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High regiocontrol in the nucleophilic ring opening of 1-aralkyl-3,4-epoxypiperidines with amines—a short-step synthesis of 4-fluorobenzyltrozamicol and novel anilidopiperidines

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ABSTRACT

Nucleophilic ring-opening reactions of three 1-aralkyl-3,4-epoxypiperidines with a series of aliphatic and aromatic amines have been investigated. Reactions in protic solvents, preferably 2-propanol, gave rise to 3-amino-piperidin-4-ols in ratios up to 20:1. Accordingly, 4-fluorobenzyltrozamicol, a highly potent ligand for the vesicular acetylcholine transporter was obtained directly from an epoxide ring opening in one step, without the need of chromatographic separation. Reactions in acetonitrile assisted by Li-salts, most suitable with LiBr, led regioselectively to *trans*-4-amino-piperidin-3-ols in high yields. *N*-Phenethyl substituted anilino-piperidinols as easily obtained by this method were converted into a series of new β-hydroxy substituted anilidopiperidines.

1. Introduction

The development of novel modular methodologies leading to readily accessible synthetic templates is an area of intensive investigation in pharmaceutical and organic synthesis.[1] Fragment couplings as well as intramolecular pairing of functional groups for diversity-oriented synthesis (DOS) strategies[2] or combinatorial chemistry in solution,[3] require reliable and highly effective reactions.[4] The trans-stereospecific course and facility of the nucleophilic ring opening has made three-membered rings, such as epoxides[4a,5] and activated aziridines[6] to favourable building blocks.

Recently, we have utilized a regioselective nucleophilic ring opening on an epoxycyclohexane template for an exploratory library synthesis of cyclohexane-fused morpholin-3-ones.[7] In this paper, we describe full details on the ring opening of 1-aralkyl-3,4-epoxypiperidines **7a**–**c** with aliphatic and aromatic amines by applying a Lewis acid or a non-Lewis acid promoted reaction.[8]

Polyfunctionalized piperidines are frequently found in natural products and are common structural targets in pharmaceutical research.[9] 3,4-Substituted piperidines[10] containing a beta-amino alcohol or diol moiety are of interest as they form the core of naturally occurring pseudodistomins[11] and iminosugars,[12] respectively.

4-Fluorobenzyltrozamicol (4-FBT) **3bb** (Fig. 1), labelled with fluorine-18, has been persistently used as radiotracer for imaging the vesicular acetylcholine transporter (VAChT) with positron emission tomography (PET).[13] In contrast, compounds containing the vicinally substituted 4-aminopiperidine motif appear to be more widespread in pharmaceutical related research. Examples of such molecules include the 4-anilidopiperidine analgesics **1b** (ohmefentanyl),[14a,b] **1c**[14c] and the cyclooctyl substituted J-113397 **2**,[15] which was

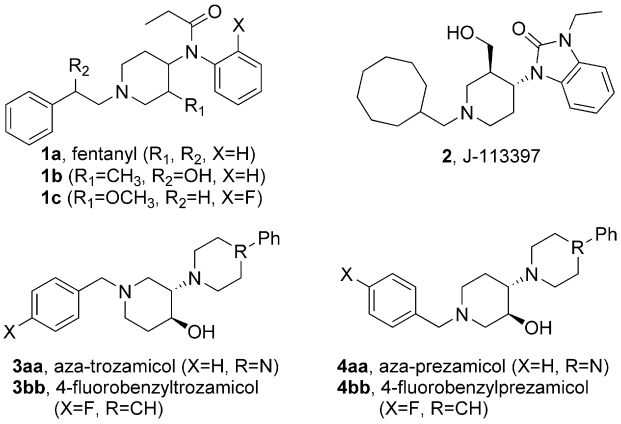

Fig. 1. Examples of different 1,3,4-substituted piperidines.

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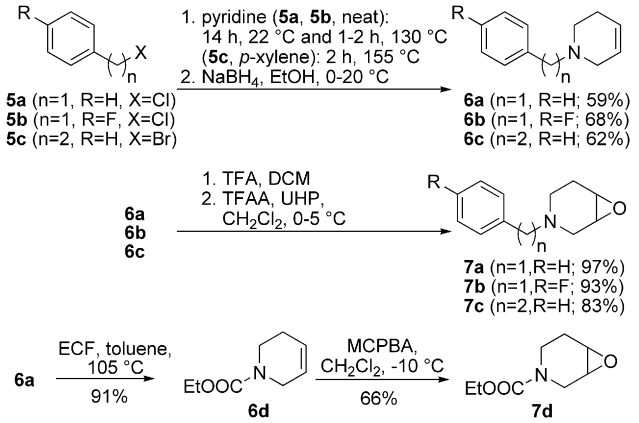
reported as first potent and highly selective nociceptin receptor (NOP) antagonist. Prezamicol derivatives (**4aa**, **4bb**) are of interest as regioisomers with different binding properties to the VAChT.[16]

Amongst a couple of different methods to obtain these kinds of structures, particularly the ring opening of 3,4-epoxypiperidines appears to be an attractive key-step if aiming at an efficient library synthesis[17a] and for involvement in stereocontrolled approaches[17b] as well. However, in contrast to methodology, processing a common acyl[16] or carbamoyl[18] protective group at the piperidine nitrogen, we choose an aralkyl substitution. This conveniently allows the combination of a suitable N-protection as well as the introduction of a pharmacophoric element that is required for binding to a biological target.

To our knowledge, highly regioselective conversions of these types of 3,4-epoxypiperidines are rare and have been scarcely published.[19] The $LiClO_4$-assisted ring opening of **7a** (Scheme 1) with a series of amines has been previously reported by Grishina and co-workers[19a,c] to lead exclusively to *trans*-4-amino-piperidin-3-ols (C4-product) with no detection of the opposite C3-regioisomer.[20]



Scheme 1. Synthesis of *N*-substituted 3,4-epoxypiperidines **7a**–**d**.

Concurrent to our work,[8] a very recent letter describing a method to yield and isolate highly enriched C4- and C3-products (up to >20:1) from the same epoxide **7a** by regioselective reaction with five different amines was published by Ikemoto and co-workers.[21] This report has prompted us to disclose our own results in this area in obtaining pure *trans*-4-amino-piperidin-3-ols and *trans*-3-amino-piperidin-4-ols.

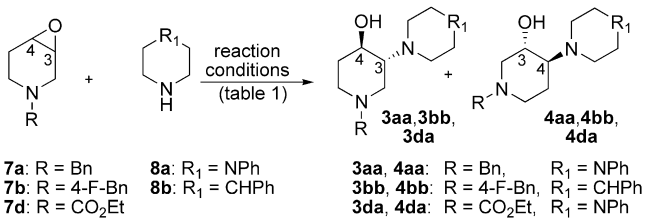
2. Results and discussion

Initially, we were interested in a convenient synthesis of trozamicol analogues such as **3bb** (Fig. 1).[16] Recently, results were published by Emond and co-workers, who disclosed members of the regioisomeric 4-cycloamino-piperidin-3-ol series, as even more favourable in terms of VAChT binding properties.[22] However, these comparisons were made with a series of structurally related piperazines (Fig. 1, azaprezamicol **4aa** with R=N) instead of the originally used piperidines (prezamicols, **4bb** with R=CH).[16] Therefore, as part of our persistent efforts in the search for new VAChT ligands for PET we elaborated a diversity-oriented short-step preparation of both regioisomeric forms, which would obviate the need for protection and deprotection steps.

2.1. Synthesis of 1-aralkyl 3,4-epoxypiperidines

Amongst a number of routes to 1-aralkyl tetrahydropyridines, which were needed as starting materials,[23] we regarded the borohydride reduction of an *N*-alkyl pyridinium salt as the most convenient approach.[23d] Pyridine was reacted first with a series of aralkyl halides (Scheme 1) either under solvent-free conditions (**5a**, **5b**) or in refluxing xylene (**5c**) to form the corresponding pyridinium salts. For the partial reduction we followed a modified protocol according to Oediger and Joop.[24] Sodium borohydride (1.3–1.8 equiv) was gradually added to a solution of the *N*-substituted pyridinium salt in ethanol at 0–20 °C leading to a clean reduction to the desired tetrahydropyridine.

Previous attempts to epoxidize the basic tetrahydropyridine **6a** with a standard oxidizing agent, such as *m*-chloroperoxybenzoic acid (MCPBA) were not chemoselective and resulted in an over-oxidation by formation of the amine-*N*-oxide as by-product.[25] Thus, a full protonation of the basic piperidine nitrogen with trifluoroacetic acid prior to the oxidation was regarded as necessary.[26] By using urea-hydrogen peroxide (UHP)[27] in combination with trifluoroacetic anhydride (TFAA) in dichloromethane (DCM) at 0–5 °C it was possible to epoxidize the amino-olefins in form of their trifluoroacetate salts to obtain the epoxides **7a**–**c** in excellent yields (Scheme 2). The *N*-ethoxycarbonyl substituted epoxide **7d**, which served as basis for a comparison, was prepared from **6a** via interchange of the *N*-benzyl group[23d,25] with ethylchloroformate (ECF) to obtain **6d** followed by epoxidation with MCPBA (Scheme 1).



Scheme 2.

