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Synthesis and conformational analysis of Substance P antagonist analogues based on a 1,7-naphthyridine scaffold

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Abstract—Two analogues of formerly described piperidine-based Substance P antagonists have been synthesised using an intramolecular Diels–Alder reaction of 1-(4-pentenyl)-3-phenyl-2(1*H*)-pyrazinones, followed by acidic methanolysis of the strained adducts to form the 8-oxo-6-phenyldecahydro [1,7]-naphthyridine-6-carboxylate esters and further conversion to the corresponding *O*-benzyl substituted 6-(hydroxymethyl) target compounds. Conformational analyses of intermediates and the final products are presented, based on ^{1}H NMR and modelling data.

1. Introduction

Substance P is a member of the tachykinins, a group of small peptides characterised by the common C-terminus Phe-X-Gly-Leu-Met-NH_2 (X=Phe or Val).[1] There are five known mammalian tachykinins: Substance P (SP), Neurokinin A (NKA), Neurokinin B (NKB), Neuropeptide K (NPK), Neuropeptide γ (NPγ). The two latter are related to NKA, but have a prolonged N-terminus. Also, about a dozen of tachykinins have been isolated from lower species.[2] Mammalian tachykinins are called neurokinins. The tachykinins have G-coupled receptors that possess seven transmembrane segments linked by intra- and extracellular loops.[3] Three receptor subtypes (NK1, NK2 and NK3) have been identified that preferably bind SP, NKA and NKB, respectively. SP, NKA and NKB are found in the central and peripheral nerve system, where they act as neurotransmitters and neuromodulators. They have been related to various biological effects, including pain transmission, neurogenic inflammation, smooth muscle contraction, vasodilatation, secretion and activation of the immune system. A multitude of neurokinin receptor antagonists has been described and has been used to confirm the physiological role of tachykinins. For NK1 receptor antagonists that constitute the most studied group, the primary sites of action have been identified. In this way, it was found that SP is related to the pathophysiology of asthma,[4] Crohn's disease, pain,[5] psoriasis, migraine, cystitis, schizophrenia, emesis and anxiety.[6]

Using screening techniques, Pfizer optimised lead-compound CP96345 (Fig. 1, **1**) in 1991, the first non-peptide SP antagonist.[7] Further optimisations led to the piperidine CP99994 (**2**),[8] which is in the clinical phase for emesis and post-operational dental pain.[9] In 1994, researchers of Merck, Sharp and Dohme showed that the benzylamine moiety of **2** could be replaced by a benzyl ether (**3**).[10] Also, it was found that high activity was preserved in the 2,2-disubstituted piperidine **4**.[11,12]

In a previous communication,[13] we reported a synthetic route towards *cis*-fused 1,7-naphthyridine **7**: this involved

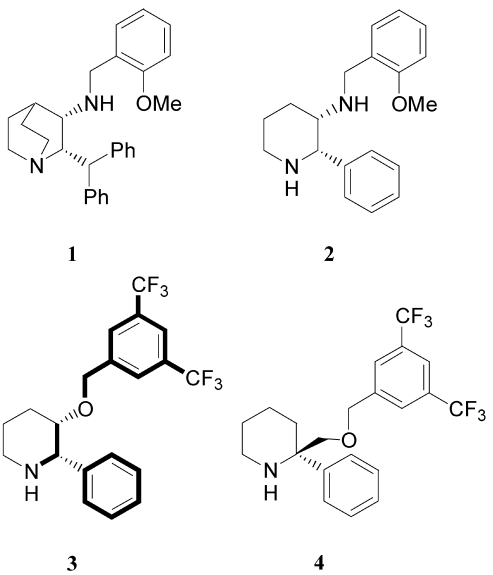

Figure 1.

Keywords: Substance P; tachykinins; antagonists; pyrazinone; intramolecular Diels–Alder.

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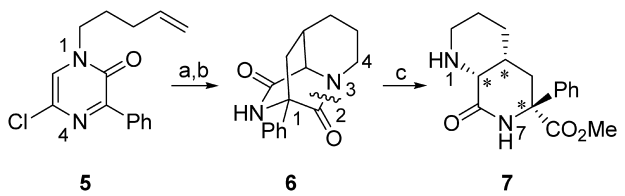


Scheme 1. (a) PhBr, reflux, 1 night; (b) EtOAc/H_2O, room temperature, 1 h (hydrolysis); (c) 2.5 equiv. CH_3SO_3H, MeOH, reflux, 1 night.

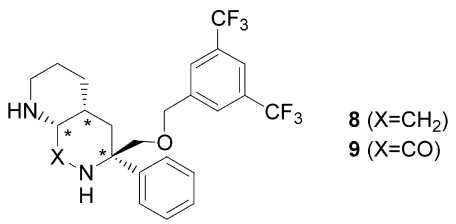


Figure 2.

the intramolecular Diels–Alder reaction of 2(1*H*)-pyrazinone **5**, followed by acidic methanolysis of the strained hydrolysed adduct **6** (Scheme 1). This approach also has been used by our group to prepare a type VI β-turn mimic.[14] Inspired by the structural resemblance between Merck piperidine **4** and 1,7-naphthyridine **7**, we also envisaged conversion of **7** to potential SP antagonists **8** and **9** (Fig. 2). Conformational analysis of **4** indicates an axial position of the phenyl group,[11] while both aromatic rings presumably are in an edge-on conformation.[15] A preferred axial orientation of the phenyl group also has been demonstrated for 1,7-naphthyridine **7**.[13,14] For diamine **8**, this conformation could be stabilised at physiological pH by an internal hydrogen bridge involving both nitrogen atoms of the mono-ammonium salt. Such hydrogen bridge is not feasible for the 8-oxo analogue **9** (X=CO). The absence of a basic nitrogen at the 7-position in **9** could lower the undesired activity for L-type Ca^{2+}-channels. This drawback associated with non-peptide SP antagonists of the first generation has been circumvented in later work of the Merck researchers by appropriate N-substitution of piperidines of type **3** and their morpholine analogues.[16]

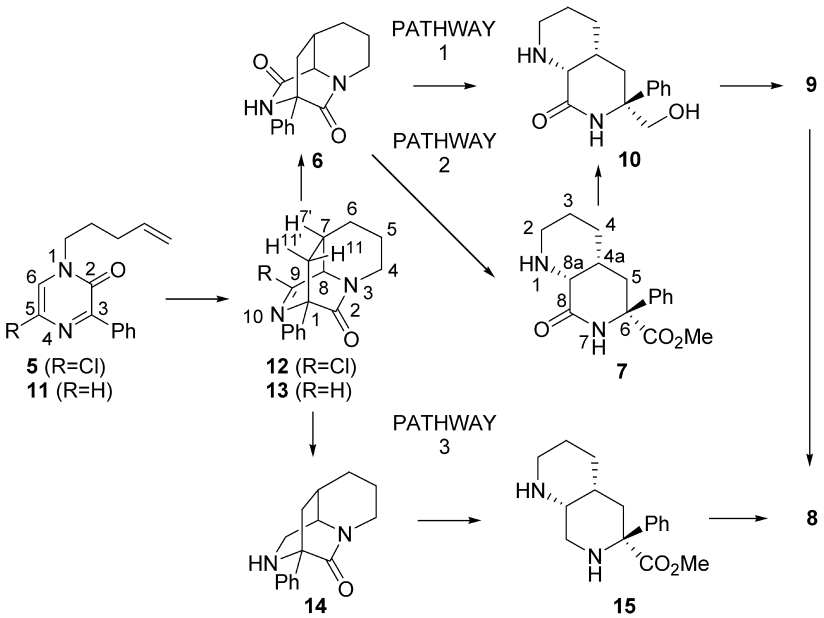
2. Results and discussion

2.1. Synthesis

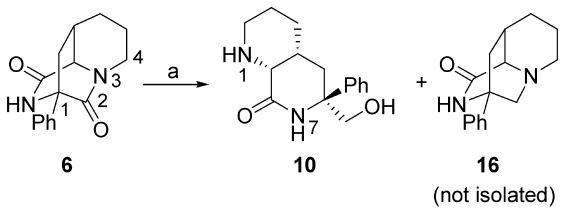
For the synthesis of **8** and **9**, we envisioned three possible pathways depicted in Scheme 2.

1. Reductive cleavage of the strained, ketone-like tertiary amide group of bislactam **6** could afford primary alcohol **10**. This may proceed via ring opening of the hemiaminal intermediate and further reduction of the aldehyde formed. Subsequent O-benzylation and reduction of the secondary amide group finally would provide target products **9** and **8**.
2. Following selective acidic methanolysis of bislactam **6** to give methyl ester **7**, the latter in turn can be submitted to chemoselective reduction of the ester group: this would again produce primary alcohol **10** as a key intermediate.
3. Intramolecular cycloaddition of **11**, the 5-H analogue of 5-Cl-pyrazinone **5**, would afford imine adduct **13** instead of imidoyl chloride **12**. Subsequent reduction of imine **13** then may yield amino lactam **14**, which can be converted to diamines **15** and **8** in a similar way as depicted in pathways 1 and 2.

Pathway 1. In an attempt to convert bislactam **6** directly into alcohol **10** via reductive cleavage of the tertiary amide group, **6** was treated with $NaBH_4$ under protic conditions (THF/H_2O). These conditions were chosen to allow protonation of N^3, thus facilitating expulsion of the amine from the hemiaminal intermediate produced in the first reduction step. However, both the desired alcohol **10** and



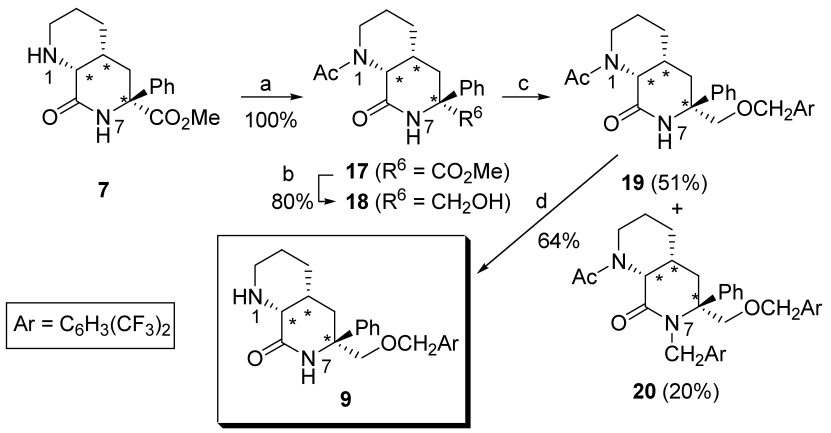
Scheme 2.



