Bioorganic & Medicinal Chemistry 19 (2011) 5716–5733

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

A novel amino-benzosuberone derivative is a picomolar inhibitor of mammalian aminopeptidase N/CD13

Carmen Maiereanu [a], Céline Schmitt [a], Nadège Schifano-Faux [b], Didier Le Nouën [a], Albert Defoin [a,*], Céline Tarnus [a,*]

[a] Université de Haute Alsace, Laboratoire de Chimie Organique et Bioorganique, EA4466 ENSCMu, 3, rue Alfred Werner, F-68093, Mulhouse Cedex, France
[b] Université de Lille 2, Laboratoire de Chimie Analytique, EA GRIIOT 4481 Faculté des Sciences Pharmaceutiques et Biologiques de Lille, 3, rue du Professeur Laguesse, B.P. 83. 59006 Lille cedex, France

ARTICLE INFO

Article history:
Received 21 March 2011
Revised 27 May 2011
Accepted 8 June 2011
Available online 19 July 2011

Keywords:
Aminobenzoheptenone
Aminopeptidase-N inhibitor
APN/CD13

ABSTRACT

A new class of low molecular weight, highly potent and selective non peptidic inhibitors of aminopeptidase N (APN/CD13) is described. We report the synthesis and in vitro evaluation of racemic substituted analogues of 7-amino-benzocyclohepten-6-one **1a**. We investigated various substitutions on the aromatic ring with phenyl and halogen groups. In vitro kinetic studies revealed that these compounds are among the most effective APN/CD13 inhibitors found so far. Hydrophobic substituents placed at position 1 or 4 on the cycloheptenone **1a** led to the potent compounds **1c–h**,**b′–c′**,**f′**,**h′** with K_i in the nanomolar range. The key finding of the present work was the observed additive effect of 1,4-disubstitutions which led to the discovery of the picomolar inhibitor **1d′** (K_i = 60 pM). The designed inhibitors retain the selectivity of our lead structure **1a** towards selected members of the aminopeptidase family, combined with an impressive increase in inhibitory potency and a conserved stability.

1. Introduction

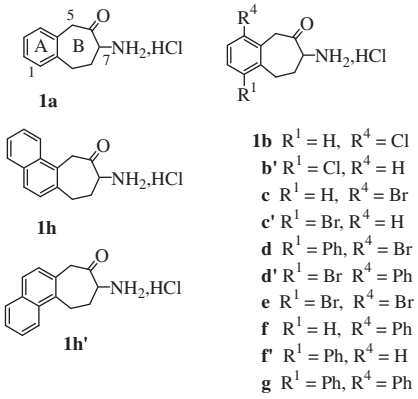
APN/CD13 is a membrane-bound, zinc-dependent homodimeric enzyme and a member of the M1 family of aminopeptidases.[1] Like other members of this family, APN/CD13 possesses the consensus zinc binding motif (HEXXH-(X18)-E) in its extracellular domain, as well as the exopeptidase motif (GXMEN) for binding the free primary amino group of the N-terminal residue of its peptidic substrates. APN/CD13 removes the N-terminal amino acid from unsubstituted oligopeptides, amides or arylamides, with a broad substrate specificity,[1] although a significant preference for hydrophobic residues is observed.[1] This ectoenzyme appears to be a multifunctional protein involved in the regulation of signalling peptides as well as in various cell activation and migration processes.[2] APN/CD13 is emerging as a target of significant biological and medical importance. Indeed, several studies with bestatin,[3] active site-directed anti-APN mAb,[4] siRNA[5] and KO mice,[6] indicate that APN/CD13 is an active player in angiogenesis and tumor metastasis. In addition, overexpression of APN/CD13 has been found to correlate with immunological abnormalities such as chronic inflammatory diseases[7] and autoimmune pathologies,[8] suggesting a role of APN/CD13 in T cell function and activation. However, while a wealth of in vitro data have already been gathered, in vivo data on APN/CD13 blockade remain very scarce. Furthermore, the exact role played by APN/CD13 in the pathologies mentioned above, as well as the cellular pathways involved, remain to be elucidated. To this end, a small molecular weight, drug-like, selective inhibitor of APN/CD13 would be of immense value for dissecting the biological and pathophysiological roles of this multifunctional enzyme that depend solely on its catalytic activity.

In the recent years, several classes of APN/CD13 inhibitors have been reported, including in particular hydroxamic, phosphoric, sulfonic and boronic acids. Recent reviews provide an excellent compendium of the currently available set of APN/CD13 inhibitors.[9,10] While many of these compounds display high in vitro potency, their selectivity is, regrettably, not always well documented.

