium cyanoborohydride as reducing agent,[13] to produce benzylamine **12b** in 82% yield. This reductive amination procedure was extended to reaction of amine **12a** with phenylacetaldehyde and formaldehyde[14] to produce amines **12c**,**d** (Table 1). Final reduction of the lactam carbonyl group of **12a**–**d** using $BH_3{\cdot}DMS$[15] furnished the corresponding tricyclic piperidines **3a**–**d**. In a similar way, following *N*-acylation of amine **12a** with 2-thiopheneacetyl chloride, chemoselective $BH_3{\cdot}DMS$ reduction of the lactam versus the

Table 1. Derivatisation of amine **12a** to form **12b**–**e** and reduction (Scheme 2: condition (e) of **12a**–**e** to give piperidines **3a**–**e**: reaction conditions and yields

Compound **12/3**	R^1	R^2	Reaction conditions (d)	Yield (%) **12b**–**e**	Yield (%) **3a**–**e**
a	H	H			68
b	H	CH_2(2-MeO)C_6H_4	2-$MeOC_6H_4CHO$, $NaCNBH_3$, MeOH, AcOH	82	88
c	H	CH_2CH_2Ph	$PhCH_2CHO$, $NaCNBH_3$, MeOH, AcOH	83	66
d	CH_3	CH_3	CH_2O, $NaCNBH_3$, NaOAc/AcOH pH=5	61	71
e	H	$COCH_2C_4H_3S$	$C_4H_3SCH_2COCl$, THF	78	69

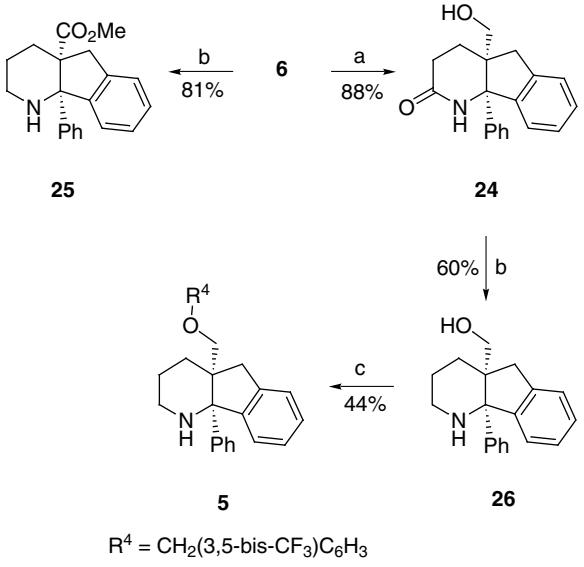


Scheme 4. *Reagents and conditions*: (a) NaH, $(CH_3O)_2CO$, reflux (b) $CH_2{=}CH{-}CN$, *t*-BuOK (cat.), *t*-BuOH (c) PhMgBr, THF, −78°C (d) $MeSO_3H$, rt (e) 20% NaOH–THF (1:1), MeOH, ΔT (f) DPPA, Et_3N, toluene, ΔT, MeOH (g) *i*-PrOH–KOH (h) $BH_3{\cdot}Me_2S$, THF, ΔT (i) L-methionine, $MeSO_3H$.

bridgehead amide function was accomplished for diamide compound **12e**, affording piperidine target compound **3e** in 69% yield.

2.3. Preparation of the 4a-amide and urea compounds 4 and 3f

In the alternative routes depicted in Scheme 3, the acyl azide and isocyanate intermediates formed in the preceding Curtius reaction could be intercepted via addition of an amine reagent at low or high temperature.[16] Thus, treatment of acid **10** with DPPA in DMF at 0°C for 2 h, followed by alternate addition of aqueous methylamine, benzylamine, or 2-methoxybenzylamine furnished amides **13a–c** in 67, 81, and 71% yield, respectively. On the other hand, smooth conversion into urea **14** was observed upon heating acid **10** with DPPA in toluene and subsequent addition of 2-methoxybenzylamine to the isocyanate intermediate. Chemoselective reduction of the lactam carbonyl group of amide **13c** and urea **14** was again accomplished using $BH_3{\cdot}DMS$ to produce the corresponding piperidine target compounds **4** (91%) and **3f** (89%).



Scheme 5. *Reagents and conditions*: $LiAlH_4$, Et_2O (b) $BH_3{\cdot}Me_2S$, THF, ΔT (c) NaH, 2,5-bis$(CF_3)_2C_6H_3CH_2Br$, DMF.

2.4. Preparation of phenolic compound 1

To prepare target compound **1**, a potential dopamine receptor ligand (Fig. 1), a sequence analogous to that described for amine **12a** was applied. Starting from 6-methoxy-1-indanone **15**, this proceeded via Michael addition of the corresponding β-ketoester to form the cyanoethyl compound **17** (yield over 2 steps 69%). Grignard reaction using phenylmagnesium bromide (**18**, 88%), and cyclisation through intramolecular Ritter reaction afforded lactam ester **19** (76%). The latter was transformed into amino lactam **22** (combined yield over 3 steps 51%). Subsequent reduction of the lactam group was effected with $BH_3{\cdot}DMS$ (71%). In the last step the methoxy group was demethylated using L-methionine in methanesulfonic acid,[17] to give the corresponding 8-hydroxy target compound **1** (83%) (Scheme 4).

2.5. Preparation of the 4a-benzyloxymethyl compound 5

To prepare target compound **5**, the bridgehead ester group of **6** has to be transformed into a complex benzyloxymethyl group according to the structure of the model NK-1 antagonist L-733,060 depicted in Fig. 1. In a first approach aimed at reducing both carbonyl functions of lactam ester **6** in one step, a large excess of $LiAlH_4$ was used as the reducing agent. However, these conditions resulted in selective reduction of the ester group to produce the primary alcohol **24**. Presumably salt formation with the $LiAlH_4$ reagent blocks the reduction of the secondary lactam group. Interestingly, a reversed chemoselectivity was observed when applying the $BH_3{\cdot}DMS$ conditions, resulting in exclusive formation of amino ester **25**. In contrast to the reaction with $LiAlH_4$, complexation with the borane reagent may facilitate reduction of the lactam group (Scheme 5). On

attempted *O*-benzylation of the primary alcohol **24**, a mixture of monobenzylated product and a dibenzylated side product was obtained. To avoid this side reaction, the lactam function was reduced in a separate step involving reaction of **24** with BH_3·DMS to form the corresponding piperidine **26**. Finally, the desired conversion to benzylether **5** was accomplished in moderate yield by slow addition of 3,5-bis(trifluoromethyl)benzyl bromide to a DMF solution of the alkoxide anion prepared from **26** and NaH.

2.6. Biological activity

Target compounds **3a**–**f**, **4** and **5** were screened as potential NK1 ligands using a [3H]substance P binding assay to human NK1 receptors stably expressed in CHO cells but were found to be inactive. Likewise, no binding affinity was found for **1** when this was submitted to a binding assay using [3H]spiperone as radioligand for human D2 receptors stably expressed in CHO cells or [125I]iodosulpride as radioligand for human D3 receptors stably expressed in CHO cells.

3. Conclusion

In this paper we have described the synthesis of conformationally constrained, tricyclic analogues of some monocyclic piperidine SP antagonists and a bicyclic dopamine receptor ligand **2**. The key step in our synthetic sequence is the intramolecular Ritter reaction of hydroxynitriles **9** and **18**, resulting in a diastereoselective ring closure to form the *cis*-fused hexahydro-1*H*-indeno[1,2-*b*]pyridines **6** and **19**. Various functional group transformations at the original bridgehead ester position, followed by reduction of the lactam group, resulted in the synthesis of target amines **1** and **3a**–**e**, urea **3f**, and amide **4**. Of particular note is the chemoselectivity observed in the reduction of lactam ester **6** when using either $LiAlH_4$ or BH_3·DMS as the reducing agent. Stepwise reduction of both the ester and lactam function eventually allowed for the synthesis of the benzyloxymethyl ether derivative **5**. No appreciable NK1 or dopamine receptor binding activity was observed for the various target compounds.

4. Experimental

Melting points were determined 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. 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 NMR spectra (δ, ppm) a Bruker Avance 300 and a Bruker AMX 400 spectrometer were used. Analytical and preparative thin layer chromatography was carried out using Merck silica gel 60 PF-224, for column chromatography 70–230 mesh silica gel 60 (E.M. Merck) was used as the stationary phase.