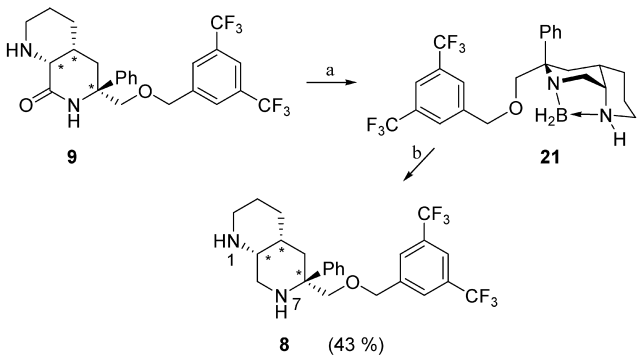
Scheme 3. (a) 4 equiv. $NaBH_4$, MeOH, 60°C, 5 days.

tertiary amine **16** were identified by chemical ionisation mass spectral analysis (CIMS) (Scheme 3). Following isolation by continuous extraction and preparative TLC, alcohol **10** was isolated in only 29% yield. Presumably, the formation of amine **16** (not isolated) is due to competitive reduction of the strained iminium ion generated from the hemiaminal. We therefore decided to attempt pathway 2.

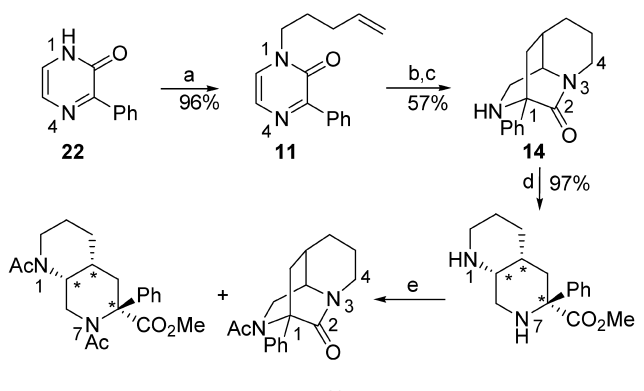
Pathway 2. Reduction of electron-deficient ester groups



Scheme 4. (a) Ac_2O, 40°C, 1 h; (b) $NaBH_4$, THF/H_2O (4:1), 60°C, 30 min; (c) $(F_3C)_2C_6H_3CH_2Br$, NaH, DMF, room temperature, overnight; (d) HCl/MeOH, 60°C, 2 days.



Scheme 5. (a) 2 equiv. BH_3·DMS, THF, reflux, 1 h; (b) HCl/MeOH, reflux, 30 min.



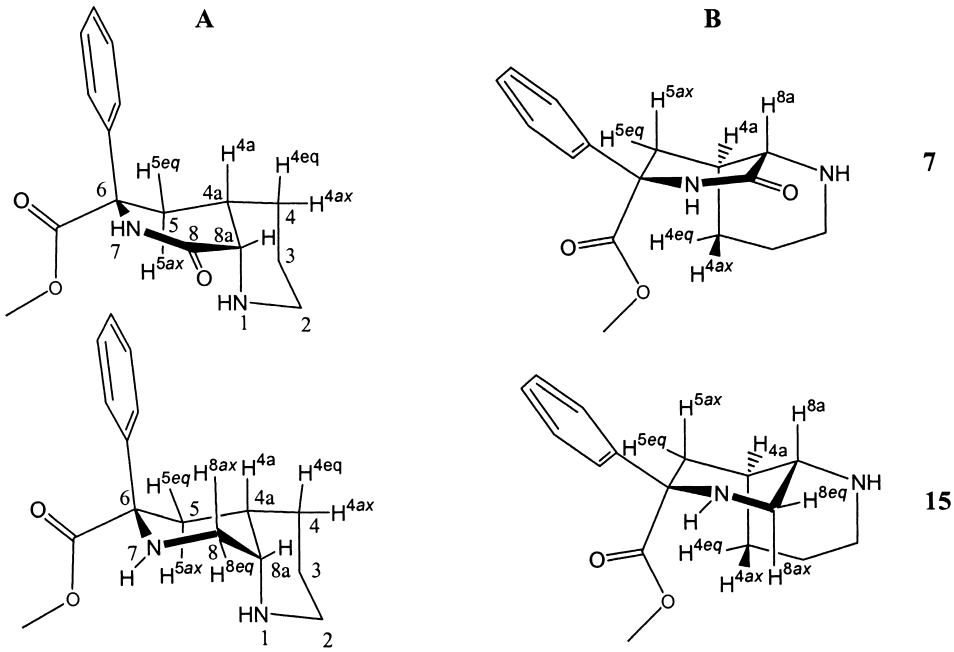
Scheme 6. (a) 5-Bromo-1-pentene, Cs_2CO_3, dioxane, 50°C, 1 week; (b) PhCl, reflux, 3 days; (c) H_2, 10% Pd/C, 40 psi, 1 night; (d) 3.5 equiv. CH_3SO_3H, MeOH, reflux, 1 night; (e) Ac_2O, 2 equiv. DMAP, 40°C, 2 h.

sometimes can be effected by $NaBH_4$. Applying this method should allow for selective conversion of ester **7** into alcohol **10**, without reducing the amide function. However, no reaction was observed when treating a methanolic solution of **7** with 2 equiv. of $NaBH_4$ at room temperature. Upon addition of two extra equivalents of $NaBH_4$ and heating to 60°C, alcohol **10** was produced along with an appreciable quantity of ring-closed bislactam **6**. Hence, to avoid competing ring closure of amino ester **7**, the amino nitrogen N^1 was protected as the *N*-Ac amide **17** (Scheme 4). Subsequent treatment of **17** with 5 equiv. of $NaBH_4$ in THF/H_2O (4:1) at 60°C afforded alcohol **18** in 80% yield. When **18** was submitted to benzylation using only 1 equiv. of NaH and 3,5-bis(trifluoromethyl)benzyl bromide, this inevitably led to formation of both the mono- and bis-benzylated product **19** and **20**. Addition of another 0.5 equiv. of NaH drove the reaction to completion, yielding 52 and 20% of purified products **19** and **20**. Final cleavage of the *N*-acetyl group of **19** was accomplished by heating amide **19** with HCl in methanol at 60°C to furnish **9** in 64% yield.

The diamine target product **8** was prepared from amino lactam **9** via reduction with 2 equiv. of BH_3·DMS in THF at reflux temperature (Scheme 5). CIMS analysis of the reaction mixture indicated the formation of the borane-bridged diamine complex **21** (MH^+ ions observed at *m/z* 485 and 484 in the expected isotopic ratio of ca. 4:1). This borane complex was destroyed by refluxing with HCl in methanol to provide diamine **8** in 43% yield.

Pathway 3. In an attempt to find a shorter pathway leading to diamine **8**, we prepared pyrazinone **22** using the base-catalysed condensation of 2-amino-2-phenylacetamide with glyoxal described by Jones (Scheme 6).[17] N-alkylation of **22**

Table 1. Experimental ^3J coupling values in the ^{1}H NMR spectra of lactam **7** and diamine **15** compared to the values calculated[18] for conformational structures **A** and **B**



	Conf.	$^3J_{4a,5eq}$		$^3J_{4a,5ax}$		$^3J_{4a,4ax}$		$^3J_{4a,4eq}$		$^3J_{8a,8ax}$		$^3J_{8a,8eq}$	
		Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.	Exp.	Theor.
7	**A**	3.0 (*gauche*)	1.9	10.0 (*anti*)	12.2	5.0 (*gauche*)	4.7	6.0 (*gauche*)	2.1	–	–	–	–
	B	– (*gauche*)	3.1	– (*gauche*)	3.8	– (*anti*)	12.3	– (*gauche*)	3.5	–	–	–	–
15	**A**	4.0 (*gauche*)	2.6	14.0 (*anti*)	12.4	–[a] (*gauche*)	4.6	–[a] (*gauche*)	2.1	3.0 (*gauche*)	3.4	2.0 (*gauche*)	2.4
	B	– (*gauche*)	2.0	– (*gauche*)	5.2	– (*anti*)	12.3	– (*gauche*)	3.6	– (*anti*)	11.2	– (*gauche*)	3.9

[a] Not determined due to overlap.

by heating with 5-bromo-1-pentene and Cs_2CO_3 in dioxane provided the corresponding *N*-pentenyl derivative **11**. When heated in chlorobenzene at reflux temperature for 3 days, **11** underwent intramolecular cycloaddition to form imine adduct **13**. After removal of the solvent, imine **13** was redissolved in THF and immediately reduced to amine **14** by hydrogenation (40 psi) over 10% Pd/C catalyst (yield: 47%). Similar to the conversion of **6** to amino ester **7**, acidic cleavage of **14** could be effected by heating with 3.5 equiv. of CH_3SO_3H in methanol to produce diamino ester **15** in 97% yield. To prevent competing ring closure upon reduction of the ester group with $NaBH_4$, diamine **15** first was converted to diamide **23** by heating in acetic anhydride with 2 equiv. of DMAP at 60°C; besides diamide **23** (73%) this also yielded a small quantity of N-acetylated ring-closed product **24**. Unfortunately, no reduction of the ester group occurred even when heating **23** with up to 10 equiv. of $NaBH_4$ in MeOH/H_2O (4:1) at reflux temperature. When compared to the easy reduction of **17**, this remarkable result may be due to the increased steric requirements in **23** for accessing the equatorial ester group that is co-planar with the N^7–Ac group.