2.2. Regio-controlled ring opening of 1-aralkyl-3,4-epoxypiperidines—synthesis of 4-FBT

An experiment for a ring opening at the outset of our study is depicted in Scheme 2. The reaction of **7a** with 4-phenylpiperazine (**8a**) in EtOH at 95 °C in a closed tube resulted in the full conversion of the starting epoxide within 6 h and in the predominant formation of the 4-hydroxypiperidinol derivative **3aa**. A small amount of a by-product was detected by TLC and identified as the regioisomer **4aa** via comparison with an authentic sample. Removal of the solvent and recrystallization of the solid residue from aqueous MeOH afforded pure **3aa** in 81% yield. From a subsequent ring opening of **7b** with 4-phenylpiperidine **8b** we obtained in a similar manner the desired 4-FBT **3bb** in 78% yield.

Encouraged by these initial results and to estimate potential solvent and chelation effects on the degree of regioselectivity, additional protic solvents were tested as well as reactions in acetonitrile (ACN) in the presence of a metal salt acting as a Lewis acid catalyst. We investigated the ring opening of the epoxides **7a** and **7b** with two amines **8a** and **8b**. Table 1 summarizes the results of both procedures. The relative ratios of isomers were determined by comparing the peak areas of the individual regioisomers, detected in the crude product mixtures by HPLC analysis (CS Multosorb RP18—7 μm, 250×4 mm).

In addition to EtOH, also other protic solvents, such as 2-propanol (IPA) and 2,2,2-trifluoroethanol[28] (TFE) were found to be well suited for a reasonably rapid conversion of the starting epoxide at 95 °C (Table 1, entries 1–3, 12 and 13). The best C3-regioselectivities[20] were observed when IPA was used as the solvent, in spite of resulting in a somewhat lower reaction rate (Table 1, entries 2 and 13). On the other hand, the shorter reaction time in TFE appeared to

Table 1
Investigation of the conditions for the formation of aminoalcohols **3**/**4** from epoxide **7** and amine **8** produced via Scheme 2

Entry	**7**+**8**[a]	Solvent (T [°C])	Salt (mol %)[b]	t (h)[c]	Ratio **3**/**4**[d]
1	**7a**+**8a**	EtOH (95)	—	6	**3aa**/**4aa** 94:6
2	**7a**+**8a**	IPA (95)	—	7	96:4
3	**7a**+**8a**	TFE (95)	—	4	92:8
4	**7a**+**8a**	ACN (85)	—	96	93:7
5	**7a**+**8a**	ACN (rt)	$LiClO_4$ (120)	12	9:91
6	**7a**+**8a**	ACN (rt)	$LiClO_4$ (20)	40	46:54
7	**7a**+**8a**	ACN (rt)	LiBr (120)	12	4:96
8	**7a**+**8a**	ACN (rt)	LiBr (20)	40	9:91
9	**7a**+**8a**	ACN (rt)	LiCl (120)	20	10:90
10	**7a**+**8a**	ACN (rt)	$NaClO_4$ (120)	240	43:57
11	**7a**+**8a**	ACN (rt)	$Mg(ClO_4)_2$ (120)	12	39:61
12	**7b**+**8b**	EtOH (95)	—	4	**3bb**/**4bb** 92:8
13	**7b**+**8b**	IPA (95)	—	6	94:6
14	**7b**+**8b**	ACN (rt)	LiBr (120)	12	5:95
15	**7b**+**8b**	ACN (rt)	$LiClO_4$ (120)	12	7:93
16	**7d**+**8a**	ACN (rt)	$LiClO_4$ (120)	18	**3da**/**4da** 37:63[e]
17	**7d**+**8a**	IPA (90)	—	18	60:40[e,f]

[a] Solutions of **7** for salt-assisted [0.1–0.25 M] and for reactions without a salt [0.5 M] were used; amine **8** was applied in a ratio of 1.08 to epoxide **7**.
[b] mol % relative to epoxide **7**.
[c] No starting epoxide was detected by TLC.
[d] Relative ratios of products, which were not isolated, but determined by HPLC, unless otherwise noted (see Supplementary data; pairs of regioisomers, **3aa**/**4aa** and **3bb**/**4bb** have approximately equal UV response factors).
[e] Determined by ^{1}H NMR analysis.
[f] Isolated yield of **3da**: 25%, **4da**: 22%.

be accompanied by a lower regioselectivity, which might be due to the strong H-bond donating properties of TFE (Table 1, entry 3). The time required for completion of the reaction in ACN as aprotic solvent was significantly increased, with preservation of the C3-regioselectivity (Table 1, entry 4).

As expected, the epoxide ring opening with an aliphatic amine in ACN was accelerated in the presence of a metal salt and was found to be completed at room temperature within up to 12 h. The conversions resulted in a regioselectivity change to yield predominantly 3-hydroxypiperidinols, derived from a C4-attack on the starting epoxide.

Among a series of alkali and earth alkali salts, which were tested as activators for ring opening of **7a**, **7b** and **7d** by cyclic amines, LiBr[29] and $LiClO_4$[30] gave the best results (Table 1, entries 5–8 and 14–16). Repeatedly, LiBr turned out to be slightly superior as additive. Thus, a C4-/C3-product ratio of up to 96:4 could be observed after reaction of epoxide (**7a** or **7b**) in the presence of 120 mol % of LiBr (Table 1, entries 7 and 14). By contrast lower ratios were obtained with $LiClO_4$ (Table 1, entries 5 and 15). The favourable effect of LiBr compared to $LiClO_4$[†] became more apparent when the amount of the added salt was reduced to 20 mol % (Table 1, entry 6 vs entry 8).

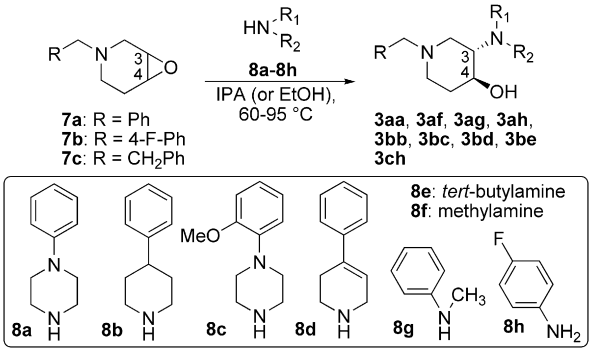
In contrast to LiBr and $LiClO_4$, the reaction in the presence of LiCl proceeded slower and gave a slightly lower regioselectivity (Table 1, entry 9). Interestingly, $Mg(ClO_4)_2$ shows good potential as activator, however, with a very poor regioselectivity (Table 1, entry 11). $NaClO_4$, which was reported to be capable of activating the regioselective aminolysis of 3,4-epoxytetrahydropyran,[30] was virtually inactive in our approach (Table 1, entry 10).

1-Ethoxycarbonyl-3,4-epoxypiperidine **7d** was similarly reacted in two experiments with **8a**. As expected, regioselectivity was low in both conversions (Table 1, entries 16 and 17). The results indicate that the existence of a localized nitrogen lone pair in 1-aralkyl-3,4-epoxypiperidines, such as **7a** or **7b**, unlike **7d**, is supposed to be required for achieving high regioselectivity.

[†] In organic solvents lithium perchlorate is a potential explosive hazard. It must be handled in small amounts and with appropriate care.

To further investigate the synthetic scope, a wider series of aliphatic and aromatic amines was applied in conversions with epoxides **7a**–**c**. The entries of Table 2 clearly show that apart of cycloamines (Table 2, entries 1, 4, 8 and 9), also small and bulky aliphatic amines (Table 2, entries 3 and 2) may all be coupled using this method.

Table 2
Synthesis of *trans*-3-amino-piperidin-4-ols **3**



Entry	Reactants	Ratio **8**/**7** [a]	Solvent (T [°C])[a]	t (h)	Product **3** (yield %)[c,d]
1	**7b**+**8b**	1.04	IPA (95)	6	**3bb** (80)
2	**7b**+**8e**	5.0	IPA (90)	18	**3be** (63)
3	**7a**+**8f**	6.1	EtOH (60)	18	**3af** (66)[e]
4	**7a**+**8a**	1.01	IPA (95)	6	**3aa** (83)
5	**7a**+**8g**	1.12	EtOH (90)	48[b]	**3ag** (70)
6	**7a**+**8h**	2.0	EtOH (85)	20	**3ah** (71)
7	**7c**+**8h**	1.9	EtOH (85)	30	**3ch** (83)
8	**7b**+**8c**	1.02	IPA (95)	6	**3bc** (64)
9	**7b**+**8d**	1.05	IPA (95)	6	**3bd** (71)

[a] Solutions of **7** [0.5–1.0 M] and **8** were reacted in a pressure tube.
[b] The conversion in IPA needed 72 h (95 °C) to go to completion.
[c] Crystallized yield (free of C4-regioisomer, as detected by TLC and ^{1}H NMR analysis).
[d] Isolated by evaporation of the reaction mixture and crystallization (see Experimental): **3bb**, **3aa**, **3ch**, **3bd** (free base); **3be**, **3bc** (2HCl salt); **3ag** (HCl salt) and **3ah** (hemioxalate salt).
[e] Both regioisomers were separated by flash chromatography (see Supplementary data), followed by crystallization as 2HBr salt: **3af** (major isomer), as 2HCl salt: **4af** (minor isomer, in 8% yield).

In addition to aliphatic amines also weakly nucleophilic anilines turned out as suitable substrates and gave the corresponding C3-products as crystalline bases or salts without the need of chromatographic separation (Table 2, entries 5–7). However, due to the reduced nucleophilicity compared to aliphatic cycloamines it was found advisable for a shorter reaction time to work in EtOH (Table 2, entry 5) and apply a substantial excess of the aniline derivative, which could be readily removed by distillation during the work-up (Table 2, entries 6 and 7).