We have recently reported the discovery of 7-amino-benzocycloheptan-6-one **1a** as a novel lead structure for selective APN/CD13 inhibition (Scheme 1).[11] This new chemotype displays an excellent ligand efficiency (LE = 0.63, according to the definition by Hopkins et al.[12]) and, therefore, represents a promising starting point for further chemical elaboration. Taking into account the preference of APN/CD13 for hydrophobic N-terminal amino acid residues,[1] we designed hydrophobic analogues of our lead compound **1a**. We first investigated the extension of the aromatic system. This strategy led to the identification of the submicromolar inhibitors **1h** and **1h′**. We then explored substitutions of cycle A in position 1 and/or 4, and discovered compounds **1f** and **1e** with K_i values in the single-digit nanomolar range. When both positions were optimally substituted, an additive effect was obtained, leading to the picomolar inhibitor **1d′**.

* Corresponding authors.
E-mail addresses: Albert.Defoin@uha.fr (A. Defoin), Celine.Tarnus@uha.fr (C. Tarnus).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.06.089



Scheme 1. Chemical structures of the novel APN/CD13 inhibitors.

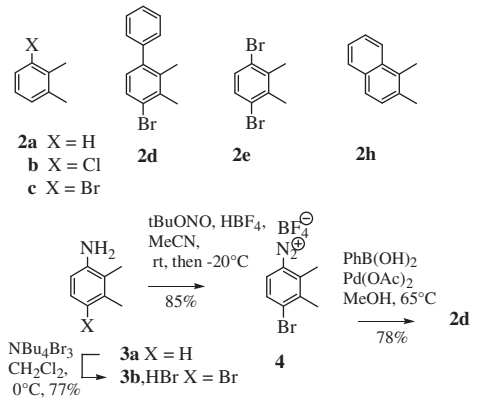
Hereafter, we describe the synthesis of these novel amino-benzosuberone analogues and report their inhibitory activities against a panel of representative metallo-aminopeptidases from the M1 and M17 families,[13,14] including porcine kidney aminopeptidase N/CD13 (EC 3.4.11.2), bovine kidney leucine aminopeptidase (EC 3.4.11.1), *Aeromonas proteolytica* aminopeptidase (EC 3.4.11.10) and the aminopeptidase activity of human leukotriene A4 hydrolase (EC 3.3.2.6). Our data show that the amino-benzocycloheptanone (amino-benzosuberone) derivative **1d′** is the most potent inhibitor of mammalian APN/CD13 known to date (K_i = 60 pM), and that it has a very high selectivity towards the M1 subfamily of one-zinc aminopeptidases, as opposed to the M17 subfamily which requires co-catalytic metal ions for activity.

2. Chemistry

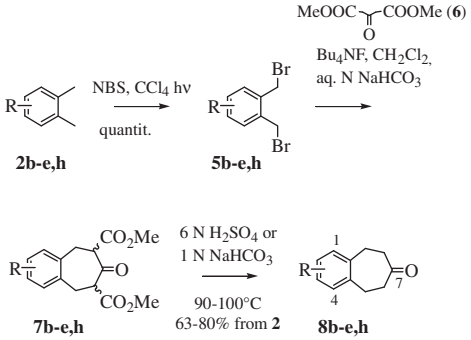
2.1. Preparation of the key intermediate ketones 8b–e,h

We followed the reaction scheme already described for the benzocycloheptenone **1a**[11] from the α,α′-dibromo derivative of the *o*-xylene **2a**. In the present work, we used the corresponding commercial o-xylene derivatives **2b**,**c**,**h** or known dibromo one **2e**[15] as starting material. The bromodimethylbiphenyl **2d** was prepared according to the litterature[16] (scheme 2) by coupling the phenylboronic acid with the diazonium salt **4**. This salt was easily obtained from the 2,3-dimethylaniline **3a** in ca. 50% overall yield, by bromination with an ammonium tribromide according to[17] and diazotation.

The general reaction scheme for the synthesis of the ketone intermediates is depicted in Scheme 3. A photochemical bis-bromination of the xylenes **2b–e**,**h** with two equivalents of N-bromosuccinimide



Scheme 2. Starting *o*-xylene derivatives and synthesis of the 4-bromo-2,3-dimethylbiphenyl **2d**.



Scheme 3. Common synthesis of the intermediate ketones **8b–e**,**h**.