In summary, pathway 2 proved to be the method of choice amongst the three routes proposed for preparing target products **9** and **8**.

2.2. Conformational analysis of the 1,7-naphthyridines

cis-Fused naphthyridines of lactam type **9** and diamine type **8** can adopt two conformations **A** and **B**, in which both rings have a (half)chair conformation (see heading of Table 1).[13] The assignment of structure **A** or **B** relies on the specific relation between the ^3J coupling patterns observed in the ^{1}H NMR spectra and the dihedral angles of vicinal protons (*gauche* or *anti*). Table 1 lists relevant ^3J values for lactam ester **7** and the analogous diamine **15**. In support of the conformational assignments, the measured coupling values are compared to theoretical values calculated by applying the equations of Haasnoot et al.[18] to geometry optimised model structures of **A** and **B** (feature implemented in Macromodel 5.0). In the case of diamine **15**, additional support for the assignment comes from the coupling values found between protons H^8 and the angular proton H^{8a}. From the comparison between measured and calculated coupling values it clearly follows that structure **A** applies to both compounds **7** and **15**, as argued below.

The ^{1}H NMR analysis of **7** was carried out in a 1:1 mixture of $CDCl_3$ and C_6D_6, resulting in optimal separation of signals. The analysis started with the assignment of the downfield angular proton H^{8a} (δ 3.17) that is flanked by N^1 and the C^8 carbonyl group. Other contiguous ring protons H^{4a} (δ 1.94), H^5 (δ 2.93 and 2.02) and H^4 (δ 1.43 and 1.22) were identified by decoupling experiments involving sequential irradiation of H^{8a} and H^{4a}. Due to coupling with the adjacent proton H^{4a}, H^{8a} was observed as a doublet ($^3J_{8a,4a}$=4 Hz) while both geminal protons H^5 appeared as a doublet of doublets. The H^5-signal at δ 2.93 displayed a coupling value of 10 Hz, indicating a *trans*-diaxial relationship of H^{5ax} and H^{4a} with regard to the piperidinone ring. The other H^5-signal (δ 2.02) corresponding to H^{5eq} revealed a small coupling (3 Hz) with H^{4a}. The ^3J values for coupling between H^{4a} and H^4 were determined from the difference in the sum of coupling constants measured for each proton H^4 before and after irradiation of H^{4a}. The values found (6 Hz in each case)[19] were consistent with their *gauche* relationship to H^{4a}. Hence, in view of the large $^3J_{4a,5ax}$ and small $^3J_{4a,5eq}$, $^3J_{4a,4ax}$, $^3J_{4a,4eq}$ values compound **7** clearly adopts conformation **A**. For structure **B**, one rather expects a large $^3J_{4a,4ax}$ value corresponding to a *trans*-diaxial disposition of H^{4ax} and H^{4a} with respect to the piperidine ring.

The conformational analysis of diamine **15** largely relies on the coupling values found between the angular proton H^{8a} and geminal protons H^8. In structure **A**, H^{8a} is *gauche* relative to both H^8 protons, whereas in form **B** proton H^{8a} is *gauche* to H^{8eq} but *anti* to H^{8ax} (*trans*-diaxial disposition of H^{8a} and H^{8ax}). Both protons H^8 in fact were observed as a doublet of doublets at δ 2.77 and 2.95, exhibiting a *gauche*-coupling of 2 and 3 Hz with H^{8a} (δ 2.62). By irradiating the multiplet of H^{8a}, one can identify H^{4a} as a hidden multiplet at δ 1.78. Further irradiation of H^{4a} revealed protons H^5. H^{5ax} appears as a triplet at δ 2.51, and H^{5eq} as a doublet of doublets at δ 2.37. The large coupling between H^{5ax} and H^{4a} again indicates a *trans*-diaxial relationship. By comparison of measured and predicted coupling values in Table 1, one may conclude that diamine **15** also has the **A**-conformation. Further assignment of the signals was carried out as described for **7**. Coupling constants and shift values that are relevant for the conformational assignment of **15** are summarised in Table 1.

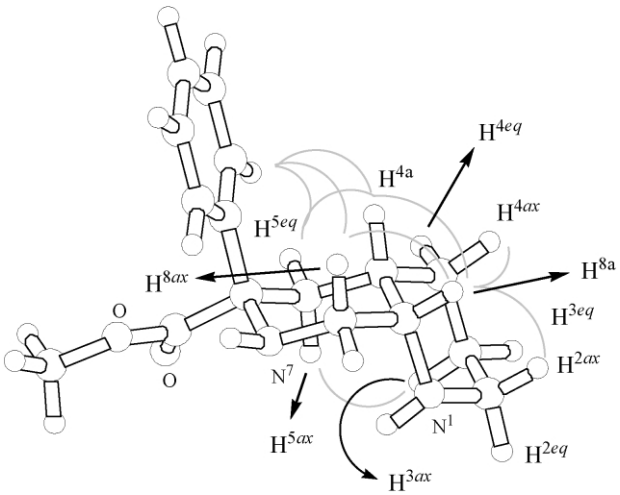


Figure 3. NOE-correlations between (non-geminal) protons in **15**.

Finally the conformational assignment of **15** was confirmed by 2D ^{1}H–^{1}H NOESY analysis which revealed a correlation of the *ortho*-protons of the phenyl group with H^{8ax}, H^{5eq} and H^{4a}. This only can apply to conformer **A** (Fig. 3).

The higher stability of **15-A** compared to **15-B** can be rationalised as follows. Structure **A** shows two 1,3-diaxial interactions of the axial phenyl group with H^{4a} and H^{8a}, while **B** displays 1,3-diaxial repulsions of the ester group with H^{8ax} and the C^{4a}–C^4 linkage. Clearly, the latter is more important. For lactam **7** a similar repulsion exists between the ester group and the C^{4a}–C^4 linkage in conformer **B**.

In contrast to amino lactam **7** that exists as conformational structure **A**, the analogous N^1–Ac compounds **17**–**20** were shown to adopt conformation **B** as seen from the relevant vicinal coupling constants in their ^{1}H NMR spectra (see Section 4). This preference for **B** can be ascribed to the strong repulsion between the N–Ac group and the coplanar C^{8a}–C^8 linkage in conformer **A**. The ^{1}H NMR spectra of the

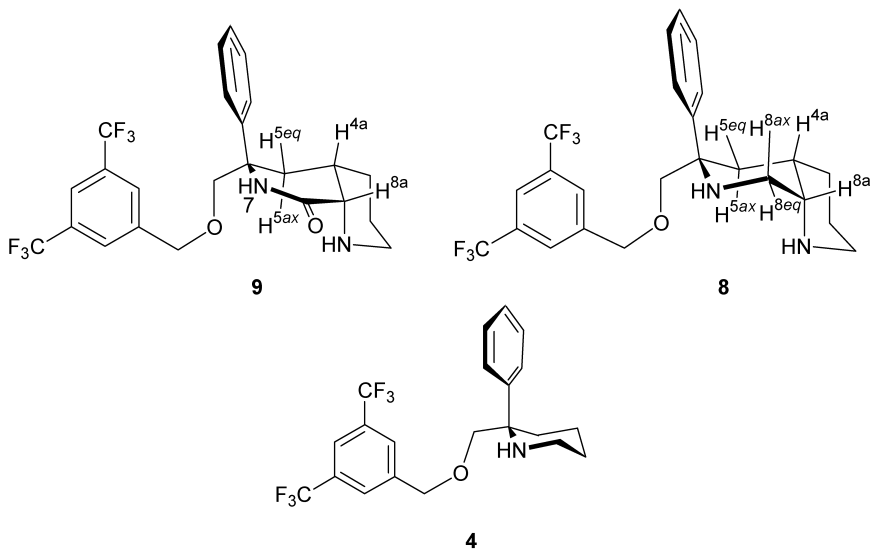
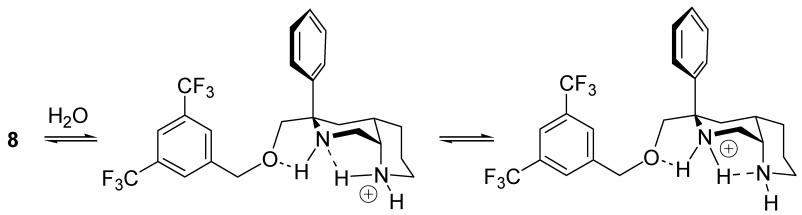


Figure 4.



Scheme 7.

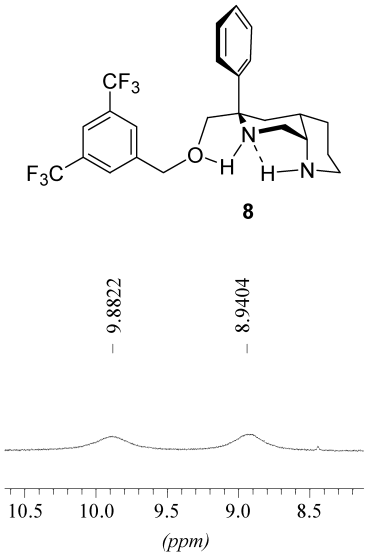


Figure 5.

N–Ac compounds were rather complex due to the *Z*/*E*-rotamerism about the N^1-acetyl linkage. The downfield shift of H^{8a} for the major rotamer (e.g. δ 5.35 vs δ 4.19 for the minor rotamer of **17**) indicates its proximity to the N–Ac carbonyl group, and hence the existence of the *Z*-rotamer.

An NMR analysis reported for model **4** revealed the axial orientation of the phenyl group (as is commonly observed for *gem*-disubstituted six-membered ring compounds).[11] Since antagonists (contrary to agonists) preferably bind to the receptor in their ground state,[20] the Ph-ax conformer presumably represents the bioactive conformation. As shown below, this Ph-ax conformation **A** also is preferred for the 1,7-naphthyridine target products **8** and **9**, and increased activity (if any) of these compounds would support the importance of this conformation (Fig. 4).