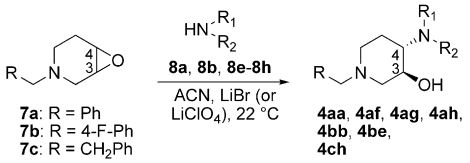
It should be noted that any attempt to analyze mixtures of **3ag**/**4ag** (Table 2, entry 5) by TLC failed. The ^{1}HNMR analysis of the crude reaction mixture revealed a ratio of 93:7 (see Supplementary data).

A second series of ring-opening reactions was carried out under metal-assisted conditions in ACN, by using either LiBr or $LiClO_4$. The desired C4-aminoalcohols were efficiently prepared and isolated as free bases (Table 3).

The obtained yields appeared to benefit from the use of LiBr as additive in direct comparison with $LiClO_4$ (Table 3, entries 1–8), thus confirming aforementioned results (see Table 1).

Next, we were interested to compare aliphatic and aromatic amines, which have been found to create high regioselectivity in both types of ring openings of **7a**–**c** with 4-thiocresol (**8s**) as a sulfur nucleophile. As depicted in Scheme 3, a reaction of **8s** with epoxide **7a**, carried out in EtOH at 60 °C, was judged as being completed by TLC after 6 h. However, a mixture of **3as**/**4as** was

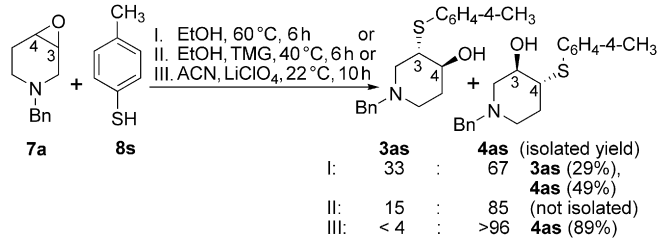
Table 3
Synthesis of *trans*-4-amino-piperidin-3-ols **4**



Entry	Reactants	Li-salt[a]	Ratio **8**/**7**	*t* (h) [b]	Product **4** (yield %)[c]
1	**7b**+**8b**	$LiClO_4$	1.04	12	**4bb** (79)
2	**7b**+**8b**	LiBr	1.04	12	**4bb** (82)
3	**7b**+**8e**	$LiClO_4$	1.3	24	**4be** (76)
4	**7b**+**8e**	LiBr	1.3	24	**4be** (82)
5	**7a**+**8f**	$LiClO_4$	4.2	12	**4af** (80)
6	**7a**+**8f**	LiBr	4.5	12	**4af** (91)
7	**7a**+**8a**	$LiClO_4$	1.07	12	**4aa** (70)
8	**7a**+**8a**	LiBr	1.07	12	**4aa** (85)
9	**7a**+**8g**	LiBr	1.05	24	**4ag** (96)
10	**7a**+**8h**	LiBr	1.25	24	**4ah** (92)
11	**7c**+**8h**	LiBr	1.25	24	**4ch** (86)

[a] 120 mol % relative to epoxide.
[b] No starting epoxide was detected by TLC.
[c] Crystallized yield (free of C3-regioisomer, as detected by TLC or H NMR analysis); Isolated after aqueous work-up followed by evaporation and crystallization (for further details see Experimental part and Supplementary data): **4bb**, **4aa**, **4ag**, **4ah**, **4be** (free base); **4af** (2HCl salt); **4ch** (HCl salt).

formed in a ratio of approximately 1:2 as determined by ^{1}H NMR analysis. Both regioisomers were readily separated by medium pressure chromatography (MPLC). A slight modification, by using 1,1,3,3-tetramethylguanidine (TMG) as strong base to deprotonate **8s** allows to reduce the reaction temperature to 40 °C, but the product distribution was found to be displaced now even further towards the regioisomer **4as**, derived from the cleavage of the epoxy C4-bond.



Scheme 3. Thiolysis of **7a** by 4-thiocresol **8s** under different conditions.

As expected, the Li-assisted reaction led to a full conversion of **7a** within 10 h at 22 °C and to a high predominance of the C4-product **4as**, which was isolated in 89% yield.[19c]

2.3. NMR—structural correlations

The structure of *trans*-3-amino-4-hydroxy- and *trans*-4-amino-3-hydroxy piperidines, obtained by C3- and C4-ring opening of epoxides **7a**–**d** was confirmed by NMR measurements in $CDCl_3$ (^{1}H, ^{13}C, ^{19}F, APT, COSY, HSQC, and HMBC at 22 °C). With combination of these methods it was possible to assign unambiguously almost all the signals for protons, carbons and fluorines as well.

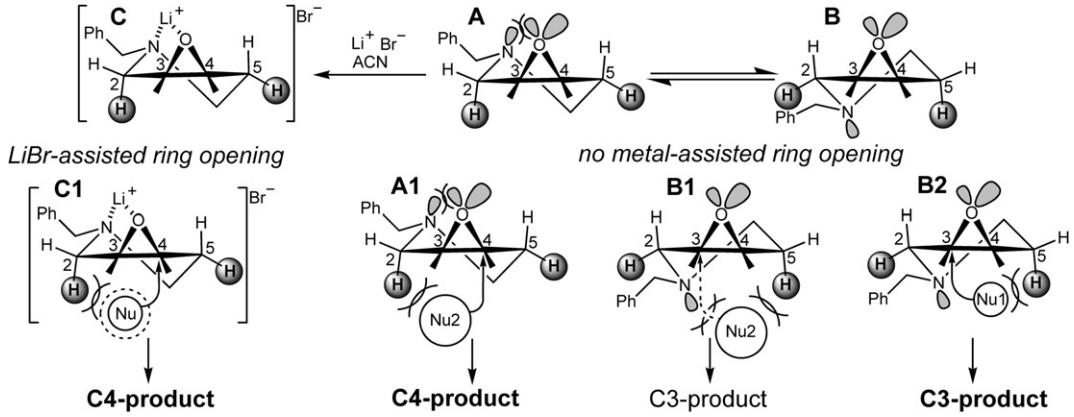
Regarding the ^{13}C-APT signals associated to the piperidin-3/-4-ol ring carbons, the secondary 5-C could be observed as signal in the range of 20–38 ppm. In case of products derived from a C4-ring opening, the piperidine 5-C is vicinal to a primary or secondary amino group (or thioether) and frequently gave an isolated signal, which is caused by stronger shielding (δ<30 ppm) relative to the corresponding 5-C in C3-products (δ>30 ppm), which is neighboured to the tertiary hydroxymethylene (4–C) carbon. Only one exceptional case was found in the **3be**/**4be** pair of regioisomers. As expected, a reverse shift was consistently observed also for the piperidin-3/-4-ol 2-C resonances.

2.4. Steric effects on regioselectivity

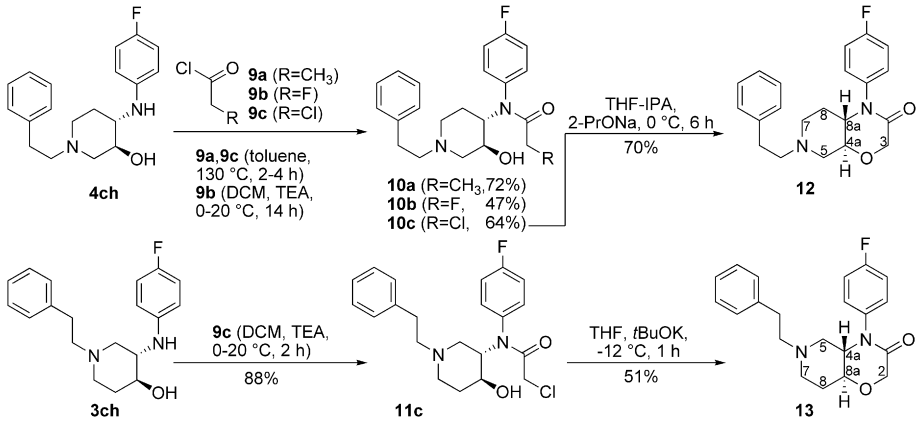
Because of the structural resemblance of 1-benzyl-3,4-epoxypiperidine **7a** with epoxycyclohexane its conformation could be regarded as half-chair with a quasi-axial and quasi-equatorial H-atom at 2-C and 5-C as well.[31] In contrast to the latter one, which rapidly equilibrate between two enantiomeric conformations,[31b] 3,4-epoxypiperidine may similarly switch its conformation, however, into forms, which appear to be energetically unequal (Scheme 4, conformers **A** and **B**). Due to mutual repulsion of one of the two *O*-lone pairs with the localized lone pair of the piperidine nitrogen in **A**, the prevalence of **B** as energetically favoured conformer is more likely.[32]

A small amine nucleophile (Nu1), intended to react axially and in accordance with the Fürst–Plattner rule[33] with the epoxide electrophile in **B** (Scheme 4, **B2**), may preferentially attack at the 3-C epoxy carbon due to the sterically unfavourable interaction (of the lone pair in Nu1) with the bonding pair of the H-atom in quasi-axial position on 5-C, located at the same side.[34]

Regarding the different regioselectivity of the thiolysis reaction in EtOH (Scheme 3) it appears that the attack of thiol **8s** on conformation **A** becomes more decisive (Scheme 4, Nu2 on **A1**). Due to its character as a softer Lewis base a repulsive force between the more spacious lone pairs on the thiol S-atom and the lone pair of



Scheme 4. Rationalization of the regiocontrol in the course of the nucleophilic ring opening of **7a**.