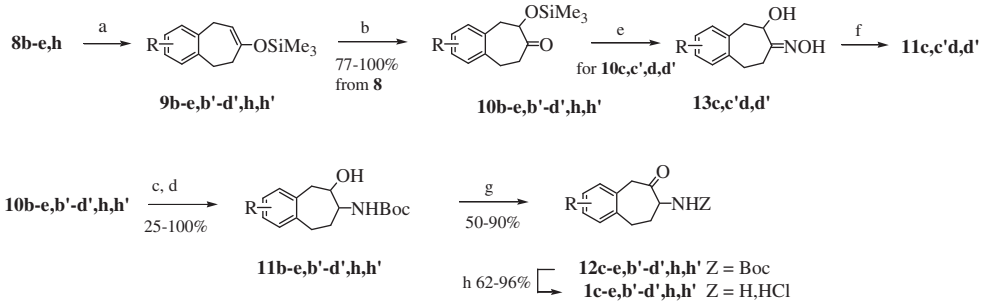
(NBS) gave quantitatively the known α,α′-dibromoxylenes **5b–c**,**e**,**h** and the new **5d**. They were cyclised with the dimethyl acetonedicarboxylate **6** into the benzocycloheptanonediesters **7b–e**,**h** as 50/50 diastereoisomeric *cis–trans* mixture. Without purification, an acidic or basic hydrolysis/decarboxylation provided easily the substituted benzocyclohepten-7-ones **8b–e**,**h** in good overall yield (60–83%) from the starting *o*-xylenes **2b–e**,**h**.

2.2. 1,4 Symmetrically-disubstituted series

The commonly used reaction pathway is described in Scheme 4. These reactions led to a desymmetrisation of the molecules, except for the symmetric dibromo derivative **8e**. In this particular case, we used the pathway described previously for the non substituted[11] series. The O-silylation reaction of the ketone **8e** into the enol ether **9e** was better performed with $TfOSiMe_3/NEt_3$[18] than with DBU/$ClSiMe_3$.[19] The enol ether **9e** was then oxidised with a peracid[20] into the silyloxyketone **10e**. This intermediate was not purified and directly reductively aminated[21] into the amido-alcohol **11e** as a *cis/trans* mixture after N-protection, in poor yield (15%) in this case. Finally the isomeric mixture of alcohol derivatives **11e** was oxidised with Dess–Martin periodinane[22] into the amido-ketone **12e**. Acidic deprotection with dry HCl in Et_2O/dioxane gave the aminoketone **2e** as stable hydrochloride in 50% yield from **11e** and in 7% overall yield from the ketone **8e**.

2.3. 1,4 Asymmetrically-disubstituted series

In the case of the asymmetric ketones **8b–d**,**h**, two methods were employed. The reaction described in Scheme 3 led to the formation of a regioisomeric mixture of the intermediate enol ethers and silyloxy-ketones of type **9** and **10** respectively, in good yield from the ketones **8b–d**,**h** (85–96%). The reductive amination which follows, converted the silyloxy-ketones into the regioisomeric pair of *cis–trans* isomeric mixtures of hydroxy-amides **11b–d**,**h**/**11b′–d′**,**h′**. These intermediates were obtained with variable yields, depending on the corresponding ketones. The monohalogeno-derivatives **11b**,**b′** and **11c**,**c′** were obtained in good yields (66% and 58%) starting from **8b** and **8c,** respectively. The reaction was less efficient for the bromo-phenyl and benzo-derivatives **11d**,**d′** and **11h**,**h′**, obtained in 29% and 37% yield from **8d** and **8h**, respectively. The separation of the four isomers by classic flash-chromatography or by semi-preparative HPLC was fastidious. The isomeric chloro- and bromo- hydroxy-amides **11b/11b′** and **11c/11c′** could hardly be purified in this way. In this series, the 1-chloro-derivative **11b′** was the only compound which was obtained pure as a *cis–trans* mixture. The four isomers of the bromo-derivatives **11c/11c′** *cis–trans* could be separated by semi-preparative HPLC and the **11h/11h′** *cis–trans* by flash-chromatography. The mixture of phenyl-bromo isomers **11d/11d′** was not resolved at this stage of the synthesis. The next step led to intermediates which were easier to isolate.



Scheme 4. Synthetic pathway for 1,4 mono- or disubstituted analogues. Reagents and conditions: (a) Me_3SiOTf, NEt_3, toluene, 80–85 °C, 2 h; (b) m-CPBA, CH_2Cl_2, 0 °C, 2 h; (c) $Ti(OiPr)_4$, 2 M NH_3 in MeOH, 6 h, then $NaBH_4$, 2 h; (d) Boc_2O, Na_2CO_3, MeOH, 2 h; (e) NH_2OH, pyridine, 68% for **11c**,**c**′, 73% for **11d**,**d**′; (f) H_2, Raney-nickel, concd NH_4OH (85–98%, see text); (g) chromatographic separation (see text), then DMP, CH_2Cl_2; (h) dry HCl 2 M in Et_2O, dioxane.