The ^{1}H NMR spectra of **9** and **8** both revealed a large *trans*-diaxial coupling of H^{5ax} and the angular proton H^{4a}, a small eq,ax coupling of H^{5eq} and H^{4a}, and small (unresolved) *gauche*-couplings of each geminal proton H^8 with H^{8a}. These findings clearly support conformation **A**. For **B** one expects a large *trans*-diaxial coupling for H^{8ax} and H^{8a}, a small *gauche* coupling for H^{8eq} and H^{8a}, and two small *gauche* couplings for each proton H^5 and H^{4a}. As already postulated for diamine **8**, an intramolecular hydrogen bridge can exist between N^1 and N^7. The strongly broadened NH signals (δ 1–6 at 303 K) indicate a fast exchange of protons. Presumably, this process involves the mono-protonated form of the diamine produced by fast exchange with water (Scheme 7). The increased basicity of diamines like $H_2NCH_2CH_2NH_2$ similarly results from the stabilisation provided by the internal hydrogen bridge in the mono-protonated form.[21]

The two NH absorptions became visible at δ 9.8 and δ 8.9 upon cooling of the CD_2Cl_2 solution of **8** to 198 K (Fig. 5). Presumably, these downfield chemical shift values result from intramolecular hydrogen bridge formation. Since both NH protons display downfield shift values one may infer that the ether oxygen is also involved in internal hydrogen bond formation, as shown in Figure 5.

The conformational structure of **8** was further examined by 2D ^{1}H–^{1}H NOESY analysis. The spectrum revealed a correlation between the phenyl *ortho*-protons and H^{5eq}, H^{4a} and H^{8ax}, confirming the axial position of the phenyl group, and hence the **A**-conformation. A correlation also was observed between the phenyl *ortho*-protons and one of the diastereotopic C^6CH_2-protons. This indicates a restricted conformational freedom, probably due to intramolecular hydrogen bond formation involving the adjacent oxygen atom. The C^6CH_2 group could be distinguished from the benzyl methylene group by the correlation found for the latter methylene protons with the *ortho*-protons of the 3,5-bis(trifluoromethyl)phenyl moiety. Correlations relevant for the structure determination of **8** are shown in Figure 6.

The ^{1}H NMR spectrum of bis-acetylated compound **23** showed severe signal broadening owing to the *Z*/*E*-rotamer exchange about the two *N*-acetyl linkages. After cooling to 223 K (400 MHz, CD_2Cl_2), two components were identified in a 77:23 ratio. For both of these H^{8ax} was observed as a triplet corresponding to *trans*-diaxial coupling with H^{8a}, while H^{8eq} was found as a doublet of doublets with a small *gauche* coupling of 4 Hz. Both protons H^5 appeared as a doublet of doublets showing relatively large coupling values of 11 and 7 Hz with H^{4a}. The large *trans*-coupling of H^{8ax} supports conformation **B**, but the coupling values found for H^5 are not compatible with this structure. Molecular modelling using MM3* suggested the existence of conformer **C**, in which the N^7 piperidine ring has a boat form that minimises the repulsion experienced by the N^7-acetyl group. The coupling constants calculated for **C** (Haasnoot et al.) are in good agreement with the experimental values (Table 2). The orientation of the N–Ac groups can be inferred from the chemical shifts of the coplanar equatorial neighbouring protons. Thus H^{2eq} and H^{8a} are coplanar with the N^1–Ac linkage and absorb at δ 3.59 and δ 4.36 for the major component of **23** while these values are reversed for the minor component (δ 4.36 and δ 3.78). These data respectively indicate the *Z* and *E*-configuration of the N^1-acetyl group. Proton H^{8eq} absorbs at similar values for the

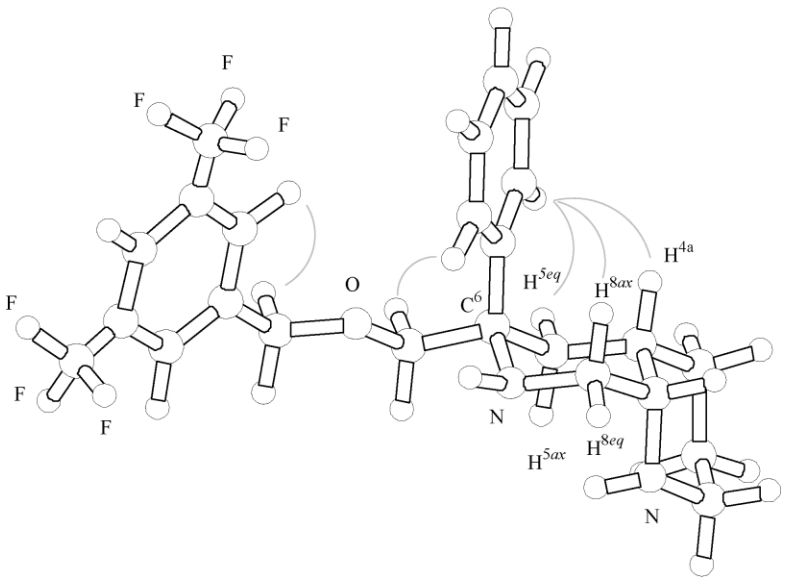
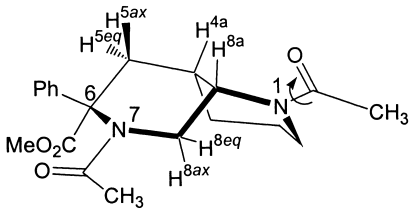
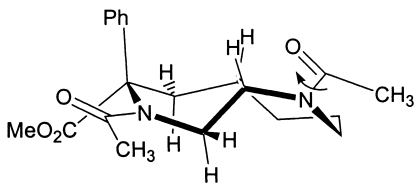


Figure 6.

Table 2. Experimental ^3J coupling values in the 1H NMR spectra of **23** compared to coupling and torsion angle values calculated for conformational structures **B** and **C**



B



C

Conformation	Angle (°)	$^3J_{8ax,8a}$	Angle (°)	$^3J_{8eq,8a}$	Angle (°)	$^3J_{5ax,4a}$	Angle (°)	$^3J_{5eq,4a}$
23-B[a]	−173.3	11.1	−60.4	4.0	−48.1	4.8	64.6	2.4
23-C[a]	170.3	10.9	−75.2	2.3	153.1	10.2	39.9	6.5
23-experimental[b]	–	12.2	–	3.9	–	10.6	–	7.4

Only the *Z*-N^1-acetyl rotamers are shown.
[a] Calculated with Macromodel 5.0.
[b] 400 MHz, CD_3Cl_3, 223 K.

major (δ 3.52) and the minor rotamer (δ 3.44), revealing a common *Z*-configuration of the N^7-acetyl group with minimal repulsion from the 6-substituents.

3. Conclusion

Specifically substituted 1,7-naphthyridines, prepared via intramolecular Diels–Alder reaction of 1-(4-pentenyl)-2(1*H*)-pyrazinones followed by acidic methanolysis of the hydrolysed adducts, can be converted into potential Substance P antagonists. The conformational structure of intermediates and final products was determined by ^{1}H NMR analysis. From examination of the coupling pattern it appears that the *cis*-fused 1,7-naphthyridine scaffold adopts a well-defined conformation, which in the case of the final products resembles the presumed bioactive conformation of known antagonists. For the diamine naphthyridines, this conformation can additionally be stabilised by intramolecular hydrogen bonding. Biological evaluation of **8** and **9** is currently in progress.

4. Experimental

4.1. General

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 1600 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 AMX 400 (**8**–**11**, **14**, **15**, **18**–**20**, **23** and **24**) and a Bruker Avance 300 (**17**) 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. Preparative TLC plates were prepared with silica gel (Kiesgel 60, 70–230 mesh) of Macherey-Nagel and Fluka. HPLC separations were carried out using a HIBAR column [Merck, cat. 151435].

For the synthesis and spectral data of **5**–**7**, see Refs. 13,14.

4.1.1. (4a*R* *,6*S* *,8a*R* *)-6-Hydroxymethyl-6-phenyloctahydro [1,7]naphthyridin-8(2*H*)-one 10. To a solution of 100 mg (0.4 mmol) of **7** in a 4:1 mixture of MeOH/H_2O was added an excess of $NaBH_4$ (747 mg, 20 mmol). This solution was stirred during 5 days at room temperature. Next, a saturated solution of NH_4Cl was added. After evaporation of MeOH, a continuous extraction was carried out with CH_2Cl_2 for 1 night. Evaporation of the solvent yielded crude **10** that was further purified using column chromatography (silica gel, 10% MeOH/CH_2Cl_2), and crystallised from Et_2O. Yield: 29 %; colourless crystals, mp 123°C (Et_2O); IR (KBr, cm^{-1}): 1652.0 (C═O); ^1H NMR (400 MHz, DMSO-d_6): 8.12 (s, 1H, H^7), 7.40–7.24 (m, 5H, H-arom.), 4.5–3.5 (s, very broad, NH+OH+H_2O), 3.59 (d, *J*=11 Hz, 1H, CH_2OH), 3.52 (d, *J*=11 Hz, 1H, CH_2OH), 3.35 (d, *J*=5 Hz, H^{8a}), 2.99 (m, 1H, H^{2eq}), 2.72 (m, 1H, H^{2ax}), 2.35 (dd, *J*=14, 11 Hz, 1H, H^{5ax}), 1.95 (dd, *J*=14, 4 Hz, 1H, H^{5eq}), 1.85 (m, 1H, H^{4a}), 1.60–1.35 (m, 4H, H^3+H^4); ^{13}C NMR (100 MHz, DMSO-d_6): 168.9 (C^8), 143.9 (C-*ipso*), 128.2, 126.7, 126.1 (C-*ortho*+C-*meta*+C-*para*), 69.1 (CH_2OH), 62.2 (C^6), 55.1 (C^{8a}), 40.1 (C^2), 31.7 (C^5), 27.4 (C^{4a}), 27.2, 20.0 (C^4+C^3); *m*/*z* (E.I., %): 260 (4, $M^{\cdot+}$), 229 (13, $M^{\cdot+}-CH_2OH$), 217 (100, $M^{\cdot+}-C_2H_5N$), 96 (82, $C_6H_{10}N^+$); exact mass calculated for $C_{15}H_{20}N_2O_2$: 260.1525, found: 260.1522.