4.1. Preparation of hexahydro-1*H*-indeno[1,2-*b*]pyridine 6

4.1.1. Methyl 1-oxo-2-indanecarboxylate (7). To a stirred suspension of NaH (5.0 g, 80% in mineral oil, 167 mmol) in 20 mL dimethyl carbonate was added dropwise a solution of 1-indanone (10 g, 75.8 mmol) in 70 mL dimethyl carbonate. The mixture was refluxed at 80°C for 2 h. After cooling to rt, H_2O (200 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was subjected to chromatography (850 g of silica gel, 4:1 hexane/EtOAc), followed by crystallisation (from *i*-Pr_2O) to yield 11.9 g (83%) of **7** as a white crystalline solid: mp (°C): 59.8–60.1; IR (KBr, cm^{-1}): 3462, 2954, 1735, 1708; ^1H NMR (400 MHz, $CDCl_3$, ppm): keto–enol (42–58%), δ 7.76 (d, 1H, *J*=8 Hz), 7.63 (ddd, 1H, *J*=8, 8, 1 Hz), 7.50 (dd, 1H, *J*=8, 1 Hz), 7.40 (ddd, 1H, *J*=8, 8, 1 Hz), 3.85 (s, 0.58 OH–enol), 3.79 (s, 3H), 3.73 (dd, 1H, *J*=8, 4 Hz), 3.55 (dd, 0.42 H, *J*=17, 4 Hz), 3.37 (dd, 1H, *J*=17, 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 30.2, 32.4, 52.7, 53.1, 120.7, 124.6, 124.7, 126.5, 126.8, 127.8, 129.3, 135.2, 135.4, 153.5, 169.5, 199.3; EIMS [*m*/*z* (%)]: 190 (M^+, 57), 159 (M^+-OCH_3, 18), 158 (M^+-HOCH_3, 21), 130 ($M^+-HCO_2CH_3$, 100), 77 ($C_6H_5^+$, 33); HRMS: calculated for $C_{11}H_{10}O_3$ 190.0629, found 190.0633.

4.1.2. Methyl 2-(cyanoethyl)-1-oxo-2-indanecarboxylate (8). To a solution of the keto ester **7** (2 g, 10.5 mmol) in *t*-BuOH (25 mL) was added KOtBu (0.32 g, 2.8 mmol) and acrylonitrile (1.4 mL, 21.3 mmol). The heterogeneous reaction mixture was stirred at rt for 72 h. H_2O (25 mL) was added and the suspension was extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was subjected to chromatography (250 g of silica gel, 3:1 hexane/EtOAc) and crystallisation (from *i*-Pr_2O) to provide 2.38 g (93%) of the nitrile **8**: mp (°C): 76.8–77.3; IR (KBr, cm^{-1}): 2955, 2248, 1738, 1710; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.79 (d, 1H, *J*=8 Hz), 7.67 (ddd, 1H, *J*=8, 8, 1 Hz), 7.51 (d, 1H, *J*=8 Hz), 7.44 (ddd, 1H, *J*=8, 8, 1 Hz), 3.72 (d, 1H, *J*=18 Hz), 3.70 (s, 3H), 3.15 (d, 1H, *J*=18 Hz), 2.58 (m, 2H), 2.37 (m, 1H), 2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 13.1, 30.4, 37.4, 53.0, 58.8, 119.1, 125.1, 126.5, 128.2, 134.5, 135.9, 152.3, 170.6, 201.0; EIMS [*m*/*z* (%)]: 243 (M^+, 27), 228 (M^+-CH_3, 45), 212 (M^+-OCH_3, 42), 211 (M^+-HOCH_3, 39), 184 ($M^+-CO_2CH_3$, 100), 183 ($M^+-HCO_2CH_3$, 66), 130 ($M^+-CO_2CH_3$, $-CH_2CH_2CN$, 100), 77 ($C_6H_5^+$, 26); HRMS: calculated for $C_{14}H_{13}NO_3$ 243.0895, found 243.0894.

4.1.3. Methyl 2-(cyanoethyl)-1-hydroxy-1-phenyl-2-indanecarboxylate (9). To a stirred suspension of freshly ground Mg turnings (0.16 g, 6.6 mmol) and I_2 (one crystal) in dry THF (10 mL) was added (via a large cannula) a solution of bromobenzene (0.73 mL, 6.9 mmol) in dry THF (5 mL) dropwise at room temperature. The Grignard reagent began to form immediately, and the solution of bromobenzene was added at such a rate that reflux was maintained. After the addition was complete, the mixture was stirred at rt for an additional 30 min. The mixture was

cooled to −78°C and a solution of the ketone **8** (1.0 g, 4.1 mmol) in dry THF (5 mL) was added dropwise (via a large cannula). The mixture was then warmed to rt overnight and a saturated solution of NH_4Cl (20 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extracts were washed (H_2O, 5×20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to chromatography (100 g of silica gel, 3:1 hexane/EtOAc) and crystallisation from *i*-Pr_2O to yield 1.04 g (79%) of **9** as a colourless crystalline solid: mp (°C): 186.4–186.6; IR (KBr, cm^{-1}): 3450, 3040, 2950, 2200, 1735; ^1H NMR (400 MHz, $CDCl_3$, ppm)—mixture of diastereomers (d.e.=50%):δ 7.31–7.08 (m, 9H), 3.73–3.64 (s, 1H), 3.53 (d, 1H, *J*=16 Hz), 3.18–3.07 (s, 3H), 2.99–2.96 (d, 1H, *J*=16 Hz), 2.50 (m, 1H), 2.10–2.05 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 13.6, 13.9, 28.3, 30.6, 37.1, 38.0, 51.6, 52.1, 63.0, 64.3, 88.0, 88.7, 118.9, 119.4, 124.3–145.8, 172.9, 173.7; EIMS [*m*/*z* (%)]: 321 (M^+, 31), 281 (M^+-CH_2CN, 76), 261 ($M^+-HCO_2CH_3$, 20), 249 (M^+-HOCH_3, $-CH_2CN$, 47), 233 ($M^+-HCO_2CH_3$, −CO, 41), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 33); HRMS: calculated for $C_{20}H_{19}NO_3$ 321.1365, found 321.1361.

4.1.4. *cis*-(4a*R,9b*R**) Methyl-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylate (6).** The alcohol **9** (2 g, 6.2 mmol) was added to 20 mL of CH_3SO_3H at 0°C and the mixture was stirred at rt for 8 h. Ice water (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatographic purification (100 g of silica gel, 50:1 CH_2Cl_2/MeOH) and crystallisation (from EtOH) afforded 1.84 g (92 %) of the lactam **6** as a white crystalline solid: mp (°C): 204.1–204.3; IR (KBr, cm^{-1}): 3443, 3161, 3037, 2943, 1720, 1650; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.73 (s (br), 1H), 7.28–7.36 (m, 3H), 7.20 (m, 4H), 7.00 (m, 2H), 3.90 (d, 1H, *J*=15 Hz), 3.28 (s, 3H), 3.10 (ddd, 1H, *J*=18, 12, 6 Hz), 2.94 (d, 1H, *J*=15 Hz), 2.43 (ddd, 1H, *J*=18, 6, 4 Hz), 2.28 (ddd, 1H, *J*=16, 6, 4 Hz), 2.05 (ddd, 1H, *J*=16, 12, 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 28.1, 28.5, 39.7, 51.5, 56.5, 73.6, 124.3, 124.6, 127.0, 127.8, 127.9, 128.5, 139.6, 140.7, 145.5, 172.0, 172.9; EIMS [*m*/*z* (%)]: 321 (M^+, 2), 293 (M^+-CO, 26), 265 ($M^+-CH_2CH_2CO$, 100), 233 (M^+-CO, $-HCO_2CH_3$, 17), 205 (M^+, $-CH_2CH_2CO$, $-HCO_2CH_3$, 29), 77 ($C_6H_5^+$, 11); HRMS: calculated for $C_{20}H_{19}NO_3$ 321.1365, found 321.1363.

4.2. Preparation of the 4a-amino compounds 3a–e

4.2.1. *cis*-(4a*R,9b*R**)-2-Oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylic acid (10).** The ester **6** (0.1 g, 3.3 mmol) was dissolved in 30 mL of 20% NaOH and THF (1:1). Sufficient MeOH was added to homogenise the mixture, and this solution was refluxed under nitrogen for 12 h. THF and MeOH were removed under reduced pressure, and the aqueous mixture was adjusted to a pH of 7 with concentrated HCl. Extraction of the aqueous phase with EtOAc (3×25 mL), drying ($MgSO_4$) and concentration under reduced pressure gave the crude acid which was further purified by chromatography (20 g of silica gel, 38.5:12:0.5 CH_2Cl_2/EtOAc/AcOH) and crystallisation (from EtOH) to afford 0.07 g (70%) of the acid **10** as a colourless crystalline solid: mp (°C): 273.7–274.0; IR (KBr, cm^{-1}): 3445, 3247, 2931, 2200, 1735, 1649; ^1H NMR (400 MHz, CD_3OD, ppm): δ 7.25 (m, 7H), 7.00 (m, 2H), 3.68 (d, 1H, *J*=16 Hz), 2.88 (ddd, 1H, *J*=18, 12, 6 Hz), 2.85 (d, 1H, *J*=16 Hz), 2.30 (ddd, 1H, *J*=18, 6, 4 Hz), 2.19 (ddd, 1H, *J*=15, 6, 4 Hz), 2.00 (ddd, 1H, *J*=15, 12, 6 Hz); ^{13}C NMR (100 MHz, CD_3OD, ppm): δ 29.2, 29.9, 40.8, 74.4, 97.2, 125.4, 126.0, 128.7, 128.8, 128.8, 128.9, 129.7, 141.2, 142.2, 147.5, 174.8, 175.7; EIMS [*m*/*z* (%)]: 307 (M^+, 0.1), 279 (M^+-CO, 19), 251 ($M^+-CH_2CH_2CO$, 100), 206 (M^+-CO_2H, $-CH_2CH_2CO$, 21), 77 ($C_6H_5^+$, 11); HRMS: calculated for $C_{18}H_{17}NO_2$ 279.1259, found 279.1258.