A second synthetic route was considered for the monobromo and bromo-phenyl series. It started from the oxime mixtures **13c**,**c**′ and **13d**,**d**′, obtained from the corresponding silyloxy-ketones **10c**,**c**′ and **10d**,**d**′ by classical means. The reduction of the oxime function in amine by hydrogenolysis over Raney-nickel in the presence of ammonia and the following N-protection led to the same hydroxy-amide isomeric mixtures as described in our previous method. In this case, the diastereoisomeric monobromo-oximes **13c** and **13c**′ could be easily separated by both fractional crystallisation and flash chromatography, in reasonable yield of 33–35% for each isomer, and their reduction occurred with good yield (85% for **13c**, 98% for **13c**′). By contrast, the phenyl-bromo-oxime mixture **13d**,**d**′ was not resolved, but the global yield of the final hydroxy-amide mixture **11d/11d**′ from the ketone **8d** was greatly improved (57% vs 29%).

Then, the oxidation of these various hydroxy-amides by the Dess–Martin periodinane as before, led to the corresponding keto-amide **12b**′,**c**,**c**′,**h**,**h**′. The isomeric mixture **11d/11d**′ was oxidised in 55% yield into the ketone mixture which could then be resolved by semi-preparative HPLC into the pure isomers **12d** and **12d**′, in 17% and 38% yield, respectively.

All ketoamides **12c**,**d**,**h**,**b**′**–d**′,**h**′ were deprotected with dry HCl in Et_2O/dioxane into the corresponding crystallised amines of type **1**, in good yield (77–95%).

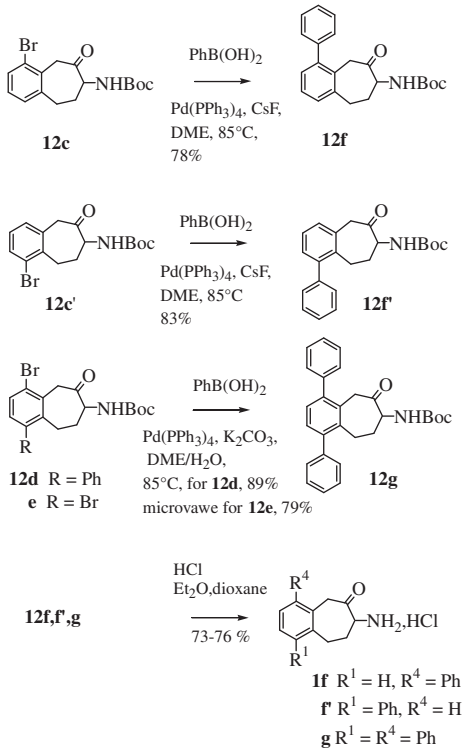
2.4. Synthesis of the mono- and di-phenyl keto-amines 1f,f′,g

These compounds were obtained directly from the bromo-keto-amides **12c**,**c**′,**e** in two chemical steps according to Scheme 5. The Suzuki coupling reaction, performed with the monobromo derivatives **12c**,**c**′ using the phenylboronic acid in dimethoxyethane (DME) as the solvent and cesium fluoride as the base gave the mono-phenyl compounds **12f**,**f**′ in good yield (ca. 80%). The 1,4-diphenyl derivative **12g** was obtained by two different routes with similar results. The coupling of the phenyl-bromoamide **12d** under the conditions described above, using aqueous potassium carbonate as the base and conventional reflux heating, gave **12g** in excellent yield. The second route started from the dibromo-amide **12e**; a double coupling under microwave irradiation gave **12g** in good yield.

After our standard acidic deprotection step, the final keto-amines **1f**,**f**′,**g** were obtained in ca. 75% yield from **12c**,**c**′,**e**, respectively.

2.5. Stereostructure and conformation of the hydroxy-amides 11b–d,e,h,b′–d′,h′

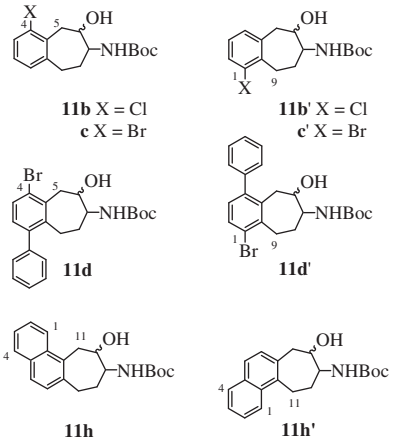
The structure of the different isomers of the hydroxy-amides mentioned in Scheme 6 was easily determined by NMR spectroscopy. The ^1H NMR spectra of the *trans*-isomers were well resolved



Scheme 5. Synthesis of the mono- and di-phenyl compounds ***1f f′ g***.

at room temperature, so that all H–H coupling could be precisely measured. No significant differences were observed with the various substituents: For all *trans*-isomers, the large value of the coupling between the five adjacent protons: one H-5 and H-6 (ca. 10 Hz), H-6 and H-7 (8.6–10.8 Hz), H-7 and Hb-8 (11.0–12.0 Hz), Hb-8 and one H-9 (11–12 Hz) corresponded to five axial protons in a chair conformation (see Fig. 1 for **11c** and **11c**′). These axial protons in the 5 and 9 positions were generally Hb-5 and Hb-9, but Ha-5 for **11b**-*trans* and **11c**-*trans*, and Ha-9 for **11b**-*trans* and **11c**-*trans*. In the naphtho series, for **11h**-*trans* these five protons were respectively Ha-11, H-10, H-9, Hb-8 and Ha-7, and for **11h**′-*trans* Ha-7, H-8, H-9, Hb-10 and Hb-11.