4.1.2. Methyl (4a*R* *,6*S* *,8a*R* *)-1-acetyl-8-oxo-6-phenyl decahydro[1,7]naphthyridine-6-carboxylate 17. A solution of 200 mg of **7** in 50 mL acetic anhydride was stirred at 40°C during 1 h. Removal of reagent and acetic acid formed afforded **17** in quantitative yield. Transparent oil; IR (NaCl, cm^{-1}): 1735.3 (C═O-ester), 1675.6 (C═O-lactam), 1636.4 (C═O-acetyl); ^1H NMR (300 MHz, $CDCl_3$). Major rotamer (74%): 7.43–7.32 (m, 5H, H-arom.), 6.79 (s, 1H, H^7), 5.36 (d, *J*=5 Hz, 1H, H^{8a}), 3.76 (s, 3H, CO_2CH_3), 3.70 (broad d, *J*=13 Hz, 1H, H^{2eq}), 3.07 (td, *J*=13, 3 Hz, 1H, H^{2ax}), 2.98 (ddd, *J*=15, 3, 2 Hz, 1H, H^{5eq}), 2.28 (dd, *J*=15, 5 Hz, 1H, H^{5ax}), 2.17 (s, 3H, $COCH_3$), 2.10 (m, 1H, H^{4a}), 1.83 (m, 1H, H^{3eq}), 1.74 (dt, *J*=13, 3 Hz, 1H, H^{4eq}), 1.44 (qt, *J*=13, 4 Hz, 1H, H^{3ax}), 1.67 (qd, *J*=13, 3 Hz, 1H, H^{4ax}). Minor rotamer (26%): 7.43–7.32 (m, 5H, H-arom.), 6.98 (s, 1H, H^7), 4.52 (broad d, *J*=13 Hz, 1H, H^{2eq}), 4.19 (d, *J*=6 Hz, 1H, H^{8a}), 3.76 (s, 3H, CO_2CH_3), 2.89 (m, 1H, H^{5eq}), 2.48 (td, *J*=13, 3 Hz, 1H, H^{2ax}), 2.41 (dd, *J*=15, 5 Hz, 1H, H^{5ax}), 2.14 (m, 1H, H^{4a}), 1.96 (s, 3H, $COCH_3$), H^{3eq}, H^{4eq} en H^{3ax} are hidden, 0.84 (m, 1H, H^{4ax}); ^{13}C NMR (75 MHz, $CDCl_3$). Major rotamer: 171.6, 170.7, 168.9 (CO), 141.3 (C-*ipso*), 129.1, 128.4, 124.2 (C-*ortho*+C-*meta*+C-*para*), 64.4 (C^6), 52.3 (CO_2CH_3+C^{8a}), 43.5 (C^2), 38.2 (C^5), 33.4 (C^{4a}), 26.9, 25.5 (C^3+C^4), 21.5 ($COCH_3$). Minor rotamer: most signals are not resolved; *m*/*z* (E.I., %): 330 (27, $M^{\cdot+}$), 287 (69, $M^{\cdot+}-Ac$), 271 (100, $M^{\cdot+}-CO_2CH_3$), 229 (20, $M^{\cdot+}-CH_2CO-CO_2Me$), 212 (42, $C_{14}H_{14}NO^+$), 186 (26, $C_{12}H_{12}NO^+$), 152 (33, $C_8H_{10}NO_2^+$), 96 (38, $C_6H_{10}N^+$); exact mass calculated for $C_{18}H_{22}N_2O_4$: 330.1580, found: 330.1583.

4.1.3. (4a*R* *,6*S* *,8a*R* *)-1-Acetyl-6-(hydroxymethyl)-6-phenyloctahydro[1,7]naphthyridin-8(2*H*)-one 18. To an ice-cooled solution of 193 mg (0.58 mmol) **17** in 20 mL THF/H_2O (4:1) was added 111 mg (5 equiv.) of $NaBH_4$. This mixture was stirred at 60°C during 30 min. After cooling, the unreacted $NaBH_4$ was destroyed by adding 20 mL of 10% HCl/H_2O. Next, THF was evaporated followed by addition of water and CH_2Cl_2. After separation of the organic phase, the water phase was extracted three times with CH_2Cl_2 and the combined organic layers were dried on anhydrous K_2CO_3. Filtration and evaporation of the solvent yielded alcohol **18**. Yield: 80%; transparent oil; IR (NaCl, cm^{-1}): 3377.2, 3303.7 (NH, OH), 1676.5 (C═O); ^1H NMR (400 MHz, $CDCl_3$). Major rotamer (70%): 7.66 (s, 1H, H^7), 7.42–7.27 (m, 5H, H-arom.), 5.01 (d, *J*=7 Hz, 1H, H^{8a}), 3.72–3.60 (m, 2H, CH_2OH+H^{2eq}), 3.18 (broad t, *J*=12 Hz, 1H, H^{2ax}), 3.00 (broad s, 1H, OH), 2.59 (dd, *J*=14, 8 Hz, 1H, H^{5eq}), 2.14 (m, 1H, H^{4a}), 2.09 (s, 3H, $COCH_3$), 1.93 (dd, *J*=14, 5 Hz, 1H, H^{5ax}), 1.83, 1.67, 1.39, 1.30 (m, 4H, H^3+H^4). Minor rotamer (30%): 7.75 (s, 1H, H^7), 7.42–7.27 (m, 5H, H-arom.), 4.43 (d, *J*=13 Hz, 1H, H^{2eq}), 3.99 (d, *J*=7 Hz, H^{8a}), 3.72–3.55 (m, 2H, CH_2OH+H^{2ax}), 3.24 (broad s, 1H, OH), 2.71 (dd, *J*=14, 9 Hz, 1H, H^{5eq}), 2.24 (m, 1H, H^{4a}), 1.63 (s, 3H, $COCH_3$), H^{5ax}, H^3 and H^4 are hidden; ^{13}C NMR (100 MHz, $CDCl_3$). Major rotamer: 171.3, 171.1 (CO), 142.5 (C-*ipso*), 129.1, 127.7, 125.5 (C-*ortho*+C-*meta*+C-*para*), 70.7 (CH_2OH), 61.6 (C^6), 51.8 (C^{8a}), 43.8 (C^2), 36.9 (C^5), 31.6 (C^{4a}), 30.3, 24.9 (C^3+C^4), 21.6 ($COCH_3$). Minor rotamer: CO not resolved, 142.4 (C-*ipso*), 129.2, 127.9, 125.5 (C-*ortho*+C-*meta*+C-*para*), 70.3 (CH_2OH), C^6 not resolved, 56.2 (C^{8a}), 38.9 (C^2), 36.3 (C^5), 31.8 (C^{4a}), 31.1, 24.1 (C^3+C^4), 21.2 ($COCH_3$); *m*/*z* (E.I., %): 302 (9, $M^{\cdot+}$), 271 (100, $M^{\cdot+}-CH_2OH$), 259 (51, $M^{\cdot+}-Ac$), 229 (29, $M^{\cdot+}-CH_2OH-CH_2CO$), 212 (60, $C_{14}H_{14}NO^+$), 186 ($C_{12}H_{12}NO^+$), 152 (46, $C_8H_{10}NO_2^+$); exact mass calculated for $C_{17}H_{22}N_2O_3$: 302.1630, found: 302.1627.

4.1.4. (4a*R* *,6*S* *,8a*R* *)-1-Acetyl-6-({[3,5-bis(trifluormethyl) benzyl]oxy}methyl)-6-phenyloctahydro[1,7] naphthyridin-8(2*H*)-one 19 and bis-benzylated compound 20. To a suspension of 24 mg (1 mmol) of NaH in 5 mL of dry THF was added 312 mg (1.0 mmol) of **18** in 20 mL of dry THF. This mixture was stirred for 30 min at 45°C. After cooling, 195 μL (1 equiv.) of 3,5-bis(trifluormethyl)benzyl bromide was added, and the reaction mixture was stirred at room temperature for 2 h. When the reaction was found to be incomplete (TLC monitoring: silica gel, 5% MeOH/CH_2Cl_2, rf: 0.07 (**18**), 0.22 (**19**), 0.89 (side product **20**), another 12 mg (0.5 equiv.) of NaH was added, and stirring was continued for 2 h. Next, the reaction mixture was worked up with 50 mL of H_2O. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried on anhydrous K_2CO_3, filtered, and concentrated. The residue was purified by preparative TLC (silica gel, 5% MeOH/CH_2Cl_2) to yield two fractions: *Fraction 1*. **20**: yield: 20%; white solid, mp 188–191°C (MeOH/CH_2Cl_2); IR (KBr, cm^{-1}): 1675.1 (C═O); ^1H NMR (400 MHz, $CDCl_3$). Major rotamer: 7.77–7.24 (m, 11H, H-arom.), 5.51 (d, *J*=16 Hz, 1H, NCH_2Ar), 5.23 (d, *J*=7 Hz, 1H, H^{8a}), 4.44 (d, *J*=16 Hz, 1H, NCH_2Ar), 4.32 (d,