4.2.2. *cis*-(4a*R,9b*R**) Methyl *N*-(2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-carbamate (11).** To a stirred mixture of the acid **10** (0.15 g, 0.5 mmol) and DPPA (0.63 mL, 3 mmol) in dry toluene (15 mL) was added dropwise Et_3N (1 mL, 7.5 mmol). The mixture was heated under reflux for 20 min at which point MeOH (15 mL) was added. After the addition was complete, the mixture was heated to reflux for an additional 2 h. The mixture was diluted with EtOAc (15 mL) and the solution washed successively with H_2O (10 mL), 1N HCl (10 mL) and aqueous $NaHCO_3$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (65 g of silica gel, 20:1 CH_2Cl_2/MeOH) of the oily residue and crystallisation from EtOH afforded 0.16 g (90%) of the carbamate **11** as a colourless crystalline solid: mp (°C): 260.5–260.9; IR (KBr, cm^{-1}): 3328, 3190, 3148, 3059, 2954, 1712, 1654; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.20 (s, 1H), 7.35 (m, 7H), 7.03 (m, 2H), 3.48 (s, 3H), 3.43 (d, 1H, *J*=15 Hz), 3.25 (d, 1H, *J*=15 Hz), 2.63 (m, 2H), 2.24 (ddd, 1H, *J*=16, 5, 5 Hz), 1.90 (ddd, 1H, *J*=16, 16, 6 Hz); ^{13}C NMR: solubility is too low; EIMS [*m*/*z* (%)]: 336 (M^+, 6), 308 (M^+-CO, 3), 305 (M^+-OCH_3, 2), 280 ($M^+-CH_2CH_2CO$, 74), 261 ($M^+-H_2NCO_2CH_3$, 100), 77 ($C_6H_5^+$, 11); HRMS: calculated for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1467.

4.2.3. *cis*-(4a*R,9b*R**)-4a-Amino-9b-phenyl-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*]pyridin-2-one (12a).** To a stirred solution of the carbamate **11** (0.16 g, 0.48 mmol) in *i*-PrOH (10 mL) was added KOH (0.38 g, 6.7 mmol). The mixture was heated at reflux for 16 h. The solvent was removed under reduced pressure and H_2O (15 mL) was added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual material was subjected to chromatography (45 g of silica gel, 16.7:1 CH_2Cl_2/MeOH) and crystallisation from EtOH to yield 0.11 g (83%) of the amine **12a** as a colourless crystalline solid: mp (°C): 258.6–260.2; IR (KBr, cm^{-1}): 3382, 3175, 3052, 2922, 1662, 1603; ^1H NMR (400 MHz, DMSO-D_6, ppm): δ 8.35 (s, 1H), 7.35 (d, 1H, *J*=6 Hz), 7.25 (m, 6H), 6.90 (d, 2H, *J*=7 Hz), 2.83 (d, 1H, *J*=16 Hz), 2.70 (d, 1H, *J*=16 Hz), 2.64 (ddd, 1H, *J*=18, 10, 6 Hz), 2.08 (ddd, 1H, *J*=18, 6, 5 Hz), 1.73 (m, 2H), 1.20 (s, 2H); ^{13}C NMR (100 MHz, DMSO-D_6, ppm): δ 27.4, 31.6, 44.8, 61.0, 73.3, 124.5, 124.7, 127.0, 127.5, 127.6, 127.7, 139.7, 141.5, 147.1, 170.3; EIMS [*m*/*z* (%)]: 278 (M^+, 1), 277 (M^+-H, 1),

250 (M^+-CO, 50), 234 (M^+-CONH_2, 19), 222 ($M^+-CH_2CH_2CO$, 93), 221 ($M^+-CH_2CH_2CO$, –H, 100), 77 ($C_6H_5^+$, 10); HRMS: calculated for $C_{18}H_{18}NO_2$ 278.1419, found 278.1415.

4.2.4. *cis*-(4a*R,9b*R**)-4a-[(2-Methoxybenzyl)amino]-9b-phenyl-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*] pyridin-2-one (12b).** The pH of a stirred solution of the amine **12a** (0.58 g, 2.08 mmol) in MeOH (10 mL) under argon atmosphere was adjusted to ca. 5 by adding AcOH dropwise. The solution was cooled to 0°C and $NaCNBH_3$ (0.16 g, 2.3 mmol) and 2-methoxybenzaldehyde were added. The mixture was stirred at rt for 12 h. HCl (1N, 10 mL) was added and the mixture was concentrated under reduced pressure. H_2O (25 mL) and subsequently NH_4OH (25 mL) were added to the residue. The aqueous mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (115 g of silica gel, 20:1 CH_2Cl_2/MeOH) of the solid residue and crystallisation (from EtOH) afforded 0.68 g (82%) of the benzylamine **12b** as a colourless crystalline solid: mp (°C): 233.5–234.9; IR (KBr, cm^{-1}): 3370, 3054, 2931, 1776; ^1H NMR (400 MHz, DMSO-D_6, ppm): δ 8.47 (s, 1H), 7.43 (d, 1H, J=8 Hz), 7.28 (m, 6H), 7.16 (dd, 1H, J=8, 2 Hz), 7.10 (d, 1H, J=8 Hz), 6.82 (m, 4H), 3.53 (m, 2H), 3.46 (s, 3H), 2.90 (d, 1H, J=15 Hz), 2.80 (d, 1H, J=15 Hz), 2.53 (ddd, 1H, J=17, 15, 5 Hz), 2.12 (br d, 1H, J=15 Hz), 1.98 (br d, 1H, J=17 Hz), 1.66 (ddd, 1H, J=15, 15, 5 Hz); ^{13}C NMR (100 MHz, DMSO-D_6, ppm): δ 26.8, 27.2, 41.4, 42.8, 54.9, 64.3, 73.9, 110.3, 120.2, 124.4, 124.7, 127.3, 127.4, 127.6, 127.7, 128.0, 128.6, 128.9, 139.6, 141.0, 147.0, 157.0, 170.9; EIMS [*m*/*z* (%)]: 398 (M^+, 9), 370 (M^+-CO, 7), 342 ($M^+-CH_2CH_2CO$, 31), 221 ($M^+-CH_2C_6H_4$–*o*-OCH_3, 82), 206 ($M^+-NHCH_2C_6H_4$–*o*-OCH_3, 16), 121 ($CH_2C_6H_4$–*o*-OCH_3^+, 31), 91 ($C_7H_7^+$, 100), 77 ($C_6H_5^+$, 20); HRMS: calculated for $C_{26}H_{26}N_2O_2$ 398.1994, found 398.2000; Anal. calcd: C 78.36; H 6.58; N 7.03. Found: C 78.22; H 6.81; N 6.94.

4.2.5. *cis*-(4a*R,9b*R**)-9b-Phenyl-4a-[(phenylethyl)amino]-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*]pyridin-2-one (12c).** This was prepared from **12a** and phenylacetaldehyde using a procedure analogous to that for **12b**. Chromatography (16.7:1 CH_2Cl_2/MeOH) and crystallisation from EtOH yielded 0.12 g (83%) of phenethylamine **12c** as a white crystalline solid: mp (°C): 182.5–183.2; IR (KBr, cm^{-1}): 3317, 3048, 2934, 1662; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.15 (m, 10H), 6.90 (m, 4H), 6.29 (s, 1H), 2.93 (d, 1H, J=15 Hz), 2.81 (br s, 1H), 2.68 (m, 2H), 2.57 (m, 2H), 2.48 (m, 1H), 2.18 (ddd, 1H, J=17, 3, 3 Hz), 1.99 (ddd, 1H, J=14, 5, 3 Hz), 1.85 (ddd, 1H, J=14, 13, 3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 27.3, 27.4, 36.6, 41.9, 44.5, 64.5, 74.4, 123.8, 124.9, 125.9, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 139.5, 139.7, 140.1, 146.0, 172.4; EIMS [*m*/*z* (%)]: 382 (M^+, 5), 354 (M^+-CO, 8), 326 ($M^{+\cdot}-CH_2CH_2CO$, 75), 291 ($M^{+\cdot}-CH_2C_6H_5$, 100), 262 ($M^{+\cdot}-NHCH_2CH_2C_6H_5$, 17), 234 ($M^{+\cdot}-NHCH_2CH_2C_6H_5$, –CO, 59), 206 ($M^{+\cdot}-NHCH_2CH_2C_6H_5$, $-CH_2CH_2CO$, 24), 91 ($C_7H_7^+$, 100), 77 ($C_6H_5^+$, 20); HRMS: calculated for $C_{26}H_{26}N_2O$ 382.2045, found 382.2049; Anal. calcd: C 81.46; H 6.85; N 7.32. Found: C 81.76; H 7.00; N 7.44.