The *cis*-isomer **11c**′ could be fully analysed at 330 K and the weaker values of $J(6,7)$ and $J(5b,6)$ (2.2 and 7.2 Hz respectively) were consistent for an equatorial H-6 in a chair conformation. A *trans*-diaxial relation was likely observed between H-7 and Hb-8 and Hb-8 and the axial Hb-9. This chair conformation is identical to the one determined previously for the benzo-unsubstituted analogue of type **11**[11] ($R^1 = R^4 = H$).



Scheme 6. Structures of the hydroxy-amides selected for conformational analysis by NMR.

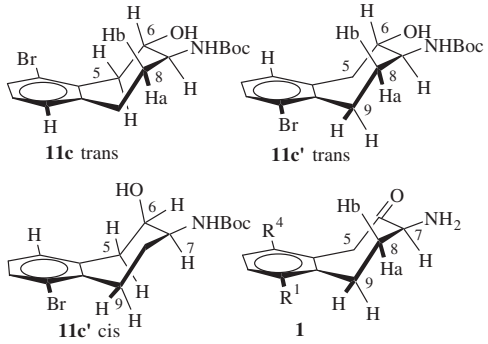


Figure 1. Conformation of the hydroxy-amides **11c,c′** and ketone derivative **1**.

Trans- and *cis*-isomers were easily characterised by the δ-values of the protons NH and H-6, H-7 (respectively H-10 and H-9 for **11h**, H-8 and H-9 for **11h′**): these protons appeared nearly at 5.05, 4.1 and 3.8 ppm for the *cis*-isomers, at 4.5, 3.35 and 3.7 ppm for the *trans*-isomers, respectively.

The structural determination of the regioisomeric hydroxy-amides **11b/11b′**, **11c/11c′**, **11d/11d′**, **11h/11h′** was deduced from the spatial deshielding of the *peri* H-atom caused by the aromatic halogen atom (Cl or Br in position 4 or 1) in the three halogeno-series, or by the naphthalene ring in the last series (Fig. 1 and Scheme 5). The equatorial Ha-5 proton in the 4-halogenated isomers **11b** and **11c**, or the equatorial one Ha-9 in the 1-halogenated regioisomers **11b′** and **11c′**, were spatially close to the halogen atom (see Fig. 1 for **11c** and **11c′**) and thus strongly deshielded with ca. 0.7–0.9 ppm. The same effect was observed for the Ha-11 proton in **11h** and **11h′** in the naphtho series. These equatorial protons appeared at 3.5–3.8 ppm while the corresponding axial ones Hb-5, Hb-9 or Hb-11 appeared at 2.8–3.1 ppm. The phenyl group at position 1 or 4 in **11d**,**d′** had only a weak effect on these protons.

2.6. Conformation of the amino-ketones of type 1

In contrast to the hydroxy-amides of type **11**, whose regular chair conformation was supported by the numerous H–H *trans*-diaxial relations, the amino-ketones of type **1** seemed to adopt a slightly altered chair conformation. Indeed, the coupling constants between the axial H-7 and axial Hb-8 (respectively H-9 and Hb-8 for **1h**, H-9 and Hb-10 for **1h′**) remained large (11–12 Hz), but the coupling constants between Hb-8 and the axial H-9 (or the corresponding Hb-8 and Ha-7 protons for **1h**, Hb-10 and Hb-11 for **1h′**) were weaker (7.6–10.2 Hz), as for the corresponding *trans*-alcohol-amides of type **11**. The chair conformation was favoured by the hydrogen bond between the carbonyl and amine functions and its alteration was due to the steric hindrance between the 1-substituent and the equatorial H-9 and/or between the 4-substituent and the equatorial H-5 (or between the H-1 and equatorial H-11 protons for the naphthalenic derivatives **1h** and **1h′**) (see Fig. 1).

The conformation of the keto-amides of type **12** seemed to be more altered and was not studied here.