Scheme 5. Synthesis of hexahydro-pyrido oxazin-ones **12** and **13**.

the piperidine nitrogen as depicted in **B1** (Scheme 4) might take place. A similar regioselectivity has been reported in ring-opening reactions of 3,4-epoxytetrahydropyran.[30]

In case of the nucleophilic ring-opening reactions assisted by a Li–salt, the metal-ion appears to be chelated both with the epoxy O- and the piperidine N atom. Primarily, there is an electronic activation both on 3-C and 4-C through the epoxide oxygen, which is co-ordinated to the lithium cation. In addition a 'frozen' conformation **C** is more likely, which will be attacked by the nucleophile Nu (Nu1 or Nu2) preferentially at the 4-C epoxy carbon from steric reasons, which are quite similar to the non-chelate case (Scheme 4, **C1**).

2.5. Synthesis of hexahydro-pyrido oxazin-ones

Intrigued by the opportunity of achieving an efficient dual regiocontrol we sought to further develop this method to obtain two potential new molecular entities (NMEs). Thus, starting either from ring opened product **4ch** or **3ch** a simple two-step access to conformationally rigid fluorinated anilidopiperidine analogues **12** and **13** was conceived. Both pathways and the synthesis of new 3-hydroxyfentanyl derivatives **10a** and **10b** as well are depicted in Scheme 5.

Due to the steric demand and reduced nucleophilicity of the phenylamino group in addition to the competing vicinal OH-group a selective and efficient N-acylation was anticipated to be difficult. While the fluoroacetyl derivative **10b** was obtained under standard conditions in only 47% yield, the conversions of **9a** and **9c** in toluene at 130 °C without an added base gave an improvement to gain **10a** and **10c** in reasonable yields. The hexahydro-1*H*-pyrido[3,4-*b*][1,4] oxazin-2(3*H*)-one **12** was finally obtained from **10c** applying an approved ring-closure protocol.[7]

We next examined the conversion of **3ch** into the expected lactame **13** by the corresponding pathway. The initial N-chloroacetylation to form **11c** was found to proceed smoothly, but for its subsequent ring closure under similar conditions as described for **12**, we were faced with a greater extent of hydrolysis back to the anilinoalcohol **3ch**. Therefore, a modified protocol with a THF solution of potassium *tert*-butanolate at −12 °C for 1 h was adapted to obtain hexahydro-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one **13** after removal of **3ch** by flash chromatography.

3. Conclusion

In summary, we present an efficient 3-pot/4-step approach for the preparation of 3-amino-4-hydroxypiperidines and its regioisomers. In contrast to former methodology, processing a common *N*-acyl or *N*-carbamoyl protective group at the 3,4-epoxypiperidine, which exclusively led to a low regioselectivity, the 1-aralkyl group allows for applying tuned experimental protocols resulting in a high regioselection. Thus, avoiding a deprotection step and a time consuming chromatographic separation it was possible to obtain 4-FBT in an overall yield of up to 51% (3-pot/4-step=68%+93%+80%), starting from simple starting materials. The high regioselectivity observed appears to be induced mainly by steric reasons.

4. Experimental part

4.1. General

NMR spectra were recorded using Varian spectrometers (Varian Gemini, Varian Mercury). Mass spectra were recorded on an FT-ICR APEX II (Bruker Daltonics) and a Mariner Biospectrometry Workstation (Applied Biosystems). Analytical TLC was performed on silica gel coated sheets (Macherey–Nagel 60 F_{254}, 0.25 mm thickness) with the following mixtures of solvents: Sm2 ($CHCl_3$, MeOH, NH_3; 10:1:0.1); sm4 ($CHCl_3$, MeOH; 12:1). Organic solvents were purified by standard procedures. Starting amines (**8a**–**h**) were commercial products.

4.2. Preparation of *N*-aralkyl-1,2,3,6-tetrahydropyridines

The required 1,2,3,6-tetrahydropyridines **6a**,[23d] and **6c**[35] were prepared according to an approved protocol.[24] The preparation of **6b** outlined below represents a typical procedure.

*4.2.1. Representative procedure of 1-(4-fluorobenzyl)-1,2,3,6-tetrahydropyridine (**6b**).* A mixture of pyridine (2.0 g, 25.2 mmol) and 4-fluorobenzylchloride (3.62 g, 25 mmol) was stirred at 22 °C for 24 h. The resulting highly viscous material was heated to ~130 °C for 1 h while the pyridinium salt solidified as a reddish mass. It was crushed, dissolved by stirring in EtOH (20 mL), and $NaBH_4$ (1.22 g, 32 mmol) was gradually added at 0–3 °C within 6 h. The resulting mixture was stirred for 14 h at 10–20 °C, H_2O (15 mL) and Celite (1 g) were added and stirring was continued for 5 h. The solid was filtered off, washed with EtOH (3×3 mL) and the filtrate was concentrated to a volume of ~15 mL. After addition of aqueous NaOH (0.25 M, 15 mL), the two-phase mixture was extracted with MTBE (4x15 mL). The combined organic phase was washed with brine (15%, 15 mL), dried (Na_2CO_3), filtered and evaporated. The residual orange oil (5.1 g) was purified by distillation to provide **6b** (3.25 g, 68%), as a slightly yellowish oil, $bp_{(12\ mbar)}$ 114–116 °C; ^1H NMR (300.1 MHz, $CDCl_3$): δ_H 2.12–2.20 (m, 2H, 3-H_2), 2.54 (t-like, *J*=5.5 Hz, 2H, 2-H_2), 2.95 (m, 2H, 6-H_2), 3.54 (s, 2H, ArCH_2N), 5.62–5.69 (m, 1H, 4-H), 5.72–5.80 (m, 1H, 5-H), 6.95–7.04 (m, 2H, Ar: 3′-H, 5′-H), 7.28–7.35 (m, 2H, Ar: 2′-H, 6′-H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 26.28 (3-C), 49.70 (2-C), 52.85 (6-C), 62.26 (ArCH_2N), 115.09 (d, *J*=21.01 Hz, 2C_{Ar}, 3′-C, 5′-C), 125.38 (4-C), 125.42

(5-C), 130.70 (d, J=7.74 Hz, 2C_{Ar}, 2′-C, 6′-C), 134.23 (d, J=2.21 Hz, 1C_{Ar}, 1′-C), 162.11 (d, J=244.4 Hz, 1C_{Ar}, 4′-C); ^{19}F NMR (282.3 MHz, $CDCl_3$): δ_F −116.46 (m, 1F_{Ar}, 4′-F); LRMS (ESI) m/z=192.12 (MH^+, 100%); HRMS (ESI) calcd for $C_{12}H_{14}FN$ $[M+H]^+$: 192.11830; found: 192.11830.

4.3. Epoxidation of 1-aralkyl-1,2,3,6-tetrahydropyridines

*4.3.1. Representative procedure of 1-(4-fluorobenzyl)-3,4-epoxypiperidine (**7b**).* A mixture of UHP (1.85 g, 19.6 mmol) in dry DCM (16 mL) was stirred at 5 °C while a solution of TFAA (4.12 g, 2.74 mL, 19.6 mmol) in DCM (8 mL) was gradually added within 15 min. The resulting mixture was stirred at 0–2 °C for 1 h. A cold solution prepared from **6b** (2.68 g, 14 mmol) and trifluoroacetic acid (TFA, 2.08 g, 18.2 mmol) in DCM (10 mL) was added at 2–6 °C within 5 min. After stirring at 0–3 °C for 20 min, the temperature was reduced to −15 to −10 °C. A solution of Na_2SO_3 (1.52 g, 12 mmol) and K_2CO_3 (3.46 g, 25 mmol) in H_2O (18 mL) was carefully added to the vigorously stirred mixture without allowing the temperature to raise above 10 °C. After addition, the mixture was stirred for 2 min and a test of the aqueous (upper) layer with KI-starch paper displayed a negative result for the presence of peroxide. The organic phase was separated and the aqueous layer was extracted with DCM (2×10 mL). The combined organic phase was washed with $NaHCO_3$ (7.5%, 8 mL), dried (Na_2CO_3), filtered and evaporated. The residue (3.6 g) was dissolved in MTBE (12 mL), filtered through a plug of silica gel 60 (40–63 μm, ~2 g) and evaporated to leave a product (2.82 g, 97%), which turned out to be pure enough for subsequent transformations. The product was further purified by bulb-to-bulb distillation in vacuo (1–2 mbar) at 130–150 °C (air-bath temperature) to yield **7b** (2.70 g, 93%), as a colourless oil; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ_H 1.91–2.00 (2 m, 2H, 5-H_2), 2.18 (ddd, J=11.7, 9.4, 4.7 Hz, 1H, 6-H_a), 2.29 (m, 1H, 6-H_b), 2.66 (d, J=13.3 Hz, 1H, 2-H_a), 2.97 (ddd, J=13.3, 3.9, 1.6 Hz, 1H, 2-H_b), 3.18–3.24 (m, 2H, 3-H, 4-H), 3.40 (s, 2H, PhCH_2N), 6.98 (m, 2H_{Ar}, 3′-H, 5′-H), 7.24 (m, 2H_{Ar}, 2′-H, 6′-H); ^{13}C NMR (100.0 MHz, $CDCl_3$): δ_C 25.66 (1C_{sec}, 5-C), 45.87 (1C_{sec}, 6-C), 50.73 (1C_{tert}, 3-C {or 4-C}), 51.35 (1C_{tert}, 4-C {or 3-C}), 52.38 (1C_{sec}, 2-C), 61.59 (1C_{sec}, 4F-PhCH_2N), 115.12 (d, J=22.1 Hz, 2C_{Ar}, 3′-C, 5′-C), 130.55 (d, J=8.8 Hz, 2C_{Ar}, 2′-C, 6′-C), 133.79 (d, J=4.4 Hz, 1C_{Ar}, 1′-C), 162.12 (d, J=246.2 Hz, 1C_{Ar}, 4′-C); ^{19}F NMR (376.4 MHz, $CDCl_3$): δ_F −116.18 (m, 1F_{Ar}, 4′-F); LRMS (ESI) m/z=208.12 (MH^+, 100%); HRMS (ESI) calcd for $C_{12}H_{14}FNO$ $[M+H]^+$: 208.11322; found: 208.11322.