4.2.6. *cis*-(4a*R,9b*R**)-4a-(Dimethylamino-9b-phenyl-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*]pyridin-2-one (12d).** To a stirred solution of amine **12a** (0.3 g, 1.1 mmol) in a AcOH/NaOAc buffer (pH 5, 10 mL) was added a solution of formaldehyde (37 wt%, 1 mL). The mixture was stirred at room temperature until it was homogeneous. $NaCNBH_3$ (0.3 g) was added slowly to the reaction mixture (portions of 0.05 g). After 24 h the reaction mixture was brought to pH 1 with aq. 1 M HCl. The mixture then was brought to pH 8 with NH_4OH. The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified using column chromatography (50 g alumina, EtOAc) and crystallisation from EtOAc to yield 0.20 g (61%) of dimethylamine **12d** as a white crystalline solid: mp (°C): 177.8–178.0; IR (KBr, cm^{-1}): 3179, 3060, 2931, 1668; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27–7.15 (m, 6H), 7.12 (dd, 2H, J=8, 2 Hz), 7.02 (d, 1H, J=7 Hz), 6.54 (s (br), 1H), 3.30 (d, 1H, J=15 Hz), 2.89 (d, 1H, J=15 Hz), 2.61 (ddd, 1H, J=18, 8, 7 Hz), 2.34 (ddd, 1H, J=14, 7, 6 Hz), 2.18 (ddd, 1H, J=18, 7, 6 Hz), 2.10 (s, 6H), 1.85 (ddd, 1H, ^2J=14, 8, 7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 172.65, 148.07, 141.58, 139.59, 128.28–76.99, 76.68, 75.06, 71.22, 41.66, 41.22, 30.05, 25.01; EIMS [*m*/*z* (%)]: 306 (M^+, 79), 278 (M^+-CO, 29), 250 ($M^+-CH_2CH_2CO$, 100), 235 ($M^+-CH_2CH_2CONH$, 85), 234 ($M^+-CO-N(CH_3)_2$, 67), 206 ($M^+-N(CH_3)_2-CH_2CH_2CO$, 56) HRMS: calculated for $C_{20}H_{22}N_2O$: 306.1732, found 306.1735; Anal. calcd: C 78.40, H 7.24, N 9.14, found C 78.65, H 7.40, N 8.93.

4.2.7. *cis*-(4a*R,9b*R**)-N^1-(2-Oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-2-(2-thienyl)-acetamide (12e).** To a stirred solution of the amine **12a** (0.28 g, 1.02 mmol) in dry THF (25 mL) under argon atmosphere was added 2-thiopheneacetyl chloride (0.19 mL, 1.52 mmol). The mixture was stirred at room temperature for 30 min, and the solvent was removed under reduced pressure. Water (25 mL) was added to the residue, and the aqueous mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (3×15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residual material was subjected to chromatography (40 g silicagel, EtOAc) and crystallisation from EtOAc to afford 0.31 g (78%) of the amide **12e** as a white crystalline solid: mp (°C): 251.5–251.7; IR (KBr, cm^{-1}): 3377, 3043, 2908, 1652; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.63 (s, 1H), 7.39–7.25 (m, 8H), 6.89–6.85 (m, 3H), 6.55 (dd, 1H, J=3 Hz), 6.42 (s (br), 1H), 3.54–3.44 (m, 3H), 3.12 (d, 1H, J=16 Hz), 2.46–2.42 (m, 2H), 2.08–2.03 (m, 1H), 1.70 (ddd,1H, J=14, 9, 5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 170.08, 168.94, 146.04–124.12, 73.77, 62.40, 42.11, 37.05, 28.21, 27.13; EIMS [*m*/*z* (%)]: 402 (M^+, 1), 346 ($M^+-CO-CO$, 4), 261 ($M^+-C_4H_3SCH_2CONH_2$, 100) HRMS: calculated for $C_{24}H_{22}N_2O_2S$: 402.1402, found 204.1405; Anal. calcd: C 71.62, H 5.51, N 6.96, found C 71.42, H 5.66, N 6.87.

4.2.8. *cis*-(4a*R,9b*R**)-9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-ylamine (3a).** To a stirred solution of the lactam **12a** (0.13 g, 0.46 mmol) in dry THF (20 mL) was added, via a cannula, a solution of BH_3·DMS

in THF (2 M, 0.46 mL, 0.92 mmol). The reaction mixture was refluxed for 1 h. After concentration under reduced pressure, 20 mL of a saturated solution of HCl in MeOH (20 mL) was added to the residue and the solution was refluxed for 0.5 h. Following concentration under reduced pressure, MeOH (20 mL) was added and the solution was again evaporated. Water (20 mL) was added and the solution was brought to pH 9 by careful addition of K_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (75 g of silica gel, 12:1 CH_2Cl_2/MeOH) of the oily residue followed by crystallisation from EtOH yielded 0.079 g (65%) of piperidine **3a** as a colourless crystalline solid: mp (°C):113.2–113.9; IR (KBr, cm^{-1}): 3335, 3060, 2927, 2852; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.35 (m, 9H), 3.0 (d, 1H, J=10 Hz), 2.76 (ddd, 1H, J=10, 10, 2 Hz), 2.57 (d, 2H, J=15 Hz), 1.60 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.7, 35.9, 41.8, 44.9, 61.7, 74.0, 123.3, 125.5, 127.0, 127.3, 127.6, 127.9, 128.3, 141.9, 143.8, 146.3; EIMS [m/z (%)]: 264 (M^+, 8), 248 (M^+-NH_2, 95), 221 ($M^+-C_3H_7$, 100); HRMS: calculated for $C_{18}H_{20}N_2$: 264.1627, found 264.1622.

4.2.9. *cis*-(4a*R,9b*R**)-*N*-(9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-*N*-(2-methoxybenzyl)-amine (3b).** This was prepared from **12b** using the same procedure as for **3a**. Chromatography was carried out using 24:1 CH_2Cl_2/MeOH. Recrystallisation from EtOH yielded 0.21 g (88%) of piperidine **3b** as a colourless crystalline solid: mp (°C): decomposition at 93.1; IR (KBr, cm^{-1}): 3336, 3063, 2928, 2850; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27 (m, 5H), 7.16 (m, 8H), 3.79, (d, 1H, J=15 Hz), 3.63 (d, 1H, J=15 Hz), 3.51 (s, 3H), 3.01 (br d, 1H, J=12 Hz), 2.76 (ddd, 1H, J=12, 12, 3 Hz), 2.67 (d, 1H, J=15 Hz), 2.57 (d, 1H, J=15 Hz), 2.18 (m, 1H), 1.91 (m, 2H), 1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.1, 30.2, 42.1, 42.7, 43.7, 54.9, 65.4, 74.0, 109.8, 120.4, 123.5, 125.3, 127.0, 127.4, 127.7, 128.2, 128.7, 128.8, 129.1, 139.9, 142.5, 146.1, 157.3; EIMS [m/z (%)]: 384 (M^+, 1), 263 (M^+-CH_2Ar, 4), 247 ($M^+-H_2NCH_2Ar$, 100); HRMS: calculated for $C_{26}H_{28}N_2O$: 384.2202, found: 384.2203.

4.2.10. *cis*-(4a*R,9b*R**)-*N*-(9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-*N*-phenylethylamine (3c).** This was prepared from **12c** using the same procedure as for **3a** except that chromatography was carried out using 24:1 CH_2Cl_2/MeOH instead of 33:1 CH_2Cl_2/MeOH. Recrystallisation from EtOH yielded 0.29 g (66%) of piperidine **3c** as a colourless crystalline solid: mp (°C): 204.1–204.3; IR (KBr, cm^{-1}): 3443, 3161, 3037, 2943, 1720, 1650; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.73 (s, 1H), 7.36–7.00 (m, 9H), 3.90 (d, ^2J=15 Hz, 1H), 3.28 (s, 3H), 3.10 (3xd, ^2J=18 Hz, ^3J=10 Hz, ^3J=6 Hz, 1H), 2.94 (d, ^2J=15 Hz, 1H), 2.43 (ddd, ^2J=18 Hz, ^3J=6 Hz, ^3J= 5 Hz, 1H), 2.28 (ddd, ^2J=16 Hz, ^3J=6 Hz, ^3J=5 Hz, 1H), 2.05 (ddd, ^2J=16 Hz, ^3J=10 Hz, ^3J=6 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.2, 31.0, 37.0, 41.9, 43.0, 45.7, 65.0, 73.7, 123.3, 125.3, 125.8, 127.0, 127.1, 127.3, 127.7, 128.1, 128.2, 128.6, 140.2, 142.2, 143.0, 146.3; EIMS [m/z (%)]: 368 (M^+, 1), 247 ($M^+-PhCH_2CH_2NH_2$, 100); HRMS: calculated for $C_{26}H_{28}N_2$ 368.2252, found 368.2244.

4.2.11. *cis*-(4a*R,9b*R**)-*N*-(9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-*N*,*N*-dimethylamine (3d).** This was prepared from **12d** using the same procedure as for **3a** except that chromatography was carried out using 60 g alumina and 95:5 CH_2Cl_2/EtOAc as the eluent. Recrystallisation from CH_2Cl_2/hexane yielded 0.29 g (66%) of piperidine **3d** as a colourless crystalline solid: mp (°C): 164–165; IR (KBr, cm^{-1}): 3317), 3056, 2996, 2945, 1592; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.27–7.15 (m, 8H), 6.93 (d, 1H, J=6 Hz), 3.12 (d, 1H, J=15 Hz), 3.02–2.95 (m, 1H), 2.82–2.75 (m, 1H), 2.57 (d, 1H, J=15 Hz), 2.41 (s, 6H,), 2.35–2.31 (m, 1H), 2.02–1.90 (m, 1H), 1.45–1.39 (m, 1H), 1.27–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 147.71–122.99, 75.06, 69.75, 44.81, 42.15, 41.09, 25.88, 24.55, 16.50; EIMS [m/z (%)]: 292 (M^+, 8), 248 ($M^+-N(CH_3)_2$, 74), 247 ($M^+-HN(CH_3)_2$, 100), 220 ($M^+-N(CH_3)_2-C_2H_4$, 45), 170 ($M^+-C_6H_5-N(CH_3)_2$, 11) HRMS: calculated for $C_{20}H_{24}N_2$ 292.1939, found 292.1935. Anal. calcd: C 82.15, H 8.27, N 9.58, found C 82.01, H 8.02, N 9.37.