3. Aminopeptidase inhibition and discussion

All compounds, evaluated as racemic mixtures, behaved as competitive inhibitors of the panel aminopeptidases. The inhibition constants (K_i) are reported in Table 1. We have previously reported that the aminobenzosuberone scaffold **1a** was stable in aqueous solutions at the physiological pH used for the kinetic studies.[11] We have also proposed that the ketone function most probably binds in its hydrate form to the zinc ion and to the catalytic glutamic acid residue in the APN/CD13 active site, thus mimicking the transition state that forms during peptide bond hydrolysis. This binding mode would be in line with the excellent ligand efficiency (0.63) of this very small lead structure.[11]

In the present work, we investigated various substituents in position 1 and/or 4 of the benzo aromatic ring A of our lead structure **1a**, in order to assess the effect of electrostatic and steric variations on binding and to determine the best match to the APN/CD13 active site. Since APN has a preference for hydrophobic substrates,[1] we focused on phenyl and halogen groups with large van der Waals radii. Halogen atoms are known to influence structure–activity relationships far beyond the mere steric aspects[23] and many impressive examples of the use of halogen substituents in hit-to-lead conversion have been reported in the recent years.[24]

Our data show that all derivatives of the lead structure **1a** display sub-micromolar inhibition constants towards the 'one zinc' APN/CD13, with an improved selectivity against the 'two zinc' family of enzymes represented here by the mammalian and bacterial LAPc and APaero, respectively. No inhibitory activity was observed up to an inhibitor concentration of 100 μM towards the aminopeptidase activity of human LTA_4H (data not shown).

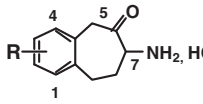
3.1. Extension of the aromatic system

We first investigated the extension of the fused ring system with two compounds, **1h** and **1h′**, bearing a fused benzo[3,4] or benzo[1,2] ring, respectively. The observed improvement in inhibitory potency is consistent with our previously published SAR studies in the 3-amino-2-tetralone series.[25] Both extensions improved binding affinity, with compounds **1h** (K_i = 0.1 μM) being 10 times more active than our lead structure **1a**, and **1h′** showing an even larger increase in potency, with a K_i value of 40 nM.

3.2. Substitution in position 1

To assess substitutions at position 1 of the benzo-ring A of our lead compound **1a**, we synthesised the phenyl, chloro and bromo analogues **1f′**,**b′**,**c′**. All modifications led to an increased inhibitory potency, with the following rank order Br > Cl > phenyl (K_i values of 20, 90 and 250 nM, respectively. This SAR revealed steric tolerance in this position as well as a clear preference for bromide. As a matter of fact, the bromo derivative **1c′** was the most potent inhibitor in this series with a 50-fold increase in potency when compared to **1a**, and was also 5–10 times more active than the phenyl- or chloro-substituted analogues.

Table 1
Inhibition data of aminopeptidase activity[a]

Compounds			K_i (μM)		
			APN [b] [EC 3.4.11.2] 'One zinc'	LAPc[c] [EC 3.4.11.1]	APaero[d] [EC 3.4.11.10]
				'Two zinc enzymes'	
	R^1	R^4			
1a	H	H	1	>100	900
1b′	Cl	H	0.090	>100	>100
1c′	Br	H	0.020	>100	>100
1f′	Ph	H	0.250	>100	>100
1c	H	Br	0.040	>100	213
1f	H	Ph	0.007	>100	28
1d	Ph	Br	0.070	>100	>100
1d′	Br	Ph	0.00006[e]	70	39
1e	Br	Br	0.006	>100	>100
1g	Ph	Ph	0.040	50	>100
1h	Benzo[3,4]		0.100	>100	>100
1h′	Benzo[1,2]		0.040	>100	>100

[a] All substances were evaluated as racemic mixtures. K_i (μM) values were determined from Dixon plots at a substrate concentration set to the K_m value for the corresponding enzyme (see Section 5). Inactive compounds were tested up to their solubility limit under the assay conditions that is, 100 μM.
[b] APN: porcine aminopeptidase-N (EC 3.4.11.2).
[c] LAPc: cytosolic leucine aminopeptidase from bovine kidney (EC 3.4.11.1).
[d] APaero: *Aeromonas proteolytica* aminopeptidase (EC 3.4.11.10).
[e] Dixon plot for APN inhibition with **1d′** is reported in Figure 2.

3.3. Substitution in position 4

We also selected bromo and phenyl groups for investigating potential substitutions in position 4. Both variations had a pronounced positive effect on binding affinity. In sharp contrast to substitutions in position 1, however, the phenyl derivative **1f** was, with a K_i value of 7 nM, a more potent inhibitor than the bromo analogue **1c**, which was, comparatively, five times less active (K_i = 40 nM) on APN. Among all monosubstituted analogues in position 1 or 4, **1f** was clearly the best inhibitor.