*4.3.2. 1-Phenethyl-3,4-epoxypiperidine (**7c**).* Following the representative procedure in Section 4.3.1, by using **6c** (3.75 g, 20 mmol), UHP (2.65 g, 28 mmol) and TFAA (5.9 g, 3.93 mL, 28 mmol) to provide **7c** (3.74 g, 92%), as a slightly yellowish oil. A sample (625 mg) was further purified by isocratic MPLC using MTBE with 1% additive of 32% solution of trimethylamine in IPA to obtain **7c** (562 mg, 83%), as a colourless oil; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.97–2.17 (m, 2H, 5-H_2), 2.32 (ddd, J=11.7, 8.8, 4.7 Hz, 1H, 6-H_a), 2.39 (m, 1H, 6-H_b), 2.54–2.61 (m, 2H, PhCH_2–CH_2N), 2.75–2.83 (m, 3H, 2-H_a, PhCH_2–CH_2N), 3.09 (ddd [br], J=13.5, 4.1, 1.2 Hz, 1H, 2-H_b), 3.24–3.28 (m [br], 2H, 3-H, 4-H), 7.12–7.32 (2 m, 5H_{Ar}, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 25.66 (1C_{sec}, 5-C), 33.64 (PhCH_2CH$_2$N), 46.34 (1C_{sec}, 6-C), 50.63 (1C_{tert}, 3-C [or 4-C]), 51.38 (1C_{tert}, 4-C [or 3-C]), 52.37 (1C_{sec}, 2-C), 59.98 (PhCH$_2$CH_2N), 126.15 (1C_{Ar}, 4′-C), 128.49 (2C_{Ar}, 3′-C, 5′-C), 128.74 (2C_{Ar}, 2′-C, 6′-C), 140.27 (1C_{Ar}, 1′-C); LRMS (ESI) m/z=204.08 (MH^+, 100%); HRMS (ESI) calcd for $C_{13}H_{17}NO$ $[M+H]^+$: 204.13829; found: 204.13829.

4.4. Non-Lewis acid-catalysed epoxide ring opening of 7a–c

*4.4.1. Representative procedure of (3SR,4SR)-1-(4-fluorobenzyl)-3-(4-phenylpiperidin-1-yl)piperidin-4-ol (**3bb**).* A mixture of epoxide **7b** (0.12 g, 0.58 mmol) and 4-phenylpiperidine (**8b**, 0.097 g, 0.6 mmol) in IPA (0.8 mL) was stirred in a closed reaction vial (4 mL volume) and heated to 95–98 °C (bath temperature) for 6 h, till the completion of the reaction, as indicated by TLC analysis (sm2). The solvent was evaporated and the viscous residue was dissolved in $CHCl_3$ (5 mL), filtered through a plug of silica gel 60 (40–63 μm, ~0.6 g) and evaporated. The solid was recrystallized from MeOH/H_2O (4:1, 1.5 mL) to yield **3bb** (0.171 g, 80%), as white crystals, mp 144–146 °C; R_f=0.50 (sm2); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.61 (m, 1H, 5-H_a), 1.63–2.02 (m, 6H, 2-H_a, 6-H_a, 3′-H_2, 5′-H_2), 2.04 (ddd, J=11.7, 4.7, 2.3 Hz, 1H, 5-H_b), 2.26 (dt-like, J=11.7, 2.3 Hz, 1H, 2′-H_a), 2.46 (tt-like, J=11.7, 4.1 Hz, 1H, 4′-H), 2.54 (dt-like, J=10.5, 3.5 Hz, 1H, 3-H), 2.72 (m, 1H, 6′-H_a), 2.79–2.88 (m [br], 2H, 6-H_b, 6′-H_b), 2.96–3.06 (m, 2H, 2-H_b, 2′-H_b), 3.46 (ddd, J=10.5, 10.0, 4.7 Hz, 1H, 4-H), 3.50 (AB, J=13.5 Hz, 2H, ArCH_2N), 3.70 (s [br], 1H, OH), 7.01 (m, 2H_{Ar}, 3″-H, 5″-H), 7.16–7.34 (m, 7H_{Ar}, 2″-H, 6″-H, 2‴-H, 6‴-H); ^{13}C NMR (75.449 MHz, $CDCl_3$): δ_C 32.38 (1C_{sec}, 5-C), 34.24 (1C_{sec}, 3′-C [or 5′-C]), 34.46 (1C_{sec}, 5′-C [or 3′-C]), 43.06 (1C_{tert}, 4′-C), 46.10 (1C_{sec}, 2′-C), 50.17 (1C_{sec}, 2-C), 51.66 (1C_{sec}, 6-C), 53.76 (1C_{sec}, 6′-C), 62.36 (1C_{sec}, ArCH_2N), 67.61 (1C_{tert}, 4-C), 68.21 (1C_{tert}, 3-C), 115.56 (d, J=22.1 Hz, 2C_{Ar}, 3″-C, 5″-C), 126.31 (1C_{Ar}, 4‴-C), 126.91 (2C_{Ar}, 2‴-C, 6‴-C), 128.56 (2C_{Ar}, 3‴-C, 5‴-C), 130.47 (d, J=7.7 Hz, 2C_{Ar}, 2″-C, 6″-C), 134.18 (d, J=3.3 Hz, 1C_{Ar}, 1″-C), 146.28 (1C_{Ar}, 1‴-C), 162.13 (d, J=245.5 Hz, 1C_{Ar}, 4″-C); ^{19}F NMR (282.3 MHz, $CDCl_3$): δ_F −116.25 (m, 1F_{Ar}, 4″-F); LRMS (ESI) m/z=369.25 (MH^+, 100%). Anal. Calcd for $C_{23}H_{29}FN_2O$ (%): C, 74.97; H, 7.93; N, 7.60. Found: C, 74.95; H, 8.02; N, 7.56.

*4.4.2. (3SR,4SR)-1-Benzyl-4-(4-phenylpiperazin-1-yl)piperidin-3-ol (**3aa**).* According to representative procedure in Section 4.4.1, colourless powder, yield: 83%; mp 123–125 °C [MeOH/H_2O (5:1)] (lit.[22] mp 131–132 °C); R_f=0.39 (sm2); ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.62 (m, 1H, 5-H_a), 1.96 (m, 1H, 2-H_a), 1.98 (m, 1H, 6-H_a), 2.06 (m, 1H, 5-H_b), 2.59 (dt-like, J=10.0, 3.5 Hz, 1H, 3-H), 2.64 (m, 2H, 2′-H_a, 6′-H_a), 2.87 (m [overlapped], 1H, 6-H_b), 2.93 (m, 2H, 2′-H_b, 6′-H_b), 3.04 (m, 1H, 2-H_b), 3.17 (m, 4H, 3′-H_2, 5′-H_2), 3.48 (m, 1H, 4-H), 3.54 (s, 2H, PhCH_2N), 3.59 (s [br], 1H, OH), 6.84–6.94 (m, 3H_{Ar}, 6‴-H, 2‴-H, 4‴-H), 7.22–7.38 (m, 7H_{Ar}, 3‴-H, 5‴-H, 2″-H, 6″-H); ^{13}C_APT NMR (75.4 MHz, $CDCl_3$): δ_C 32.34 (1C_{sec}, 5-C), 48.78 (2C_{sec}, 3′-C, 5′-C), 50.13 (2C_{sec}, 2′-C, 6′-C), 50.16 (1C_{sec}, 2-C), 51.67 (1C_{sec}, 6-C), 63.19 (1C_{sec}, ArCH_2N), 67.57 (1C_{tert}, 4-C), 67.79 (1C_{tert}, 3-C), 116.39 (2C_{Ar}, 2‴-C, 6‴-C), 120.05 (1C_{Ar}, 4‴-C), 127.24 (1C_{Ar}, 4″-C), 128.39 (2C_{Ar}, 3″-C, 5″-C), 129.11 (2C_{Ar}, 2″-C, 6″-C), 129.22 (2C_{Ar}, 3‴-C, 5‴-C), 138.22 (1C_{Ar}, 1″-C), 151.41 (1C_{Ar}, 1‴-C); LRMS (ESI) m/z=352.26 (MH^+, 100%). Anal. Calcd for $C_{22}H_{29}N_3O$ (%): C, 75.18; H, 8.32; N, 11.96. Found: C, 75.35; H, 8.63; N, 11.79.