4.2.12. *cis*-(4a*R,9b*R**)-*N*^{1}-(9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-2-(2-thienyl)acetamide (3e).** This was prepared from **12e** by following the same procedure as for **3a** except that chromatography was carried out using EtOAc as the eluent instead of 33:1 CH_2Cl_2/MeOH. Recrystallisation from CH_2Cl_2/hexane yielded 0.15 g (69%) of piperidine **3e** as a colourless crystalline solid: mp (°C): 151–152; IR (KBr, cm^{-1}): 3392, 3298, 3048, 2921, 1663; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31–7.25 (m, 4H), 7.15–7.09 (m, 3H), 7.02 (dd, 1H, J=5, 3 Hz), 7.03–7.01 (m, 1H), 6.88–6.86 (m, 2H, J=7 Hz), 6.69 (dd, 1H, J=3 Hz), 6.04 (s (br), 1H), 3.63–3.51 (m, 2H), 3.42 (d, 1H, J=16 Hz), 2.93 (d, 1H, J=16 Hz), 2.89–2.87 (m, 1H), 2.73–2.68 (m, 1H), 2.62–2.58 (m, 1H), 2.01 (s (br), 1H), 1.64–1.52 (m, 1H), 1.36–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 169.18, 128.45–122.60, 73.35, 62.51, 42.25, 41.48, 38.23, 31.15, 22.13; EIMS [m/z (%)]: 388 (M^+, 2), 248 ($M^+-C_4H_3SCH_2CONH$, 23), 247 ($M^+-C_4H_3SCH_2CONH_2$, 100), 218 ($M^+-C_4H_3SCH_2CONH-CH_2NH_2$, 8), 97 ($C_4H_3SCH_2^+$, 11); HRMS: calculated for $C_{24}H_{24}N_2OS$: 388.1609, found 388.1602; Anal. calcd: C 74.19, H 6.23, N 7.21, found C 73.99, H 6.09, N 7.21.

4.3. Preparation of the 4a-amide and urea compounds

4.3.1. *cis*-(4a*R,9b*R**)-*N*^{4a}-Methyl-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxamide (13a).** To a cold (0°C), stirred solution of the acid **10** (0.75 g, 2.4 mmol) in dry DMF (5 mL) was DPPA (0.9 mL, 3.9 mmol) and Et_3N (0.91 mL, 6.6 mmol). After reaction for 2 h at 0°C to form the acyl azide, $MeNH_2$ (40 wt% in water, 0.30 g, 3.9 mmol) was added. The reaction was allowed to proceed by stirring at rt for 16 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The oily residue was subjected to chromatography (125 g of silica gel, 33:1 CH_2Cl_2/MeOH) and recrystallysation from

CH_2Cl_2 to afford 0.52 g (67%) of the carboxamide **13a** as a white crystalline solid: mp (°C): 221.3–221.9; IR (KBr, cm^{-1}): 3332, 3180, 3030, 1642; ^1H NMR (300 MHz, DMSO-D_6, ppm): δ 8.49 (s (br), 1H), 7.36–7.13 (m, 7H), 7.06 (q (br), 1H, J=4 Hz), 6.93–6.90 (m, 2H), 3.46 (d, 1H, J=16 Hz), 2.86 (d, 1H, J=16 Hz), 2.77–2.66(m, 1H), 2.16 (d, 3H, J=4 Hz), 2.12–1.97 (m, 2H), 1.81–1.70 (m, 1H); ^{13}C NMR (75 MHz, DMSO-D_6, ppm): δ 172.5, 170.9, 147.6, 142.0, 140.3, 128.3, 127.9, 127.7, 127.4, 127.2, 125.0, 124.8, 88.3, 73.3, 56.2, 29.9, 28.9, 26.1; EIMS [m/z (%)]: 320 (M^+, 15), 289 ($M^+-CH_3NH_2$, 21), 264 ($M^+-CH_2CH_2CO$, 80), 263 ($M^+-OCNCH_2CH_3$, 100); HRMS: calculated for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1529.

4.3.2. *cis*-(4a*R,9b*R**)-*N*^{4a}-Benzyl-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxamide (13b).** This was prepared from acid **10** and benzylamine using the procedure given for **13a**. Column chromatography (95:5 CH_2Cl_2/MeOH) and crystallisation from EtOH afforded 81% of carboxamide **13b** as a white crystalline solid: mp (°C): 251.2–251.5; IR (KBr, cm^{-1}): 3331, 3192, 3032, 1632; ^1H NMR (300 MHz, DMSO-D_6, ppm): δ 8.61 (s (br), 1H), 7.82 (t (br), 1H), 7.37–7.10 (m, 10H), 7.9–7.96 (m, 2H), 7.62–7.60 (m, 2H), 4.19 (dd, 1H, J=15, 6 Hz), 3.80 (dd, 1H, J=15, 5 Hz), 3.51 (d, 1H, J=16 Hz), 2.91 (d, 1H, 16 Hz), 2.76–2.65 (m, 1H), 2.09–1.81 (m, 3H); ^{13}C NMR (100 MHz, DMSO-D_6, ppm): δ 172.0, 170.9, 148.1, 141.9, 139.6, 139.5, 128.3, 128.1, 127.9, 127.6, 127.2, 172.1, 126.8, 126.6, 124.9, 124.8, 72.9, 56.2, 55.3, 52.7, 30.8, 28.8; EIMS [m/z (%)]: 396 (M^+, 30), 340 ($M^+-CO-CO$, 100), 290 ($M^+-NHCH_2C_6H_5$, 19), 262 ($M^+-CONHCH_2C_6H_5$, 99), 91 ($C_6H_5CO^+$, 97); HRMS: calculated for $C_{26}H_{24}N_2O_2$ 396.1838, found 396.1841.

4.3.3. *cis*-(4a*R,9b*R**)-*N*^{4a}-(2-Methoxybenzyl)-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxamide (13c).** This was prepared from acid **10** and 2-methoxybenzylamine using the procedure given for **13a**. Column chromatography (33:1 CH_2Cl_2/MeOH) and crystallisation from EtOH afforded 71% of carboxamide **13c** as a white crystalline solid: mp (°C): 257.3–258.0; IR (KBr, cm^{-1}): 3327, 3186, 3037, 2918, 1636; ^1H NMR (400 MHz, DMSO-D_6, ppm): δ 8.55 (s, 1H), 7.57 (t, 1H, J=6 Hz), 7.40–6.62 (m, 13H), 4.02 (dd, 1H, J=16, 6 Hz), 3.85 (dd, 1H, J=16, 6 Hz), 3.71 (s, 3H), 3.52 (d, 1H, J=15 Hz), 2.95 (d, 1H, J=15 Hz), 2.68 (ddd, 1H, J=18, 12, 6 Hz), 2.05 (m, 2H), 1.85 (ddd, 1H, J=18, 12, 5 Hz); ^{13}C NMR: solubility was too low; EIMS [m/z (%)]: 426 (M^+, 32), 370 ($M^+-CH_2CH_2CO$, 34), 305 ($M^+-CH_2C_6H_4$–o-OCH_3, 4), 263 ($M^+-OCNCH_2C_6H_4$–o-OCH_3, 75), 204 ($M^+-CONHCH_2C_6H_4$–o-OCH_3, $-CH_2CH_2CO$, 75), 121 ($-CH_2C_6H_4$–o-OCH_3^+, 100), 77 ($C_6H_5^+$, 22); HRMS: calculated for $C_{27}H_{26}N_2O_3$ 426.1943, found 426.1951; Anal. calcd: C 76.03; H 6.14; N 6.57. Found: C 75.80; H 6.01; N 6.45.

4.3.4. *cis*-(4a*R,9b*R**)-*N*^{4a}-(2-Methoxybenzyl)-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxamide (4).** This was prepared from **13c** by applying the procedure given for **3a** except that chromatography was carried out using 33:1 CH_2Cl_2/MeOH instead of 12:1 CH_2Cl_2/MeOH. After crystallisation from EtOH, 0.29 g (91%) of piperidine **4** was isolated as a colourless crystalline solid: mp (°C): 154.1–154.4; IR (KBr, cm^{-1}): 3335, 3287, 3032, 2949, 1637; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.75 (br t, 1H, J=6 Hz), 7.37–6.86 (m, 13H), 4.39 (dd, 1H, J=14, 6 Hz), 4.14 (dd, 1H, J=14, 6 Hz), 3.92 (s, 3H), 3.54 (d, 1H, J=16 Hz), 3.04 (m, 1H), 2.85 (ddd, 1H, J=12, 12, 3 Hz), 2.66 (d, 1H, J=16 Hz), 2.41 (br.s, 1H), 1.95 (m, 2H), 1.51 (ddd, 1H, J=13, 13, 3 Hz), 1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.3, 34.0, 39.0, 40.3, 41.0, 55.16, 55.8, 71.4, 110.0, 120.6, 122.8, 126.6, 126.9, 126.9, 127.1, 127.6, 127.7, 128.4, 129.8, 142.1, 143.0, 145.4, 157.6, 173.7; EIMS [m/z (%)]: 291 ($M^+-CH_2C_6H_4$–o-OCH_3, 2), 248 ($M^+-NHCH_2C_6H_4$–o-OCH_3, 100), 220 ($M^+-CH_2NHCH_2C_6H_4$–o-OCH_3, 8), 121 ($CH_2C_6H_4$–o-OCH_3^+, 9), 91 ($C_7H_7^+$, 25), 77 ($C_6H_5^+$, 6); HRMS: calculated $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2146; Anal. calcd: C 78.61; H 6.84; N 6.79. Found: C 78.63; H 6.91; N 6.69.