J=12 Hz, 1H, OCH_2Ar), 4.03 (d, J=12 Hz, 1H, OCH_2Ar), 3.71–3.61 (m, 3H, C^{6}CH_2O+H^{2eq}), 3.20 (t, J=12 Hz, 1H, H^{2ax}), 2.76 (dd, J=14, 9 Hz, 1H, H^{5eq}), 2.19 (m, 1H, H^{4a}), 2.10 (s, 3H, COCH$_3$), 2.08 (dd (hidden), 1H, H^{5ax}), 1.94–1.26 (m, 4H, H^3+H^4). Minor rotamer: most signals are hidden under the major rotamer; ^{13}C NMR (100 MHz, $CDCl_3$). Major rotamer: 171.073, 171.047 (C^8+*C*OCH$_3$ (lb=0.5 Hz)), 142.4, 141.4 (C-*ipso* (Ar)), 139.2 (C-*ipso* (Ph)), 131.8 (q, J=34 Hz, CCF_3), 131.4 (q, J=32 Hz, *C*CF$_3$), 129.5, 128.2, 125.3 (C-*ortho*+C-*meta*+C-*para* (Ph)), 127.0 (broad s, 2×C-*ortho*), 123.2 (q, J=271 Hz, CF_3), 123.0 (q, J=271 Hz, CF_3), 121.9 (m, C-*para* (Ar)), 120.5 (m, C-*para* (Ar)), 76.3 (C^6*C*H$_2$O), 71.6 (O*C*H$_2$Ar), 66.2 (C^6), 52.1 (C^{8a}), 47.9 (N*C*H$_2$Ar), 43.6 (C^2), 39.2 (C^5), 30.9 (C^4), 30.5 (C^{4a}), 25.0 (C^3), 21.4 (CO*C*H$_3$). Minor rotamer: most signals are not resolved; *m/z* (E.I., %): 754 (9, M$^{\cdot+}$), 735 (15, M$^{\cdot+}$−F), 711 (45, M$^{\cdot+}$−Ac), 527 (15, M$^{\cdot+}$−$C_9H_5F_6$), 497 (100, M$^{\cdot+}$−$CH_2OC_9H_5F_6$), 455 (13, M$^{\cdot+}$−CH$_2$CO−$CH_2OC_9H_5F_6$), 438 (49, $C_{23}H_{18}NOF_6^+$), 227 (32, $C_9H_5F_6^+$), 152 (45, $C_8H_{10}NO_2^+$); exact mass calculated for $C_{35}H_{30}F_{12}N_2O_3$: 754.2065, found: 754.2070. *Fraction 2*. **19**: yield: 52%; white crystals, mp 103–105°C (MeOH/CH_2Cl_2); IR (KBr, cm^{-1}): 1681.3 (C═O), 1629.8 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$). Major rotamer (67%): 7.77 (s, 1H, H-*para* (Ar)), 7.51 (s, 2H, H-*ortho* (Ar)), 7.41–7.30 (m, 5H, Ph-H), 6.70 (s, 1H, H^7), 5.17 (d, J=6 Hz, 1H, H^{8a}), 4.58 (d, J=13 Hz, 1H, CH_2Ph), 4.41 (d, J=13 Hz, 1H, CH_2Ph), 3.70–3.61 (m, 3H, C^{6}CH_2O+H^{2eq}), 3.24 (broad t, J=12 Hz, 1H, H^{2ax}), 2.58 (dd, J=14, 8 Hz, 1H, H^{5eq}), 2.11 (s, 3H, COCH$_3$), 1.90 (dd, J=14, 4 Hz, 1H, H^{5ax}), 1.87 (m, 1H, H^{4a}), 1.79, 1.51–1.33 (m, 4H, H^3+H^4. Minor rotamer (33%): 7.77 (s, 1H, H-*para* (Ar)), 7.51 (s, 2H, H-*ortho* (Ar)), 7.41–7.30 (m, 5H, Ph-H), 7.02 (s, 1H, H^7), 4.58 (d, J=13 Hz, 1H, CH_2Ph), 4.47 (broad d, J=12 Hz, 1H, H^{2eq}), 4.35 (d, J=13 Hz, 1H, CH_2Ph), 4.04 (d, J=6 Hz, H^{8a}), H^{2ax} is hidden, 2.74 (dd, J=14, 9 Hz, 1H, H^{5eq}), 2.24 (m, 1H, H^{4a}), 1.69 (s, 3H, COCH$_3$), H^{5ax}, H^3 and H^4 are hidden; ^{13}C NMR (100 MHz, $CDCl_3$). Major rotamer: 170.5, 169.7 (CO), 143.5 (C-*ipso* (Ar)), 140.1 (C-*ipso* (Ph)), 131.8 (q, J=33 Hz, *C*CF$_3$), 129.0, 127.7, 125.0 (C-*ortho*+C-*meta*+C-*para* (Ph)), 127.1 (broad s, C-*ortho*, (Ar)), 123.2 (q, J=271 Hz, CF_3), 121.7 (m, C-*para* (Ar)), 78.6 (O*C*H$_2$Ph), 71.8 (C^6*C*H$_2$O), 60.1 (C^6), 51.8 (C^{8a}), 43.5 (C^2), 37.8 (C^5), 32.4 (C^{4a}), 29.9, 25.3 (C^3+C^4), 21.5 (CO*C*H$_3$). Minor rotamer: most signals are not resolved; *m/z* (E.I., %): 528 (6, M$^{\cdot+}$), 509 (6, M$^{\cdot+}$−F), 485 (34, M$^{\cdot+}$−Ac), 301 (7, M$^{\cdot+}$−$C_9H_5F_6$), 271 (100, M$^{\cdot+}$−$CH_2OC_9H_5F_6$), 229 (18, M$^{\cdot+}$−CH$_2$CO−$CH_2OC_9H_5F_6$), 227 (11, $C_9H_5F_6^+$), 212 (41, $C_{14}H_{14}NO^+$), 152 (30, $C_8H_{10}NO_2^+$); exact mass calculated for $C_{26}H_{26}F_6N_2O_3$: 528.1848, found: 528.1847.

4.1.5. (4a*R,6*S**,8a*R**)-6-{[3,5-Bis(trifluormethyl)benzyl]-oxy} methyl-6-phenyloctahydro[1,7]naphthyridin-8(2*H*)-one 9.** A solution of 50 mg (0.1 mmol) of **19** in HCl-saturated methanol was stirred at 60°C for 2 days. Next, the solvent and HCl were evaporated. After addition of 10% K_2CO_3/H_2O to the residue, the aqueous mixture was extracted three times with CH_2Cl_2. The combined organic phases were dried on anhydrous K_2CO_3, filtered and evaporated. The residue was purified by preparative TLC (silica gel, 10% MeOH/CH_2Cl_2) to afford **9**. Yield: 64% (81% with recovery of starting material); transparent oil; IR (NaCl, cm^{-1}): 1662.7 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): 7.75 (s, 1H, H-*para* (Ar)), 7.47 (s, 2H, H-*ortho* (Ar)), 7.41–7.29 (m, 5H, Ph-H), 6.67 (s, 1H, H^7), 4.63 (d, J=13 Hz, 1H, OCH_2Ph), 4.39 (d, J=13 Hz, 1H, OCH_2Ph), 3.87 (d, J=9 Hz, 1H, C^{6}CH_2O), 3.74 (d, J=9 Hz, 1H, C^{6}CH_2O), 3.28 (d, J=4 Hz, 1H, H^{8a}), 3.06 (broad d, J=11 Hz, 1H, H^{2eq}), 2.64 (td, partially hidden, 1H, H^{2ax}), 2.62 (t, J=13 Hz, 1H, H^{5ax}), 2.48 (s, 1H, H^1), 1.84 (m, 1H, H^{4a}), 1.70 (broad d, J=13 Hz, 1H, H^{5eq}), 1.66–1.41 (m, 4H, H^3+H^4); ^{13}C NMR (100 MHz, $CDCl_3$): 172.9 (C^8), 143.0 (C-*ipso* (Ph)), 131.7 (q, J=33 Hz, *C*CF$_3$), 128.6, 127.4, 125.6 (C-*ortho*+C-*meta*+C-*para* (Ph)), 127.0 (broad s, C-*ortho* (Ar)), 123.2 (q, J=271 Hz, CF_3), 121.6 (m, C-*para* (Ar)), 78.8 (C^6*C*H$_2$O), 71.7 (O*C*H$_2$Ph), 61.9 (C^6), 57.8 (C^{8a}), 46.7 (C^2), 32.5 (C^5), 28.3 (C^4), 27.7 (C^{4a}), 21.4 (C^3); *m/z* (E.I., %): 486 (10, M$^{\cdot+}$), 443 (100, M$^{\cdot+}$−C_2H_5N), 259 (6, M$^{\cdot+}$−$C_9H_5F_6$), 229 (25, M$^{\cdot+}$−$CH_2OC_9H_5F_6$), 227 (20, $C_9H_5F_6^+$), 186 (59, $C_{12}H_{12}NO^+$), 96 (94, $C_6H_{10}N^+$); exact mass calculated for $C_{24}H_{24}N_2O_2F_6$: 486.1742, found: 486.1734.

4.1.6. (4a*R,6*S**,8a*R**)-6-{[3,5-Bis(trifluormethyl)benzyl]-oxy} methyl-6-phenyloctahydro[1,7]naphthyridine 8.** To a solution of 28.5 mg (0.59 mmol) of **9** in 10 mL of dry THF was added 59 μL (2 equiv.) of a 2 M solution of BH_3·DMS in THF. This mixture was stirred under reflux during 1 h. Next, the solvent was evaporated and the residue was redissolved in HCl-saturated MeOH. The mixture was refluxed for 30 min to destroy the intermediate complex **21**. After cooling, a 10% solution of K_2CO_3 in H_2O was added, and the mixture extracted three times with CH_2Cl_2. The organic phase was dried on anhydrous K_2CO_3 and the residue was purified by preparative TLC (silica gel, 10% MeOH/CH_2Cl_2) to yield **8**,[22] which was crystallised from Et_2O/heptane. Yield: 43%, white crystals, mp 163–165°C (Et_2O/heptane); IR (cm^{-1}, KBr): 3429.0 (NH), 1626.1; ^{1}H NMR (400 MHz, $CDCl_3$):[23] 7.71 (s, 1H, H-*para* (Ar)), 7.48 (s, 2H, H-*ortho* (Ar)), 7.45 (d, J=7 Hz, 2H, H-*ortho* (Ph)), 7.35 (t, J=7 Hz, 2H, H-*meta*), 7.28 (t, J=7 Hz, 1H, H-*para*), 4.42 (s, 2H, OCH_2Ph), 3.64 (2×d (AB), J=9 Hz, 2H, C^{6}CH_2O), 3.56 (broad d, J=11 Hz, 1H, H^{2eq}), 3.36 (d, J=14 Hz, 1H, H^{8eq}), 2.92 (broad s, 1H, H^{8a}), 2.89 (d, J=14 Hz, 1H, H^{8ax}), 2.83 (t, J=12 Hz, 1H, H^{2ax}), 2.35 (t, J=14 Hz, 1H, H^{5ax}), 2.16 (dd, J=14 Hz, 1H, H^{5eq}), 2.11 (m, 1H, H^{3ax}), 1.94 (m, 1H, H^{4a}), 1.70–1.65 (m, 3H, H^{3eq}+H^4); ^{13}C NMR (100 MHz, $CDCl_3$): 141.2, 140.5 (C-*ipso* (Ph)+C-*ipso* (Ar)), 131.5 (q, J=33 Hz, *C*CF$_3$), 128.5, 127.1 (C-arom. (Ph), one signal is hidden), 127.0 (broad s, C-*ortho* (Ar)), 123.2 (q, J=273 Hz, CF_3), 80.9 (C$_6$*C*H$_2$O), 71.7 (O*C*H$_2$Ph), 59.8 (C^6), 54.3 (C^{8a}), 44.8 (C^2), 43.8 (C^8), 29.8 (C^5), 28.4 (C^4), 28.3 (C^{4a}), 17.8 (C^3); *m/z* (E.I., %): M$^{\cdot+}$-signal was not detected, 376 (12, M$^{\cdot+}$−$C_6H_{10}N$), 227 (9, $C_9H_5F_6^+$), 215 (100, M$^{\cdot+}$−$CH_2OCH_2C_9H_5F_6$); exact mass calculated for $C_{24}H_{26}N_2OF_6$: 472.1949, found: M$^{\cdot+}$ not detected; exact mass calculated for $C_{18}H_{16}NOF_6$: 376.1136, found: 376.1133; exact mass calculated for $C_{14}H_{19}N_2$: 215.1555, found: 215.1548.