*4.4.3. (3SR,4SR)-3-(4-Fluorophenylamino)-1-phenethylpiperidin-4-ol (**3ch**).* According to representative procedure in Section 4.4.1, white powder, yield: 83%; mp 131–132 °C (MeOH); R_f=0.42 (sm2); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ_H 1.71 (m, 1H, 5-H_a), 2.01 (m [br], 1H, 2-H_a), 2.06 (m, 1H, 5-H_b), 2.26 (dt-like, J=11.7, 3.1 Hz, 1H, 6-H_a), 2.44 (br, 1H, OH), 2.61 (A-part of AA′BB′, 2H, PhCH_2CH$_2$N), 2.78 (B-part of AA′BB′, 2H, PhCH$_2$CH_2N), 2.87 (m, 1H, 6-H_b), 3.09 (dd, J=11.7, 2.3 Hz, 2-H_b), 3.36 (br, 1H, 3-H), 3.46–3.59 (m [br], 2H, 4-H, NH), 6.62 (A-part of AA′MM′X, 2H_{Ar}, 3′-H, 5′-H), 6.89 (M-part of AA′MM′X, 2H_{Ar}, 2′-H, 6′-H), 7.20 (m, 3H_{Ar}, 2″-H, 4″-H, 6″-H), 7.29 (m, 2H_{Ar}, 3″-H, 5″-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 31.79 (1C_{sec}, 5-C), 33.78 (1C_{sec}, PhCH_2CH$_2$N), 50.92 (1C_{sec}, 6-C), 56.19 (1C_{sec}, 2-C), 57.41 (1C_{tert}, 3-C), 59.89 (1C_{sec}, PhCH$_2$CH_2N), 71.28 (1C_{tert}, 4-C), 114.95 (d, J=7.3 Hz, 2C_{Ar}, 2′-C, 6′-C), 115.98 (d, J=22.1 Hz, 2C_{Ar}, 3′-C, 5′-C), 126.20 (1C_{Ar}, 4″-C), 128.51 (2C_{Ar}, 3″-C, 5″-C), 128.81 (2C_{Ar}, 2″-C, 6″-C), 140.30 (1C_{Ar}, 1″-C), 143.55 (d, J=2.2 Hz, 1C_{Ar}, 1′-C), 156.28 (d, J=235.9 Hz, 1C_{Ar}, 4′-C); ^{19}F NMR (376.4 MHz, $CDCl_3$): δ_F −127.32 (s, 1F_{Ar}, 4″-F); ESI-MS: m/z=315.08 (MH^+, 100%). Anal. Calcd for $C_{19}H_{23}FN_2O$ (%): C, 72.58; H, 7.37; N, 8.91. Found: C, 72.35; H, 7.44; N, 8.86.

4.5. LiBr-assisted epoxide ring opening of 7a–c

*4.5.1. Representative procedure of (3SR,4SR)-1-(4-fluorobenzyl)-4-(4-phenylpiperidin-1-yl)piperidin-3-ol (**4bb**).* LiBr (0.185 g, 2.1 mmol),

which was dried by heating under a stream of dry argon, was dissolved in anhydrous ACN (2 mL). A solution of epoxide **7b** (0.248 g, 1.195 mmol) in ACN (1 mL) was added and the resulting mixture was stirred for 5 min followed by the addition of a solution of 4-phenylpiperidine (**8b**, 0.195 g, 1.21 mmol) in ACN (0.5 mL). The reaction mixture was stirred at 22 °C for 12 h. Compound **7b** was completely consumed as detected by TLC (sm2, R_f[**7b**]=0.65) and a single product appeared (sm2, R_f=0.54). The solvent was evaporated and H_2O (10 mL) was added to the residue. The heterogeneous mixture was extracted with $CHCl_3$ (1×10, 2×5 mL) and the combined organic phases were dried (Na_2CO_3), filtered and evaporated to leave a yellowish viscous residue (410 mg). After trituration with MeOH (1 mL) a crystalline product was formed. The solid was filtered off, washed with MeOH/H_2O (4:1) and dried to obtain **4bb** (0.287 g). A second crop (0.074 g) was isolated from the filtrate after evaporation and trituration in a similar way to yield in total 0.361 g (82%), as a colourless solid, mp 120.5–124 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H, 1.56 (dddd, J=12.3, 12.3, 12.3, 4.1 Hz, 1H, 5-H_a), 1.62–1.92 (m, 6H, 5-H_b, 2-H_a, 3′-H_2, 5′-H_2), 2.00 (dt-like, J=11.7, 2.9 Hz, 1H, 6-H_a), 2.25 (m, 2H, 4-H, 2′-H_a), 2.50 (tt-like, J=12.0, 3.7 Hz, 1H, 4′-H), 2.73 (m, 2H, 6′-H_2), 2.96 (m, 2H, 6-H_b, 2′-H_b), 3.21 (ddd, J=10.0, 4.6, 1.8 Hz, 1H, 2-H_b), 3.51 (AB, J=13.3 Hz, 2H, ArCH_2N), 3.62 (s [br], 1H, OH overlapped with ddd, J=10.0, 10.0, 4.7 Hz, 1H, 3-H), 7.00 (m, 2H_{Ar}, 3″-H, 5″-H), 7.17–7.33 (m, 7H_{Ar}, 2″-H, 6″-H, 2‴-H, 6‴-H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 21.71 (1C$_{sec}$, 5-C), 34.07 (1C$_{sec}$, 3′-C [or 5′-C]), 34.46 (1C$_{sec}$, 5′-C [or 3′-C]), 43.09 (1C$_{tert}$, 4′-C), 45.86 (1C$_{sec}$, 2′-C), 53.19 (1C$_{sec}$, 6-C), 53.61 (1C$_{sec}$, 6′-C), 58.97 (1C$_{sec}$, 2-C), 62.04 (1C$_{sec}$, ArCH_2N), 66.21 (1C$_{tert}$, 3-C), 69.70 (1C$_{tert}$, 4-C), 115.12 (d, J=21.0 Hz, 2C$_{Ar}$, 3″-C, 5″-C), 126.30 (1C$_{Ar}$, 4″0,0-C), 126.94 (2C$_{Ar}$, 2‴-C, 6‴-C), 128.56 (2C$_{Ar}$, 3‴-C, 5‴-C), 130.68 (d, J=7.7 Hz, 2C$_{Ar}$, 2″-C, 6″-C), 133.99 (d, J=3.3 Hz, 1C$_{Ar}$, 1″-C), 146.36 (1C$_{Ar}$, 1‴-C), 162.16 (d, J=245.5 Hz, 1C$_{Ar}$, 4″-C); ^{19}F NMR (282.3 MHz, $CDCl_3$): δ_F −116.29 (m, 1F$_{Ar}$, 4″-F); LRMS (ESI) m/z=369.25 (MH$^+$, 100%). Anal. Calcd for $C_{23}H_{29}FN_2O$ (%): C, 74.97; H, 7.93; N, 7.60. Found: C, 75.26; H, 8.10; N, 7.59.

*4.5.2. (3SR,4SR)-1-Benzyl-4-(4-phenylpiperazin-1-yl)piperidin-3-ol (**4aa**).* According to representative procedure in Section 4.5.1, colourless solid, yield: 85%; mp 121–123 °C (MeOH), (lit.[22] mp 120–121 °C); ^{1}H NMR (400.0 MHz, $CDCl_3$): δ_H 1.58 (dddd, J=12.5, 12.5, 11.7, 3.9 Hz, 1H, 5-H_a), 1.76 (ddd, J=12.5, 6.3, 3.1 Hz, 1H, 5-H_b), 1.92 (t-like, J=10.2 Hz, 1H, 2-H_a), 2.02 (dt-like, J=11.7, 2.3 Hz, 1H, 6-H_a), 2.29 (ddd, J=12.5, 10.2, 3.9 Hz, 1H, 4-H), 2.60 (ddd, J=10.2, 6.3, 3.1 Hz, 2H, 2′-H_a, 6′-H_a), 2.91 (m, 2H, 2′-H_b, 6′-H_b), 2.96 (m, 1H, 6-H_b), 3.19 (m, 4H, 3′-H_2, 5′-H_2), 3.25 (m, 1H, 2-H_b), 3.49 (s [br], 1H, OH), 3.56 (AB, J=13.3 Hz, PhCH_2N), 3.65 (ddd, J=10.2, 10.2, 4.7 Hz, 1H, 3-H), 6.85–6.95 (m, 3H_{Ar}, 6‴-H, 2‴-H, 4‴-H), 7.23–7.36 (m, 7H_{Ar}, 3‴-H, 5‴-H, 2″-H, 6″-H); ^{13}C_APT NMR (100.6 MHz, $CDCl_3$): δ_C 21.88 (1C$_{sec}$, 5-C), 48.69 (2C$_{sec}$, 3′-C, 5′-C), 50.09 (2C$_{sec}$, 3′-C, 5′-C), 53.16 (1C$_{sec}$, 6-C), 59.08 (1C$_{sec}$, 2-C), 62.95 (1C$_{sec}$, ArCH_2N), 66.30 (1C$_{tert}$, 3-C), 69.37 (1C$_{tert}$, 4-C), 116.43 (2C$_{Ar}$, 2‴-C, 6‴-C), 120.10 (1C$_{Ar}$, 4‴-C),127.36 (1C$_{Ar}$, 4″-C), 128.47 (2C$_{Ar}$, 3″-C, 5″-C), 129.35 (2C$_{Ar}$, 2″-C, 6″-C), 129.37 (2C$_{Ar}$, 3‴-C, 5‴-C), 138.26 (1C$_{Ar}$, 1″-C), 151.54 (1C$_{Ar}$, 1‴-C); LRMS (ESI) m/z=352.21 (MH$^+$, 100%). Anal. Calcd for $C_{22}H_{29}N_3O$ (%): C, 75.18; H, 8.32; N, 11.96. Found: C, 75.31; H, 8.62; N, 11.83.