4.3.5. *cis*-(4a*R,9b*R**)-*N*-(2-Methoxybenzyl)-*N*′-(2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]-pyridin-4-yl)-urea (14).** To a stirred mixture of the acid **10** (0.75 g, 2.4 mmol) and DPPA (2.16 mL, 9.6 mmol) in dry toluene (10 mL) was added dropwise Et_3N (1.4 mL, 9.6 mmol), and the mixture was heated at reflux for 20 min. Then 2-methoxybenzylamine (0.7 mL, 4.8 mmol) was added. After completing the addition, the mixture was heated at reflux for an additional 1 h. After being cooled to rt, the mixture was diluted with EtOAc (15 mL) and the organic phase washed successively with H_2O (10 mL), 1N HCl (10 mL) and aqueous $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residual material was subjected to chromatography (135 g of silica gel, 33:1 CH_2Cl_2/MeOH) and crystallisation from EtOH to afford 0.95 g (88%) of the urea **14** as a white crystalline solid: mp (°C): 239.4–239.6; IR (KBr, cm^{-1}): 3359, 3299, 3056, 2926, 1666, 1639; ^1H NMR (400 MHz, DMSO-D_6, ppm): δ 8.62 (s, 1H), 7.30–6.89 (m, 13H), 6.45 (t, 1H, J=4 Hz), 5.30 (s, 1H), 4.10 (dd, 1H, J=13, 4 Hz), 3.92 (dd, 1H, J=13, 4 Hz), 3.80 (s, 3H), 3.4 (d, 1H, J=16 Hz), 3.20 (d, 1H, J=16 Hz), 2.44 (ddd, 1H, J=17, 9, 4 Hz), 2.35 (m, 1H), 2.08 (m, 1H), 1.67 (ddd, 1H, J=14, 9, 4 Hz); ^{13}C NMR (100 MHz, DMSO-D_6, ppm): δ 27.3, 28.7, 37.8, 43.2, 55.2, 62.0, 74.1, 110.4, 120.1, 124.1, 124.6, 127.3, 127.4, 127.6, 127.8, 127.9, 128.0, 128.1, 139.9, 141.0, 146.6, 156.6, 157.1, 170.2; EIMS [m/z (%)]: 441 (M^+, 0.6), 385 ($M^+-CH_2CH_2CO$, 1), 304 ($M^+-H_2NCH_2C_6H_4$–o-OCH_3, 2), 261 ($M^+-H_2NCONHCH_2C_6H_4$–o-OCH_3, 100), 121 ($CH_2C_6H_4$–o-OCH_3^+, 33), 77 ($C_6H_5^+$, 18); HRMS: calculated for $C_{27}H_{27}N_3O_3$ 441.2052, found 441.2054.

4.3.6. *cis*-(4a*R,9b*R**)-*N*-(9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)-*N*′-(2-methoxybenzyl)urea (3f).** This was prepared from **14** by applying the procedure given for **3a** except that column chromatography was carried out using as the eluent 16.7:1 CH_2Cl_2/MeOH instead of 33:1 CH_2Cl_2/MeOH. Crystallisation from EtOH yielded 0.17 g (89%) of piperidine **3f** as a colourless crystalline solid: mp (°C): 231.7–232.1; IR (KBr, cm^{-1}): 3300, 3061, 2931, 1634; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.30 (m, 11H, 6.89 (d, 1H,

J=8 Hz), 6.85 (d, 1H, J=8 Hz), 4.73 (s, 1H), 4.47 (t, 1H, J=6 Hz), 4.11 (br d, 2H, J=6 Hz), 3.84 (s, 3H), 3.35 (d, 1H, J=16 Hz), 2.97 (d, 1H, J=16 Hz), 2.92 (br d, 1H, J=12 Hz), 2.76 (ddd, 1H, J=12, 12, 2 Hz), 2.62 (br d, 1H, J=14 Hz), 2.00 (br s, 1H), 1.70 (m, 1H), 1.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.3, 31.9, 40.5, 41.6, 43.2, 55.2, 62.2, 77.0, 110.1, 120.6, 122.7, 125.5, 127.1, 127.4, 127.5, 127.8, 128.3, 128.5, 128.9, 156.1, 156.8; EIMS [m/z (%)]: 428 (M^+, 0.2), 249 ($M^+-HNCONHCH_2C_6H_4$–o-OCH_3, 6), 248 ($M^+-H_2NCONHCH_2C_6H_4$–o-OCH_3, 100), 121 ($CH_2C_6H_4$–o-OCH_3^+, 7), 91 ($C_7H_7^+$, 14), 77 ($C_6H_5^+$, 6); HRMS: calculated for $C_{18}H_{17}N$ 248.1439, found 248.1424; Anal. calcd: C 75.85; H 6.84; N 9.83. Found: C 75.56; H 6.83; N 9.64.

4.4. Preparation of phenolic compound 1

Starting from 6-methoxy 1-indanone, compound **19** was prepared according to the procedure given for compound **3a**.

4.4.1. *cis*-(4a*R,9b*R**) Methyl 6-methoxy-1-oxo-2-indanecarboxylate (16).** This was purified by column chromatography (7:3 hexanes/EtOAc) followed by crystallisation from *i*-PrOH. Yield: 91%; mp (°C): 74–75; IR (KBr, cm^{-1}): 3448, 3014, 2949, 2845, 1735, 1710; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.38 (d, 1H, J=8 Hz), 7.23 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 3.75 (dd,1H, J=16, 3 Hz), 3.47 (dd, 1H, J=8, 3 Hz), 3.30 (dd, 1H, J=16, 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 29.6, 52.7, 53.9, 55.7, 105.7, 124.0, 127.2, 136.4, 146.5, 159.8, 169.6, 199.3; EIMS [m/z (%)]: 220 (M^+, 47), 188 (M^+-HOCH_3, 20), 161 ($M^+-CO_2CH_3$, 42), 160 ($M^+-HCO_2CH_3$, 100); HRMS: calculated for $C_{12}H_{12}O_4$ 220.0736, found 220.0734.

4.4.2. *cis*-(4a*R,9b*R**) Methyl 2-(cyanoethyl)-6-methoxy-1-oxo-2-indanecarboxylate (17).** This was purified by column chromatography (7:3 hexanes/EtOAc). Yield: 76%; IR (NaCl, cm^{-1}): 2954, 2840, 2248, 1740, 1708; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40 (d, 1H, J=9 Hz), 7.25 (dd, 1H, J=9, 2 Hz), 7.18 (d, 1H, J=2 Hz), 3.83 (s, 3H), 3.69 (s, 3H), 3.62 (d, 1H, J=16 Hz), 3.08 (d, 1H, J=16 Hz), 2.58 (m, 2H), 2.37 (m, 1H), 2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 12.7, 30.0, 36.3, 52.6, 55.3, 59.2, 105.6, 118.9, 125.0, 126.9, 135.4, 145.0, 159.7, 170.3, 200.7; EIMS [m/z (%)]: 273 (M^+, 80), 241 (M^+-HOCH_3, 32), 213 ($M^+-HCO_2CH_3$, 60), 173 ($M^+-HCO_2CH_3-CH_2CN$, 100); HRMS: calculated for $C_{15}H_{15}NO_4$ 273.1001, found 273.1002.

4.4.3. *cis*-(4a*R,9b*R**) Methyl 2-(cyanoethyl)-1-hydroxy-6-methoxy-1-phenyl-2-indanecarboxylate (18).** This was purified by column chromatography (7:3 hexanes/EtOAc) and crystallisation from *i*-PrOH. Yield: 88%; mp (°C): 145–148; IR (KBr, cm^{-1}): 3420, 3030, 2950, 2839, 2255, 1723; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.25 (m, 5H), 7.13 (dd, 1H, J=8, 2 Hz), 6.90 (dd, 1H, J=8, 2 Hz), 6.65 (d, 1H, J=2 Hz), 3.72 (s, 3H), 3.54 (d, 1H, J=16 Hz), 3.23 (s, 3H), 2.87 (d, 1H, J=16 Hz), 2.73 (s (br), 1H), 2.55 (ddd, 1H, J=13, 10, 6 Hz), 2.32 (ddd, 1H, J=17, 10, 6 Hz), 2.26 (ddd, 1H, J=17, 10, 6 Hz), 2.16 (ddd, 1H, J=13, 10, 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 14.0, 28.7, 36.3, 51.7, 55.4, 64.9, 108.8, 116.0, 119.5, 125.7, 126.0, 127.8, 127.9, 132.5, 141.9, 146.3, 159.8, 172.9; EIMS [m/z (%)]: 351 (M^+, 34), 333 (M^+-H_2O, 70), 311 (M^+-CH_2CN, 36), 291 ($M^+-HCO_2CH_3$, 32), 279 ($M^+-CH_2CN-CH_3OH$, 36), 251 ($M^+-HCO_2CH_3-CH_2CN$, 54), 237 ($M^+-HCO_2CH_3-CH_2CH_2CN$, 51), 105 ($C_6H_5CO^+$, 100), 77 ($C_6H_5^+$, 50); HRMS: calculated for $C_{21}H_{21}NO_4$ 351.1471, found 351.1470; Anal. calcd: C 71.78; H 6.02; N 3.99. Found: C 71.57; H 6.12; N 3.96.