3.4. Disubstitution in positions 1 and 4

Four compounds were designed and synthesised in this series, combining phenyl and/or bromo substituents in positions 1 and 4. The addition of a phenyl moiety in position 1 to the monosubstituted bromo-derivative in position 4 (**1c**, K_i = 40 nM) led to the asymmetrical disubstituted analogue **1d** (K_i = 70 nM) which did not show any improvement in the K_i value. The symmetric dibromo-derivative **1e** (K_i = 6 nM), however, was about 5 times more active that the monosubstituted analogues **1c′** (K_i = 20 nM) and **1c** (K_i = 40 nM). The other symmetrically disubstituted diphenyl derivative **1g** (K_i = 40 nM) was slightly weaker than the monosubstituted 4-phenyl derivative (**1f**, K_i = 7 nM). Nevertheless, **1g** was more potent than the monosubstituted 1-phenyl derivative **1f′** (K_i = 250 nM).

Based on these results, we expected the asymmetrical disubstitution combining a bromo group in position 1 and a phenyl ring in position 4 to be the most interesting combination, for the corresponding monosubstitutions seemed optimal in both cases. Very gratifyingly, our expectation was fully confirmed by the outstanding inhibitory potency of the disubstituted derivative **1d′** which, with a K_i value of 60 pM, turned out to be 100 to 1000 times more potent than the corresponding monosubstituted analogues. This new structure is also 20,000 times more active than our starting lead compound **1a**. This spectacular enhancement in potency was achieved through the additive effect obtained by combining the substituents in positions 1 and 4 that fit the APN active site best. Kinetic data for APN inhibition by this particular compound are reported in Fig. 2 as a Dixon plot[34] which clearly showed that compound **1d′** remains a competitive, reversible inhibitor although its potency is close to the range of tight binding Inhibition. This is perfectly in line with the core structure of our compound series, which are cyclic substrate analogues retaining the metal chelating groups.

Not only is this novel APN/CD13 inhibitor by far more potent than any other compound investigated in this work, it is also undoubtedly among the most potent and selective non peptidic inhibitors of mammalian APN/CD13 known to date.

4. Conclusion

Metallopeptidases constitute a large family of proteolytic enzymes using a transition metal ion at their catalytic center. Small-molecule metallopeptidase inhibitors are generally designed to bind directly to the active site metal,[10] thus achieving a high ligand efficiency, often at the expense, however, of selectivity. The development of highly specific metallopeptidase inhibitors is a technically challenging, yet medically important scientific endeavour, in view of the prominent role played by metallopeptidases in many pathologies. We recently reported the discovery of aminobenzosuberone **1a** as a novel war head showing promise for the selective inhibition of the 'one zinc' mammalian aminopeptidase APN/CD13.[11]

In the present study, a series of highly potent analogues of aminobenzosuberone **1a** is reported. Our data demonstrate that very large improvements in potency can be achieved without compromising selectivity. Moreover, the novel APN inhibitors reported here remain well within the boundaries of Lipinski's rule-of-five which delimits 'drug-like' chemical space.[27] With a molecular weight of only 329 Da, there is still ample room for fine tuning the pharmacological properties of our highly selective, picomolar inhibitor **1d′**. Alternatively, it may be possible to tune the selectivity of this compound series towards related aminopeptidases of pharmaceutical interest, such as *Plasmodium falciparum* aminopeptidase N.[28]

We strongly believe that **1d′**, as well as other potent compounds reported here, will be highly valuable chemical probes for investigating APN/CD13 and for delineating its physiological and pathological roles that require catalytic activity.

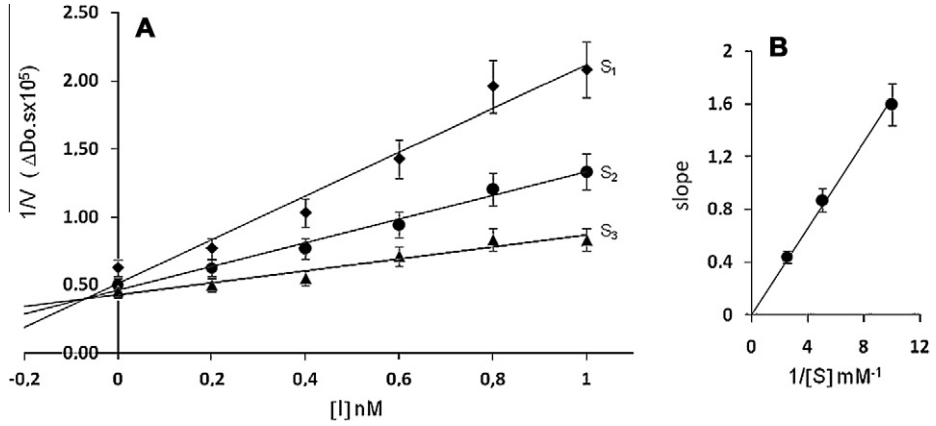


Figure 2. Kinetic data for APN inhibition by compound **1d**′. (A) Dixon plot: the effect of the inhibitor on the enzyme rate is determined at 3 substrate concentrations ($S_1 = K_m/2$, $S_2 = K_m$ and $S_3 = 2\ K_m$) over a range of inhibitor concentrations [I], from 0.2 to 1 nM. The concentration of APN (Specific activity, 28 Units per mg) was 0.1 mUnit per assay (12 pM). Data for each substrate concentration fall on a straight line that interact on [I] = K_i = 0.06 nM. With an average experimental error of 10% (n = 3). (B) The replot of the slopes of the Dixon plot is a straight line through the origin, indicating a pure competitive inhibition.[34]