*4.5.3. (3SR,4SR)-4-(4-Fluorophenylamino)-1-phenethylpiperidin-3-ol (**4ch**).* According to representative procedure in Section 4.5.1, slowly crystallizing compound, which was converted into the monohydrochloride of **4ch**; colourless solid, yield: 86%; mp 124.5–127 °C (EtOH/MTBE); R_f=0.38 (sm2); For NMR, the base was liberated with aqueous K_2CO_3; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.44 (m, 1H, 5-H_a), 2.10 (ddd, J=12.3, 7.0, 4.1 Hz, 1H, 5-H_b), 2.21 (m [overlapped], 1H, 2-H_a), 2.24 (m [overlapped], 1H, 6-H_a), 2.65 (m, 2H, PhCH$_2$CH_2N), ~2.7 (m [br], 1H, OH), 2.80 (m, 2H, PhCH_2CH$_2$N), 2.83 (m [overlapped], 1H, 6-H_b), ~3.1 (br, 1H, NH), 3.12 (m [br, overlapped], 1H, 4-H), 3.15 (m [br, overlapped], 1H, 2-H_b), 3.60 (ddd, J=8.2, 8.2, 4.1 Hz, 1H, 3-H), 6.64 (A-part of AA′MM′X, 2H_{Ar}, 3′-H, 5′-H), 6.90 (M-part of AA′MM′X, 2H_{Ar}, 2′-H, 6′-H), 7.17–7.33 (m, 5H_{Ar}, 2″-H, 6″-H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C 29.91 (1C$_{sec}$, 5-C), 33.79 (1C$_{sec}$, PhCH_2CH$_2$N), 52.01 (1C$_{sec}$, 6-C), 58.21 (2C [not resolved]: 1C$_{tert}$, 4-C; 1C$_{sec}$, 2-C), 60.07 (1C$_{sec}$, PhCH$_2$CH_2N), 70.98 (1C$_{tert}$, 3-C), 115.30 (d, J=7.2 Hz, 2C$_{Ar}$, 2′-C, 6′-C), 115.93 (d, J=22.6 Hz, 2C$_{Ar}$, 3′-C, 5′-C), 126.25 (1C$_{Ar}$, 4″-C), 128.56 (2C$_{Ar}$, 3″-C, 5″-C), 128.81 (2C$_{Ar}$, 2″-C, 6″-C), 140.24 (1C$_{Ar}$, 1″-C), 143.72 (d, J=1.7 Hz, 1C$_{Ar}$, 1′-C), 156.40 (d, J=236.7 Hz, 1C$_{Ar}$, 4′-C); ^{19}F NMR (376.4 MHz, $CDCl_3$): δ_F −127.13 (s, 1F$_{Ar}$, 4″-F); LRMS (ESI) m/z=315.12 (MH$^+$, 100%). Anal. Calcd for $C_{19}H_{23}FN_2O\cdot HCl\cdot ¼EtOH\cdot ¼MTBE$ (%): C, 64.83; H, 7.47; N, 7.29. Found: C, 64.83; H, 7.71; N, 7.12.

4.6. Two-step synthesis of hexahydro-pyrido oxazin-ones 12 and 13

*4.6.1. 2-Chloro-N-(4-fluorophenyl)-N-((3RS,4RS)-3-hydroxy-1-phenethylpiperidin-4-yl)acetamide (**10c**).* Compound **4ch**·HCl (0.105 g, 0.3 mmol) was stirred in toluene (1.6 mL) at 60 °C, and **9c** (0.09 g, 0.8 mmol) was added in one portion. The resulting mixture was stirred at 130 °C for 2 h, while a finely dispersed solid precipitated. After cooling, the solvent and surplus of acid chloride were evaporated to leave a colourless solid, which was stirred with aqueous $NaHCO_3$ (7.5%, 4 mL) and extracted with DCM (2×5 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to give a residue, which was slurried with MTBE/PE40–60 and filtered to yield **10c** (0.075 g, 64%), as a colourless powder; The isolated compound was found to be pure by TLC; R_f=0.44 (sm4); mp 186.5–188 °C; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ_H 1.40 (dddd, J=12.5, 12.5, 12.5, 4.7 Hz, 1H, 5-H_a), 1.78 (m, 1H, 5-H_b), 2.09 (dd, 10.9, 10.2 Hz, 1H, 2-H_a), 2.18 (m [br], 1H, 6-H_a), 2.61 (A of AA′BB′, 2H, PhCH$_2$CH_2N), 2.73 (B of AA′BB′, 2H, PhCH_2CH$_2$N), 2.93 (m [br], 1H, 6-H_b), 3.26 (m [br], 1H, 2-H_b), 3.45 (m [br], 1H, 3-H), 3.78 (AB, $^2J_{HH}$=13.3 Hz, 2H, ClCH_2C=O), 4.59 (m, 1H, 4-H), 7.11–7.21 (m, 6H_{Ar}, 3′-H, 5′-H, 6′-H, 2″-H, 4″-H, 6″-H), 7.26 (m, 2H_{Ar}, 3″-H, 5″-H), 7.48 (m [br], 1H_{Ar}, 2′-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 28.73 (1C$_{sec}$, 5-C), 33.80 (1C$_{sec}$, PhCH_2CH$_2$N), 42.64 (1C$_{sec}$, ClCH$_2$C=O), 52.38 (1C$_{sec}$, 6-C), 59.69 (1C$_{tert}$, 4-C), 59.89 (1C$_{sec}$, PhCH$_2$CH$_2$N), 60.39 (1C$_{sec}$, 2-C), 68.72 (1C$_{tert}$, 3-C), 116.70 (d, $^2J_{CF}$=22.1 Hz, 1C$_{Ar}$, 5′-C [or 3′-C]), 117.14 (d, $^2J_{CF}$=22.1 Hz, 1C$_{Ar}$, 3′-C [or 5′-C]), 126.27 (1C$_{Ar}$, 4″-C), 128.56 (2C$_{Ar}$, 3″-C, 5″-C), 128.74 (2C$_{Ar}$, 2″-C, 6″-C), 132.15 (d, $^3J_{CF}$=8.8 Hz, 1C$_{Ar}$, 6′-C [or 2′-C]), 132.33 (d, $^3J_{CF}$=8.8 Hz, 1C$_{Ar}$, 2′-C [or 6′-C]), 132.71 (d, $^4J_{CF}$=4.4 Hz, 1C$_{Ar}$, 1′-C), 140.02 (1C$_{Ar}$, 1″-C), 162.98 (d, $^1J_{CF}$=250.6 Hz, 1C$_{Ar}$, 4′-C), 168.55 (1C$_{sec}$, ClCH$_2$C=O); ^{19}F NMR (376.4 MHz, $CDCl_3$): δ_F −111.27 (s, 1F$_{Ar}$, 4′-F); ESI-MS: m/z=391.04 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{24}ClFN_2O_2$ (%): C, 64.53; H, 6.19; N, 7.17. Found: C, 64.55; H, 6.02; N, 7.24.

*4.6.2. (4aRS,8aRS)-1-(4-Fluorophenyl)-hexahydro-6-phenethyl-1H-pyrido[3,4-b][1,4]oxazin-2(3H)-one (**12**).* A stock solution of 2-PrONa (3.39%, w/w) was prepared by dissolving sodium metal (0.038 g, 1.653 mmol) in hot IPA (4.5 mL) and filling up with fresh IPA to a final weight of 4 g. A mixture of **10c** (0.096 g, 0.245 mmol) in THF (3 mL) and IPA (1.5 mL) was stirred at 0–2 °C, while a solution of 2-PrONa in IPA (3.39%, w/w, 0.665 g, 0.275 mmol) was added at once. A finely dispersed precipitate (NaCl) was formed after 20 s. The suspension was stirred at 0–2 °C for 6 h. The reaction mixture was acidified with aqueous citric acid (1%, 0.5 mL) and evaporated. Water (10 mL) was added to the residue and it was made alkaline with aqueous K_2CO_3 and extracted with MTBE (3x6 mL). The organic phases were combined, dried (Na_2SO_4), filtered and reduced to a volume of ~1 mL. The crystalline precipitate was filtered, washed (MTBE/PE40–60) and dried to obtain 0.072 g. The product was recrystallized from a mixture of IPA (1 mL) and MTBE (3 mL),

followed by the addition of PE40–60 (2 mL) to yield **12** (0.061 g, 70%); as a colourless crystalline product, which was pure by TLC; R_f=0.41 (sm4), mp 156–157 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.40 (dddd, J=12.3, 12.0, 11.7, 4.1 Hz, 1H, 8-H_a), 1.51 (m, 1H, 8-H_b), 2.03 (dt-like, J=12.3, 2.9 Hz, 1H, 7-H_a), 2.14 (t-like, J=10.0 Hz, 1H, 5-H_a), 2.67 (A of AA'BB', 2H, PhCH$_2$C*H*$_2$N), 2.79 (B of AA'BB', 2H, PhC*H*$_2$CH$_2$N), 2.91 (m, 1H, 7-H_b), 3.28 (ddd, J=10.5, 4.1, 1.8 Hz, 1H, 5-H_b), 3.54 (ddd, J=11.7, 8.8, 4.7 Hz, 1H, 8a-H), 3.72 (ddd, J=10.0, 10.0, 4.1 Hz, 1H, 4a-H), 4.45 (AB, J=16.4 Hz, 2H, 3-H$_2$), 7.08–7.33 (m, 9H$_{Ar}$); ^{13}C_APT NMR (75.4 MHz, $CDCl_3$): δ_C 29.05 (1C$_{sec}$, 8-C), 33.82 (1C$_{sec}$, PhCH$_2$CH$_2$N), 51.54 (1C$_{sec}$, 7-C), 55.73 (1C$_{sec}$, 5-C), 59.63 (1C$_{sec}$, PhCH$_2$C*H*$_2$N), 60.73 (1C$_{tert}$, 8a-C), 68.94 (1C$_{sec}$, 3-C), 76.06 (1C$_{tert}$, 4a-C), 116.43 (d, $^2J_{CF}$=22.6 Hz, 2C$_{Ar}$, 3′-C, 5′-C), 126.30 (1C$_{Ar}$, 4″-C), 128.55 (2C$_{Ar}$, 3″-C, 5″-C), 128.75 (2C$_{Ar}$, 2″-C, 6″-C), 129.75 (d, $^3J_{CF}$=8.3 Hz, 2C$_{Ar}$, 6′-C, 2′-C), 133.39 (d, $^4J_{CF}$=3.3 Hz, 1C$_{Ar}$, 1′-C), 140.00 (1C$_{Ar}$, 1″-C), 161.92 (d, $^1J_{CF}$=247.1 Hz, 1C$_{Ar}$, 4′-C), 167.74 (1C$_{sec}$, *C*=O [2-C]); ^{19}F NMR (282.3 MHz, $CDCl_3$): δ_F −113.98 (m, 1F$_{Ar}$, 4′-F); ESI-MS: m/z=355.08 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{23}FN_2O_2$ (%): C, 71.17; H, 6.54; N, 7.90. Found: C, 70.92; H, 6.58; N, 7.96.