4.4.4. *cis*-(4a*R,9b*R**) Methyl 8-methoxy-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylate (19).** This was purified by column chromatography (97:3 CH_2Cl_2/MeOH) and crystallisation from EtOH. Yield: 76%; mp (°C): 333–334; IR (KBr, cm^{-1}): 3448, 3058, 2953, 2850, 1724, 1662; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.20 (m, 4H), 6.90 (m, 3H), 6.60 (d, 1H, J=2 Hz), 6.54 (s (br), 1H), 3.78 (d, 1H J=15 Hz), 3.73 (s, 3H), 3.30 (s, 3H), 2.82 (d, 1H, J=15 Hz), 2.50 (ddd, 1H, J=17, 10, 4 Hz), 2.25 (m, 2H), 2.07 (ddd, 1H, J=16, 10, 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 28.6, 29.3, 30.9, 51.9, 55.4, 59.1, 60.0, 110.7, 118.9, 124.4, 127.5, 128.3, 128.5, 130.0, 139.7, 142.8, 160.5, 171.1, 172.0; EIMS [m/z (%)]: 351 (M^+, 12), 323 (M^+-CO, 6), 295 ($M^+-CH_2CH_2CO$, 100), 264 ($M^+-CH_2CH_2CO-OCH_3$, 14), 236 ($M^+-CH_2CH_2CO-CO_2CH_3$, 100); HRMS: calculated for $C_{21}H_{21}NO_4$ 351.1471, found 351.1470; Anal. calcd: C 71.78; H 6.02; N 3.99. Found: C 71.56; H 6.22; N 3.86.

4.4.5. *cis*-(4a*R,9b*R**)-8-Methoxy-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylic acid (20).** This was purified by column chromatography (38.5:12:0.5 CH_2Cl_2/EtOAc/AcOH) and crystallisation from EtOH. Yield: 70%; mp (°C): 309–311; IR (KBr, cm^{-1}): 3391, 3246, 3019, 2933, 2850, 1731, 1661; ^{1}H NMR (400 MHz, CD_3OD, ppm): δ 7.25–7.20 (m, 4H), 7.05–7.03 (m, 2H), 6.90 (dd, 1H, J=8, 2 Hz), 6.85 (d, 1H, J=2 Hz), 3.73 (s, 3H), 3.59 (d, 1H, J=16 Hz), 2.96 (ddd, 1H, J=18, 12, 6 Hz), 2.77 (d, 1H, J=16 Hz), 2.29 (ddd, 1H, J=18, 6, 3 Hz), 2.16 (ddd, 1H, J=14, 6, 3 Hz), 2.03 (ddd, 1H, J=14, 12, 6 Hz); ^{13}C NMR (100 MHz, CD_3OD, ppm): δ 29.2, 30.3, 40.1, 55.9, 57.8, 74.4, 110.0, 116.4, 126.8, 128.7, 128.8, 128.9, 132.8, 142.2, 148.9, 161.6, 175.0, 175.7; EIMS [m/z (%)]: 337 (M^+, 13), 309 (M^+-CO, 31), 293 (M^+-CO_2, 40), 281 ($M^+-CH_2CH_2CO$, 100), 280 (M^+-CH_2CONH, 94), 234 ($M^+-OCH_3-CH_2CH_2CONH_2$, 37); HRMS: calculated for $C_{20}H_{19}NO_4$ 337.1314, found 337.1312; Anal. calcd: C 71.20; H 5.68; N 4.15. Found: C 70.95; H 5.53; N 3.95.

4.4.6. *cis*-(4a*R,9b*R**) Methyl *N*-(8-methoxy-2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*] pyridin-4-yl)carbamate (21).** This was purified by column chromatography (EtOAc) and crystallisation from CH_2Cl_2/hexanes. Yield: 90%; mp (°C): 255–256; IR (KBr, cm^{-1}): 3383, 3051, 2934, 2851, 1713, 1660; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40–7.36 (m, 3H), 7.22 (d, 1H, J=8 Hz), 7.07–7.05 (m, 2H), 6.90 (dd, 1H, J=8, 2 Hz), 6.62 (d, 1H, J=2 Hz), 6.45 (s (br), 1H), 3.75 (s, 3H), 3.53 (s, 3H), 3.45 (d, 1H, J=16 Hz), 3.08 (d, 1H, J=16 Hz), 2.79 (ddd, 1H, J=18, 4, 4 Hz), 2.62 (ddd, 1H, J=18, 12, 5 Hz), 2.33 (ddd, 1H, J=18, 5, 4 Hz), 2.01 (ddd, 1H, J=18, 12, 4 Hz), 1.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 27.4, 27.5, 41.9,

51.8, 55.5, 62.5, 74.9, 108.4, 115.6, 126.0, 127.0, 129.0, 129.5, 121.2, 139.5, 146.1, 155.4, 160.0, 171.7; EIMS [*m/z* (%)]: 366 (M^+, 23), 338 (M^+-CO, 8), 310 ($M^+-CH_2CH_2CO$, 600), 291 ($M^+-H_2NCO_2Me$, 100) HRMS: calculated for $C_{21}H_{22}N_2O_4$ 366.1580, found 366.1584; Anal. calcd: C 68.84; H 6.05; N 7.65. Found: C 68.75; H 5.93; N 7.58.

4.4.7. *cis*-(4a*R,9b*R**)-4a-Amino-8-methoxy-9b-phenyl-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*]pyridin-2-one (22).** This was purified by column chromatography (9:1 CH_2Cl_2/MeOH) and crystallisation from CH_2Cl_2/hexanes. Yield: 83%; mp (°C): 234–235; IR (KBr, cm^{-1}): 3383, 3051, 2935, 2851, 1663; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.36–7.32 (m, 3H), 7.20 (d, 1H, *J*=8 Hz), 7.11–7.09 (m, 2H), 6.88 (dd, 1H, *J*=8, 2 Hz), 6.63 (d, 1H, *J*=2 Hz), 6.26 (s (br), 1H), 3.76 (s, 3H), 2.95 (d, 1H, *J*=15 Hz), 2.77 (d, 1H, *J*=15 Hz), 2.71 (ddd, 1H, *J*=18, 10, 6 Hz), 2.43 (ddd, 1H, *J*=18, 6, 6 Hz), 2.04 (ddd, 1H, *J*=14, 10, 6 Hz), 1.82 (ddd, 1H, *J*=14, 6, 3 Hz), 0.96 (s (br), 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 27.8, 31.2, 43.8, 55.3, 62.1, 74.8, 109.2, 115.1, 126.0, 127.9, 128.2, 128.4, 131.8, 140.0, 147.0, 159.7, 171.4; EIMS [*m/z* (%)]: 308 (M^+, 5), 280 (M^+-CO, 67), 264 ($M^+-CO-NH_2$, 20), 252 ($M^+-CH_2CH_2CO$, 85), 251 ($M^+-CH_2CH_2COH$, 100), 77 ($C_6H_5^+$, 8); HRMS: calculated for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1520; Anal. calcd: C 74.00; H 6.54; N 9.08. Found: C 73.90; H 6.41; N 9.09.

4.4.8. *cis*-(4a*R,9b*R**)-8-Methoxy-9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-ylamine (23).** This was purified by column chromatography (24:1 CH_2Cl_2/MeOH) and crystallisation from EtOH. Yield: 71%; mp (°C): 155–156; IR (KBr, cm^{-1}): 3289, 3051, 2938, 2850; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.25–7.20 (m, 5H), 7.18 (d, 1H, *J*=8 Hz), 7.14–7.11 (m, 2H), 6.84 (dd, 1H, *J*=8, 2 Hz), 6.63 (d, 1H, *J*=2 Hz), 3.80 (s, 3H), 2.98–2.93 (m, 1H), 2.76 (ddd, 1H, *J*=12, 12, 2 Hz), 2.51 (d, 1H, *J*=15 Hz), 2.43 (d, 1H, *J*=15 Hz), 1.80–1.39 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.6, 35.9, 41.8, 44.1, 55.4, 61.9, 73.7, 108.7, 113.2, 126.1, 127.2, 127.8, 128.2, 133.7, 143.5, 147.7, 159.3; EIMS [*m/z* (%)]: 294 (M^+, 31), 278 (M^+-NH_2, 100), 251 ($M^+-CH_2CH_2NH$, 65); HRMS: calculated for $C_{19}H_{22}N_2O$ 294.1732, found 294.1725; Anal. calcd: C 77.52; H 7.53; N 9.52. Found: C 77.24; H 7.76; N 9.26.