4.1.7. 1-(4-Pentenyl)-3-phenyl-2(1*H*)-pyrazinone 11. To a solution of 3.5 g (19.4 mmol) of 3-phenyl-2(1*H*)-pyrazinone **22** (see Ref. 17) in 150 mL dioxane was added 8.0 g of Cs_2CO_3 (1.2 equiv.). After stirring this mixture at 50°C for 30 min, 3.0 mL of 5-bromo-1-pentene (1.5 equiv.) was added, and stirring at 50°C was continued for 1 week. Following filtration of unreacted Cs_2CO_3 and CsBr formed and removal of the solvent, the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give two

fractions consisting of O- and N-alkenylated product, respectively. Only the N-alkenylated product (**11**) was isolated. Yield: 96%; yellow oil; IR (NaCl, cm^{-1}): 1650.3 (C=O), 1591.3 (C=N); ^1H NMR (400 MHz, $CDCl_3$): 8.3–7.4 (m, 6H, H-arom.+H^6), 7.08 (d, J=4 Hz, 1H, H^5), 5.80 (ddt, J=18, 10, 7 Hz, 1H, $H^{4'}$), 5.06 (m, 2H, $H^{5'}$), 3.95 (t, J=7 Hz, 2H, $H^{1'}$), 2.14 (quart, J=7 Hz, 2H, $H^{3'}$), 1.91 (quint, J=7 Hz, 2H, $H^{2'}$); ^{13}C NMR (100 MHz, $CDCl_3$): 155.4 (C^2), 153.4 (C^3), 136.7 ($C^{4'}$), 136.0 (C-*ipso*), 129.8 (C-*para*), 128.9 (C-*meta*), 127.9 (C^6+C-*ortho*), 123.2 (C^5), 115.9 ($C^{5'}$), 49.6 ($C^{1'}$), 30.5 ($C^{3'}$), 27.5 ($C^{2'}$); *m/z* (E.I., %): 240 (46, $M^{\cdot+}$), 186 (40, $M^{\cdot+}-C_4H_6$), 172 (35, $M^{\cdot+}-C_5H_8$), 105 (100, $PhCO^+$), 77 (32, Ph^+); exact mass calculated for $C_{15}H_{16}N_2O$: 240.1263, found: 240.1258.

4.1.8. 1-Phenyl-3,10-diazatricyclo[5.3.1.0^{3,8}]undecan-2-one 14. A solution of 335 mg (1.4 mmol) of **11** in dry PhCl was refluxed for 3 days. Next, the solvent was evaporated and the residue was redissolved in dry THF. To this solution was added 50 mg of 10% Pd/C. After degassing, the mixture was hydrogenated at 40 psi (Parr-apparatus) during 1 night. The mixture was filtered and evaporated. The residue was purified by column chromatography (silica gel, 5% $MeOH/CH_2Cl_2$) followed by HPLC (silica gel, 5% $MeOH/CH_2Cl_2$). Yield: 57%; white crystals; mp 160–163°C ($MeOH/CH_2Cl_2$); IR (KBr, cm^{-1}): 3438.2 (broad, NH), 1647.2 (C=O); ^1H NMR (400 MHz, $CDCl_3$): 7.53–7.25 (m, 5H, H-arom.), 4.25 (dd, J=13, 5 Hz, 1H, H^{4eq}), 3.38 (m, 1H, H^8), 3.27 (dd, J=11, 4 Hz, 1H, $H^{9'}$), 3.14 (dd, J=11, 1 Hz, 1H, H^9), 2.87 (td, J=13, 3 Hz, 1H, H^{4ax}), 2.46 (dd, J=13, 10 Hz, 1H, $H^{11'}$), 2.35 (broad d, J=10 Hz, 1H, $H^{7'}$), 1.86 (dd, J=13, 2 Hz, 1H, H^{11}), 1.92–1.80 (m, 3H, H^5+H^6+H^{10}), 1.62 (m, 1H, H^6), 1.36 (m, 1H, H^5); ^{13}C NMR (75 MHz, $CDCl_3$): 182.5 (C^2), 139.2 (C-*ipso*), 127.8, 127.4; 127.1 (C-*ortho*+C-*meta*+C-*para*), 61.4 (C^1), 57.9 (C^8), 49.9 (C^4), 46.0 (C^9), 39.7 (C^{11}), 33.8 (C^7), 30.0, 18.5 (C^5+C^6); *m/z* (E.I., %): 242 (100, $M^{\cdot+}$), 214 (72, $M^{\cdot+}-CO$), 158 (55, $M^{\cdot+}-(CH_2)_3NCO$); exact mass calculated for $C_{15}H_{18}N_2O$: 242.1419, found: 242.1424.

4.1.9. Methyl (4a*R* *,6*S* *,8a*R* *)-6-phenyldecahydro[1,7]naphthyridine-6-carboxylate 15. To a solution of 94 mg (0.39 mmol) of **14** in 20 mL MeOH was added 131 μL (3.5 equiv.) CH_3SO_3H. This solution was stirred at reflux temperature for 1 night. Next, the solvent was evaporated, and the residue was distributed between CH_2Cl_2 and 10% K_2CO_3 in H_2O. After separation of the organic phase, the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried on anhydrous K_2CO_3, filtered and evaporated to afford pure **15**. Yield: 97 %; transparent oil; IR (NaCl, cm^{-1}): 1732.5 (C=O); ^1H NMR (400 MHz, $CDCl_3$): 7.56 (d, J=7 Hz, 2H, H-*ortho*), 7.37 (t, J=7 Hz, 2H, H-*meta*), 7.27 (t, J=7 Hz, 1H, H-*para*), 3.62 (s, 3H, CO_2CH_3), 3.20 (broad d, J=12 Hz, 1H, H^{2eq}), 2.94 (dd, J=14, 2 Hz, 1H, H^{8eq}), 2.77 (dd, J=14, 3 Hz, 1H, H^{8ax}), 2.70 (td, J=12, 3 Hz, 1H, H^{2ax}), 2.61 (m, 1H, H^{8a}), 2.51 (t, J=14 Hz, 1H, H^{5ax}), 2.37 (dd, J=14, 4 Hz, 1H, H^{5eq}), 1.77 (m, 1H, H^{4a}), 1.76 (m, 1H, H^{3ax}), 1.64 (m, 2H, H^4), 1.42 (dt, J=13, 3 Hz, 1H, H^{3eq}); ^{13}C NMR (100 MHz, $CDCl_3$): 174.4 (CO_2CH_3), 138.3 (C-*ipso*), 128.5, 127.3, 127.2 (C-*ortho*+C-*meta*+C-*para*), 63.8 (C^6), 53.2 (C^{8a}), 52.4 (CO_2CH_3), 46.2 (C^2), 46.0 (C^8), 30.7 (C^5), 29.4 (C^4), 29.3 (C^{4a}), 20.3 (C^3); *m/z* (E.I., %): 275 (1, $M^{\cdot+}$), 215 (100, $M^{\cdot+}-C_2H_4O_2$), 96 (66, $C_6H_{10}N^+$), 83 (38, $C_5H_9N^+$); exact mass calculated for $C_{16}H_{20}N_2O_2$: 274.1681, found: 274.1677.