*4.6.3. 2-Chloro-N-(4-fluorophenyl)-N-((3RS,4RS)-4-hydroxy-1-phenethylpiperidin-3-yl)acetamide (**11c**).* Triethylamine (TEA, 0.292 g, 2.88 mmol) was added to a solution of **3ch** (0.38 g, 1.2 mmol) in DCM (18 mL). The mixture was cooled to 0 °C, while a solution of chloroacetyl chloride (**9c**, 0.237 g, 2.1 mmol) in DCM (3.0 mL) was gradually added. The reaction mixture was stirred at 0–3 °C for 2 h. The starting aniline (sm2, R_f=0.43) was completely consumed as detected by TLC and a product appeared (sm2, R_f=0.37). The reaction mixture was stirred with aqueous $NaHCO_3$ (5%, 15 mL), dried (Na_2SO_4), filtered and evaporated. The residue (0.657 g) was dissolved in MeOH (5 mL). After the addition of aqueous K_2CO_3 (3%, 6 mL) the mixture was stirred at 22 °C, and a solid precipitated within 3 h. The product was filtered, washed (MeOH/H_2O) and dried to give **11c** (0.434 g, 88%), as a colourless solid, which was pure by TLC; R_f=0.30 (sm4); mp 119.5–120 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ_H 1.72–1.94 (m, 3H, 5-H_a, 2-H_a, 6-H_a), 2.00–2.06 (m [br], 2H, 5-H_b, OH), 2.58 (A of AA'BB', 2H, PhCH$_2$C*H*$_2$N), 2.76 (B of AA'BB', 2H, PhC*H*$_2$CH$_2$N), 2.91 (m [br], 1H, 6-H_b), 3.04 (ddd, J=10.5, 3.6, 2.1 Hz, 1H, 2-H_b), 3.33 (ddd, J=10.8, 10.8, 5.1 Hz, 1H, 4-H), 3.76 (AB, $^2J_{HH}$=13.5 Hz, 2H, ClC*H*$_2$C[C=O]N), 4.70 (ddd, J=10.8, 10.8, 4.3 Hz, 3-H), 7.12–7.22 (m, 6H$_{Ar}$, 3′-H, 5′-H, 6′-H, 2″-H, 4″-H, 6″-H), 7.25–7.28 (m, 2H$_{Ar}$, 3″-H, 5″-H), 7.53 (m [br], 1H$_{Ar}$, 2′-H); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ_C 34.02 (1C$_{sec}$, PhC*H*$_2$CH$_2$N), 34.32 (1C$_{sec}$, 5-C), 42.74 (1C$_{sec}$, ClH$_2$C[C=O]N), 51.89 (1C$_{sec}$, 6-C), 55.36 (1C$_{sec}$, 2-C), 59.31 (1C$_{tert}$, 3-C), 59.68 (1C$_{sec}$, PhCH$_2$CH$_2$N), 69.34 (1C$_{tert}$, 4-C), 116.88 (2d [not resolved], $^2J_{CF}$=23.8 Hz, 2C$_{Ar}$, 5′-C, 3′-C), 126.24 (1C$_{Ar}$, 4″-C), 128.55 (2C$_{Ar}$, 3″-C, 5″-C), 128.77 (2C$_{Ar}$, 2″-C, 6″-C), 131.77 (d, $^3J_{CF}$=8.8 Hz, 1C$_{Ar}$, 6′-C [or 2′-C]), 132.29 (d, $^3J_{CF}$=7.8 Hz, 1C$_{Ar}$, 2′-C [or 6′-C]), 133.53 (d, $^4J_{CF}$=3.8 Hz, 1C$_{Ar}$, 1′-C), 140.20 (1C$_{Ar}$, 1″-C), 162.87(d, $^1J_{CF}$=250.5 Hz, 1C$_{Ar}$, 4′-C), 168.02 (1C$_{sec}$, ClH$_2$C[*C*=O]N); ^{19}F NMR (282.3 MHz, $CDCl_3$): δ_F −111.36 (m, 1F$_{Ar}$, 4′-F); ESI-MS: m/z=391.15 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{24}ClFN_2O_2\cdot 1.125\times H_2O$ (%): C, 61.35; H, 6.44; N, 6.81. Found: C, 61.23; H, 6.44; N, 6.86.

*4.6.4. (4aRS,8aRS)-4-(4-Fluorophenyl)-hexahydro-6-phenethyl-2H-pyrido[4,3-b][1,4]oxazin-3(4H)-one (**13**).* A solution of **11c** (0.158 g, 0.4 mmol) in THF (3 mL) was stirred at −12 °C (ice-salt bath), while a solution of ^{t}BuOK (0.045 g, 0.4 mmol) in THF (1.5 mL) was gradually added via syringe (20 min). The reaction mixture was stirred at −12 °C for 1 h. The starting chloroacetanilide was completely consumed as detected by TLC (sm2, R_f=0.41). A spot, which was assigned to the desired product, appeared at R_f=0.60, and a second one was observed at R_f=0.45, which was identified as **3ch**, caused by hydrolysis of **11c**. The reaction mixture was acidified with aqueous citric acid (1%, 0.5 mL) and evaporated. Both products were separated via flash chromatography on silica gel 60 (40–63 μm, 15 g), applying a mixture of $CHCl_3$ (150 mL)/MeOH (30 mL)/30% NH_3 (4 mL) as eluent. The fraction eluted first was evaporated and the residue (0.11 g) was triturated with MTBE/PE40–60 to yield **13** (0.072 g, 51%), as colourless crystals; R_f=0.60 (sm2); mp 125–126 °C; ^{1}H NMR (400.0 MHz, $CDCl_3$): δ_H 1.81 (dddd, J=12.5, 12.5, 12.5, 4.7 Hz, 1H, 8-H_a), 1.83 (t-like [overlapped], J=10.9 Hz, 1H, 5-H_a), 2.05 (m, 1H, 8-H_b), 2.18 (dt-like, J=12.5, 3.1 Hz, 1H, 7-H_a), 2.56 (m, 2H, PhCH$_2$C*H*$_2$N), 2.63 (m, 3H, PhC*H*$_2$CH$_2$N, 5-H_b), 3.06 (m, 1H, 7-H_b), 3.49 (m, 1H, 8a-H), 3.76 (ddd, J=10.9, 9.4, 3.9 Hz, 1H, 4a-H), 4.43 (AB, J=16.4 Hz, 2H, 2-H$_2$), 7.09–7.20 (m, 7H$_{Ar}$, 2″-H, 4″-H, 6″-H, 2′-H, 3′-H, 5′-H, 6′-H), 7.24 (m, 2H$_{Ar}$, 3″-H, 5″-H); ^{13}C_APT NMR (100.6 MHz, $CDCl_3$): δ_C 29.86 (1C$_{sec}$, 8-C), 33.78 (1C$_{sec}$, PhCH$_2$CH$_2$N), 51.15 (1C$_{sec}$, 7-C), 55.56 (1C$_{sec}$, 5-C), 59.38 (1C$_{tert}$, 4a-C), 59.44 (1C$_{sec}$, PhCH$_2$CH$_2$N), 69.04 (1C$_{sec}$, 2-C), 78.03 (1C$_{tert}$, 8a-C), 116.46 (d, $^2J_{CF}$=22.8 Hz, 2C$_{Ar}$, 3′-C, 5′-C), 126.26 (1C$_{Ar}$, 4″-C), 128.50 (2C$_{Ar}$, 3″-C, 5″-C), 128.64 (2C$_{Ar}$, 2″-C, 6″-C), 129.46 (d, $^3J_{CF}$=8.9 Hz, 2C$_{Ar}$, 6′-C, 2′-C), 133.22 (d, $^4J_{CF}$=3.0 Hz, 1C$_{Ar}$, 1′-C), 139.00 (1C$_{Ar}$, 1″-C), 161.90 (d, $^1J_{CF}$=247.7 Hz, 1C$_{Ar}$, 4′-C), 167.83 (1C$_{sec}$, *C*=O [3-C]); ^{19}F NMR (376.4 MHz, $CDCl_3$): δ_F −113.81 (t-like, 1F$_{Ar}$, 4′-F); ESI-MS: m/z=355.16 (MH$^+$, 100%). Anal. Calcd for $C_{21}H_{23}FN_2O_2$ (%): C, 71.17; H, 6.54; N, 7.90. Found: C, 70.85; H, 6.68; N, 7.86.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.045. These data include MOL files and InChiKeys of the most important compounds described in this article.

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