4.4.9. *cis*-(4a*R,9b*R**)-4a-Amino-9b-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridin-8-ol (1).** To a stirred solution of amine **23** (0.25 g, 0.86 mmol) in 15 mL methanesulfonic acid was added L-metionine (0.38 g, 2.6 mmol). The reaction mixture was stirred at room temperature under nitrogen for seven days. Ice was added and the pH was adjusted to 7–8 with K_2CO_3. The aq. mixture was extracted with CH_2Cl_2 and the combined organic layers were dried on Na_2SO_4 and concentrated under reduced pressure. Purification was carried out by column chromatography (24:1 CH_2Cl_2/MeOH) and crystallisation from EtOH to yield 0.19 g (83%) of **1** as a white crystalline solid: mp (°C): 253–255; IR (KBr, cm^{-1}): 3289, 3248, 3052, 2937; ^1H NMR (400 MHz, DMSO-D_6, ppm): δ 9.12 (s(br), 1H), 7.23–7.15 (m, 2H), 7.08–7.03 (m, 3H), 6.65 (dd, 1H, *J*=8, 2 Hz), 6.62 (d, 1H, *J*=2 Hz), 2.81–2.79 (m, 1H), 2.56–2.50 (m, 1H), 2.28 (d, 1H, *J*=15 Hz), 2.24 (d, 1H, *J*=15 Hz), 1.73–1.65 (m, 1H), 1.63 (m, 1H), 1.41–1.33 (m, 1H), 1.27–1.21 (m, 1H), 1.17 (s(br), 1H); ^{13}C NMR (100 MHz, DMSO-D_6, ppm): δ 22.0, 36.0, 41.4, 44.2, 61.2, 73.0, 110.6, 114.1, 125.4, 126.5, 127.2, 128.0, 131.3, 144.1, 148.0, 156.5; EIMS [*m/z* (%)]: 280 (M^+, 23), 264 (M^+-NH_2, 100), 263 (M^+-OH, 46), 237 ($M^+-CH_2CH_2NH$, 72); HRMS: calculated for $C_{18}H_{20}N_2O$ 280.1576, found 280.1575; Anal. calcd: C 77.11; H 7.19; N 9.99. Found: C 77.33; H 7.42; N 9.69.

4.5. Preparation of 4a-benzyloxymethyl compound

4.5.1. *cis*-(4a*R,9b*R**)-4a-(Hydroxymethyl)-9b-phenyl-1,3,4,4a,5,9b-hexahydro-2*H*-indeno[1,2-*b*]pyridin-2-one (24).** To a stirred suspension of the ester **6** (1 g, 3.1 mmol) in dry ether (10 mL) was added at 0°C $LiAlH_4$ (5 g, 15.5 mmol). The mixture was stirred at rt under argon atmosphere for 1 h. MeOH (5 mL) and H_2O (5 mL) were added cautiously and the mixture was acidified with 1 M HCl. The aqueous phase was separated and extracted further with EtOAc (5×25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual material was subjected to chromatography (145 g of silica gel, 25:1 CH_2Cl_2/MeOH) and crystallisation from EtOH to yield 0.81 g (88%) of the alcohol **24** as a white crystalline solid: mp (°C): 86.2–87.1; IR (KBr, cm^{-1}): 3386, 3032, 2959,1647; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.28 (m, 7H), 6.95 (br s, 2H), 3.20 (d, 1H, *J*=11 Hz), 3.03 (d, 1H, *J*=15 Hz), 2.88 (d, 1H, *J*=15 Hz), 2.77 (d, 1H, *J*=11 Hz), 2.58 (ddd, 1H, *J*=18, 9, 5 Hz), 2.32 (ddd, 1H, *J*=18, 5, 5 Hz), 2.05 (ddd, 1H, *J*=15, 9, 5 Hz), 1.81 (ddd, 1H, *J*=15, 9, 5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 26.1, 28.3, 40.6, 66.0, 74.0, 96.0, 125.5, 126.2, 128.4, 128.5, 128.7, 129.1, 129.5, 141.9, 142.3, 147.9, 174.7; EIMS [*m/z* (%)]: 265 (M^+-CO, 25), 237 ($M^+-CH_2CH_2CO$, 100), 206 ($M^+-CH_2CH_2CO$, $-OCH_3$, 36), 77 ($C_6H_5^+$); HRMS calculated for $C_{18}H_{19}NO$ 265.1466, found 265.1466.

4.5.2. *cis*-(4a*R,9b*R**) Methyl 9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylate (25).** This was prepared from **6** by applying the procedure given for **3a** except for using 2.2 equiv. of BH_3·DMS. Column chromatography was carried out using as the eluent 33:1 CH_2Cl_2/MeOH to yield 0.4 g (81%) of piperidine **25** as a colourless oil: IR (NaCl, cm^{-1}): 3336, 3023, 2945, 2856, 2842, 1724; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29 (m, 3H), 7.15 (m, 4H), 7.04 (m, 2H), 3.55 (d, *J*=16 Hz, 1H), 3.43 (s, 3H), 3.07 (ddd, 1H, *J*=13, 4, 4 Hz), 2.71 (ddd, 1H, *J*=13, 13, 4 Hz), 2.59 (d, 1H, *J*=16 Hz), 2.18 (br s+ddddd, 2H, *J*=13, 13, 13, 4, 4 Hz,), 2.05 (br d, 1H, *J*=14 Hz), 1.52 (ddd, 1H, *J*=13, 13, 4 Hz), 1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.6, 33.0, 40.8, 41.2, 51.3, 55.8, 73.1, 124.1, 125.4, 126.5, 127.1, 127.3, 127.8, 127.8, 141.7, 144.0, 144.5, 174.9; EIMS [*m/z* (%)]: 307 (M^+, 4), 248 ($M^+-CO_2CH_3$, 100), 220 ($M^+-CO_2CH_3$, $-C_2H_4$, 20), 204 ($M^+-CO_2CH_3$, $-C_3H_6$, 17), 77 ($C_6H_5^+$, 6); HRMS: calculated for $C_{20}H_{21}NO_2$ 307.1572, found 307.1559.

4.5.3. *cis*-(4a*R,9b*R**)-9b-Phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridin-4-yl)methanol (26).** This was prepared from **25** according to the procedure given for **3a**.

Column chromatography was carried out using as the eluent 16.7:1 CH_2Cl_2/MeOH) to yield 0.13 g (60%) of piperidine **26** as a colourless oil: IR (NaCl, cm^{-1}): 3383, 3065, 2935; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29 (m, 3H), 7.18 (m, 3H), 7.10 (m, 2H), 7.00 (m, 1H), 3.57 (d, 1H, J=10 Hz), 3.28 (d, 1H, J=10 Hz), 2.96 (m, 1H), 2.76 (ddd, 1H, J=13, 13, 3 Hz), 2.73 (d, 1H, J=15 Hz), 2.35 (d, 1H, J=15 Hz), 2.26 (br s, 2H), 2.00 (ddd, 1H, J=15, 4, 4 Hz), 1.87 (m, 1H), 1.38 (m, 1H), 1.30 (ddd, 1H, J=15, 12, 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 23.2, 31.8, 40.3, 41.5, 50.0, 67.2, 73.2, 122.9, 125.6, 126.9, 127.0, 127.2, 127.4, 127.9, 143.1, 144.0, 146.5; EIMS [m/z (%)]: 279 (M^+, 3), 248 (M^+-CH_2OH, 100), 91 ($C_7H_7^+$, 7), 77 ($C_6H_5^+$, 7); HRMS: calculated for $C_{19}H_{21}NO$ 279.1623, found 279.1621.

4.5.4. *cis*-(4a*R,9b*R**)-3,5-Bis(trifluoromethyl)benzyl [(9b-phenyl-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]-pyridin-4-yl)methyl] ether (5).** To a stirred solution of the alcohol **22** (0.81 g, 2.9 mmol) and NaH (80%, 22 mg, 7.3 mmol) in dry DMF (5 mL) was added dropwise (via a large cannula) under argon atmosphere a solution of 3,5-bis(trifluoromethyl)benzyl bromide (0.8 mL, 4.4 mmol) in dry THF (5 mL). The mixture was stirred at rt for 1 h. MeOH (5 mL) and H_2O (10 mL) were added and the aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was subjected to chromatography (85 g of alumina, 25:1 hexane/EtOAc) and crystallisation (from hexanes) to afford 0.64 g (44%) of the ether **5** as a white crystalline solid: mp (°C): 83.5–84.1; IR (KBr, cm^{-1}): 3324, 3031, 2932, 2848, 1600, 1113; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.76 (s, 1H), 7.68 (s, 2H), 7.30 (m, 3H), 7.15 (m, 3H), 7.04 (m, 3H), 4.44 (s, 2H), 3.66 (d, 1H, J=9 Hz), 2.95 (br. d, 1H, J=11 Hz), 2.88 (d, 1H, J=9 Hz), 2.79 (d, 1H), 2.77 (ddd, 1H, J=11, 11, 3 Hz), 2.53 (d, 1H, J=15 Hz), 2.14 (br d, 1H, J=14 Hz), 1.96 (br s, 1H), 1.72 (m, 1H), 1.40 (m, 1H), 1.27 (ddd, 1H, J=14, 14, 4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.8, 30.7, 41.6, 41.8, 49.0, 71.7, 73.1, 74.7, 119.2+122.0+124.7+127.4, 123.0, 125.5, 126.9, 127.1, 127.5, 127.7, 131.0, 131.35, 131.68, 132.03, 141.6, 143.3, 144.2, 146.7; EIMS [m/z (%)]: 505 (M^+, 4), 486 (M^+-F, 7), 278 (M^+-CH_2Ar, 27), 248 ($M^+-CH_2OCH_2Ar$, 100); HRMS: calculated for $C_{28}H_{25}NOF_6$ 505.1840, found 505.1841.

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