4.1.10. Methyl (4a*R* *,6*S* *,8a*R* *)-1,7-diacetyl-6-phenyldecahydro[1,7]naphthyridine-6-carboxylate 23 and tricyclic compound 24. A solution of 250 mg of **15** and 252 mg (2 equiv.) DMAP in 50 mL acetic anhydride was stirred at 60°C for 2 h. Next, Ac_2O and the acetic acid formed were evaporated, and the residue was purified by preparative TLC (silica gel, 5% $MeOH/CH_2Cl_2$), which afforded two fractions. *Fraction 1*. **24**: yield: 13%; brown crystals, mp 125–127°C ($MeOH/CH_2Cl_2$); IR (KBr, cm^{-1}): 1694.4 (C=O), 1662.7 (C=O); ^1H NMR (400 MHz, $CDCl_3$, 318 K): 7.39–7.31 (m, 5H, H-arom.), 4.16 (dd, J=13, 5 Hz, 1H, H^{4eq}), 3.91 (dd, J=12, 3 Hz, 1H, $H^{9'}$), 3.72 (dd, J=12, 2.5 Hz, 1H, H^9), 3.47 (m, 1H, H^8), 2.92 (td, J=13, 2 Hz, 1H, H^{4ax}), 2.83 (dd, J=14, 10 Hz, 1H, $H^{11'}$), 2.43 (m, 1H, H^7), 1.94 (dd, J=14, 3 Hz, 1H, H^{11}), 1.89 (m, 1H, H^{6ax}), 1.72 (m, 1H, H^{5ax}), 1.68 (m, 1H, H^{6eq}), 1.49 (broad s, 3H, $COCH_3$), 1.35 (m, 1H, H^{5eq}); ^{13}C NMR (100 MHz, $CDCl_3$, 318 K): 177.1 (C^2), 171.9 ($COCH_3$), 137.5 (C-*ipso*), 130.6, 126.1 (broad, 2×C-*ortho*), 128.1 (C-*meta*), 127.9 (C-*para*), 67.4 (C^1), 57.3 (C^8), 50.5 (C^9), 49.8 (C^4), 36.1 (C^{11}), 32.9 (C^7), 29.5 (C^6), 24.9 (broad, $COCH_3$), 17.6 (C^5); *m/z* (E.I., %): 284 (54, $M^{\cdot+}$), 256 (14, $M^{\cdot+}-CO$), 242 (100, $M^{\cdot+}-CH_2CO$), 241 (25, $M^{\cdot+}-Ac$), 213 (88, $M^{\cdot+}-Ac-CO$), 158 (22, $M^{\cdot+}-Ac-(CH_2)_3NCO$), 156 (34, $C_{11}H_{10}N^+$); exact mass calculated for $C_{17}H_{14}N_2O_2$: 284.1525, found: 284.1521. *Fraction 2*. **23**: yield: 73%; white crystals, mp 166°C ($MeOH/CH_2Cl_2$); IR (KBr, cm^{-1}): 1742.5 (C=O-ester), 1644.0 (C=O-lactam) ^1H NMR (400 MHz, CD_2Cl_2, 223 K). Major rotamer (77%): 7.36–7.25 (m, 5H, H-arom.), 4.37 (m, 1H, H^{8a}), 3.60 (t, J=11 Hz, 1H, H^{8ax}), 3.59 (d (hidden), 1H, H^{2eq}), 3.56 (s, 3H, CO_2CH_3), 3.52 (dd, J=11, 4 Hz, 1H, H^{8eq}), 2.87 (broad t, J=11 Hz, 1H, H^{2ax}), 2.63 (dd, J=14.5, 7 Hz, 1H, H^{5eq}), 2.19 (s, 3H, $COCH_3$), 2.10 (dd, J=13.5, 11 Hz, 1H, H^{5ax}), 1.98 (s, 3H, $COCH_3$), 1.80 (m, 1H, H^{4eq}), 1.60 (m, 1H, H^{3eq}), 1.54 (m, 1H, H^{4a}), 1.23 (m, 2H, H^{4ax}+H^{3ax}). Minor rotamer (23%): 7.36–7.25 (m, 5H, H-arom.), 4.4 (hidden, 1H, H^{2eq}), 3.93 (t, J=12 Hz, 1H, H^{8ax}), 3.77 (m, 1H, H^{8a}), 3.6 (hidden, 3H, CO_2CH_3), 3.44 (dd, J=11.5, 2.5 Hz, 1H, H^{8eq}), 2.72 (dd, J=15, 8 Hz, 1H, H^{5eq}), 2.38 (broad t, J=13 Hz, 1H, H^{2ax}), 2.22 (s, 3H, $COCH_3$), 2.1 (hidden, 1H, H^{5ax}), 1.79 (s, 3H, $COCH_3$), H^3 and H^4 are hidden, 1.70 (m, 1H, H^{4a}); ^{13}C NMR (100 MHz, CD_2Cl_2, 233 K), Major rotamer: 172.4 (CO_2CH_3), 170.6, 169.7 (2×$COCH_3$), 137.3 (C-*ipso*), 127.44, 127.36, 127.1 (C-*ortho*+C-*meta*+C-*para*), 65.3 (C^6), 52.6 (CO_2CH_3), 44.4 (C^{8a}), 43.4 (C^2), 41.7 (C^8), 39.7 (C^5), 27.7 (C^4), 26.2 (C^{4a}), 23.4 (C^3), 22.44, 22.39 (2×$COCH_3$). Minor rotamer: C=O, C-arom. and C^6 are not resolved/hidden, 52.7 (CO_2CH_3), 48.9 (C^{8a}), 43.8 (C^8), 39.4 (C^5), 37.6 (C^2), 27.8 (C^4), 27.0 (C^{4a}), 23.1 (C^3), 21.6, 21.8 (2×$COCH_3$); *m/z* (E.I., %): 358 (17, $M^{\cdot+}$), 326 (45, $M^{\cdot+}-CH_3OH$), 315 (44, $M^{\cdot+}-Ac$), 299 (16, $M^{\cdot+}-CO_2Me$), 284 (17, $M^{\cdot+}-CH_3OH-Ac$), 257 (100, $M^{\cdot+}-CH_2CO-CO_2Me$), 181 (27, $C_{14}H_{13}^+$), 138 (11, $C_8H_{12}NO^+$); exact mass calculated for $C_{20}H_{26}N_2O_4$: 358.1893, found: 358.1894.

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References

1. For a recent review on SP and its receptor, see: (a) Harisson, S.; Geppetti, P. *Int. J. Biochem. Cell Biol.* **2001**, *33*, 555–576. (b) Saria, A. *Eur. J. Pharmacol.* **1999**, *375*, 51–60.
2. For a review, see: Nakanishi, S. *Ann. Rev. Neurosci.* **1991**, *14*, 123–136.
3. (a) Erspamer, V.; Melchiorri, P. *Trends Pharmacol. Sci.* **1980**, *1*, 391–395. (b) Mussap, C. J.; Geraghty, D. P.; Burcher, E. *J. Neurochem.* **1993**, *60*, 1987–2009.
4. (a) Joos, G. F.; Germonpré, P. R.; Pauwels, R. A. *Allergy* **2000**, *55*, 321–337. (b) Joos, G. F.; Pauwels, R. A. *Curr. Opin. Pharmacol.* **2001**, *1*, 235–241.
5. Snijdelaar, D. G.; Dirksen, R.; Slappendel, R.; Crul, B. J. P. *Eur. J. Pain* **2000**, *4*, 121–135.
6. Rupniak, N. M. J.; Kramer, M. S. *Trends Pharmacol. Sci.* **1999**, *20*, 485–490.
7. Snider, R. M.; Constantine, J. W.; Lowe, J. A., III.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J. *Science* **1991**, *251*, 435–437.
8. Desai, M. C.; Lefkowitz, S. J.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911–4913.
9. Dionne, R. A.; Max, B. M.; Gordon, S. M.; Parada, S.; Sang, C.; Gracely, R. H.; Sethna, N. F.; MacLean, D. B. *Clin. Pharmacol. Ther.* **1998**, *64*, 562–568.
10. Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.
11. Stevenson, G. I.; MacLeod, A. M.; Huscroft, I.; Cascieri, M. A.; Sadowski, S.; Baker, R. *J. Med. Chem.* **1995**, *38*, 1264–1266.
12. For reviews on SP antagonists, see: (a) Swain, C. *Exp. Opin. Ther. Patents* **1996**, *6*(2), 169–174. (b) Eliott, J.; Seward, E. M. *Exp. Opin. Ther. Patents* **1997**, *7*(1), 43–54. (c) Seward, E. M.; Swain, C. J. *Exp. Opin. Ther. Patents* **1999**, *9*(5), 571. (d) Leroy, V.; Mauser, P.; Gao, Z.; Peet, N. P. *Exp. Opin. Investig. Drugs* **2000**, *9*(4), 735.
13. Rombouts, F. J. R.; De Borggraeve, W.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron Lett.* **2001**, *42*, 7397–7399.
14. Rombouts, F. J. R.; De Borggraeve, W. M.; Delaere, D.; Froeyen, M.; Toppet, S. M.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2003**, *10*, 1868–1878.
15. Takeuchi, Y.; Shands, E. F. B.; Beusen, D. D.; Marshall, G. R. *J. Med. Chem.* **1998**, *41*, 3609–3623.
16. (a) Harrison, T.; Owens, A. P.; Williams, B. J.; Swain, C. J.; Baker, R.; Hutson, P. H.; Sadowski, S.; Cascieri, M. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 209–212. (b) Ladduwahetty, T.; Baker, R.; Cascieri, M. A.; Chambers, M. S.; Haworth, K.; Keown, L. E.; MacIntyre, D. E.; Metzger, J. M.; Owen, S.; Rycroft, W.; Sadowski, S.; Seward, E. M.; Shepheard, S. L.; Swain, C. J.; Tattersall, F. D.; Watt, A. P.; Williamson, D. W.; Hargreaves, R. J. *J. Med. Chem.* **1996**, *39*, 2907–2914.
17. Jones, R. G. *J. Am. Chem. Soc.* **1949**, *71*, 79.
18. Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792.
19. Coupling values are slightly changed by irradiation. Thus, apparent coupling values are measured.
20. (a) Jencks, W. P. In *Proceedings of the XVIII Solvay Conference on Chemistry*; van Binst, G., Ed.; Springer: Berlin, 1986; p 59. (b) Franklin, T. J. *Biochem. Pharmacol.* **1989**, *29*, 853.
21. (a) Aue, D. H.; Webb, H. M.; Bowers, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 2699–2701. (b) Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973**, *95*, 3504–3510.
22. Due to the very low rf value of **8** (0.05 on silica gel, eluent: 10% MeOH/CH_2Cl_2), alumina is probably a better stationary phase for this purification. MeOH was used to isolate the product from the silica gel. Subsequently the filtrate was concentrated, the residue was redissolved in CH_2Cl_2 and the solution filtered to remove the silica gel precipitate.
23. At room temperature, the amine protons of **8** are coalesced with water (δ 1–6). Both protons were detected as broad singlets at δ 9.88 and δ 8.94 in a cooled solution (198 K, CD_2Cl_2).