5. Experimental part

5.1. General

Flash chromatography: silica gel (*Merck 60*, 230–400 mesh). TLC: Al-roll silica gel (*Merck 60*, F_{254}). Mp: *Kofler* hot bench, corrected. IR spectra (ν in cm^{-1}): *Nicolet 405 FT-IR*. ^1H and ^{13}C NMR (400 MHz and 100.6 MHz resp.) spectra: *Bruker Avance 400*, tetramethylsilane (TMS), or natrium (D_4)-trimethylsilylpropionate (D_4-TSP) in D_2O (^1H NMR) and $CDCl_3$, or MeOD-D_4 [$\delta(CDCl_3) = 77.0$, $\delta(CD_3OD) = 35.0$ with respect to TMS] (^{13}C NMR) as internal references; δ in ppm and J in Hertz. High resolution MS were measured on a *Bruker MicrOTof* spectrometer in *Institut de Chimie*, UMR 7177 CNRS, ULP, Strasbourg, France, or *Agilent Technologies 6510* (QTof) spectrometer in ENSCMu, *Université de Haute Alsace*, Mulhouse, France or *Waters Micromass Q-Tof Ultima API*, *Basilea Pharmaceuticals*, Basel. Microanalyses were carried out by the *Service Central de Microanalyses du CNRS*, F-69390 Vernaison or by the *Service de Microanalyse*, UMR 7565 CNRS *Université Henri Poincaré* F-54506 Vandoeuvre-les-Nancy.

5.2. Reagents and solvents

5% Pd/C and Raney-nickel were obtained from Fluka, other reactants were purchased from usual provider. Dess–Martin periodinane (DMP) was prepared according to,[22] or purchased in CH_2Cl_2 solution and NMR-titrated by oxidation of benzyl alcohol. Usual solvents were freshly distilled, dry EtOH and MeOH distilled over Mg/MgI_2, dry THF over Na and benzophenone, dry Et_2O was distilled and stored over Na, CH_2Cl_2 was distilled over P_2O_5 and kept over Na_2CO_3. NEt_3 was distilled before use.

6. Syntheses of the xylenes 2d,e, 3b and 4

6.1. 4-Bromo-2,3-dimethylaniline hydrobromide (3b)

To a solution of **3a** (2.5 mL, 20.1 mmol) in dry CH_2Cl_2 (50 mL) was added $NBu_4{\cdot}Br_3$ (10.2 g, 20.1 mmol, 1 equiv) at 0 °C under Argon, then the solution was stirred at 0 °C for 15 min. The precipitate of **3b**·HBr (4.33 g, 75%) was isolated by filtration, washed with Et_2O and dried under vacuum.

Compound **3b**·HBr: colorless crystals, mp 258–60 °C. IR (KBr): 2921, 2577, 1531, 1510, 1456, 1180, 1001, 905, 824, 801, 543 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 2.36 (s, 3H, Me-2); 2.48 (s, 3H, Me-3); 7.13 (d, 1H, H-6); 7.58 (d, 1H, H-5); J(5,6) = 8.6 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 15.6 (Me-2); 20.7 (Me-3); 123.6 (C(6)); 127.3 (C(4)); 130.5 (C(2)); 132.7 (C(5)) 134.4 (C(3)); 140.5 (C(1)). Free base (by stirring with aqueous Na_2CO_3), ^1H NMR ($CDCl_3$): same values as in lit.[15]

6.2. 4-Bromo-2,3-dimethylbenzenediazonium tetrafluoroborate (4)

To a solution of **3b**·HBr (4.12 g, 14.7 mmol) in CH_3CN (10 mL) were added 50% aqueous HBF_4 (5.6 mL, 44 mmol, 3 equiv) and then with stirring at −20 °C dropwise *t*BuONO (2.2 mL, 16.1 mmol, 1.1 equiv). The solution was stirred at −20 °C for further 45 min, Et_2O (20 mL) was then added and the precipitate of **4** (3.46 g, 78%) was isolated by filtration and washing with Et_2O (10 mL).

Compound **4**: colorless crystals, mp 162–171 °C. (KBr): 3568, 3048, 2256, 1548, 1430, 1386, 1300, 1196, 1083, 1029, 896, 823 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 8.30 (d, 1H, J(5,6) = 9.0 Hz, H-6); 8.07 (d, 1H, J(5,6) = 9.0 Hz, H-5); 2.76 (s, 3H, Me-2); 2.50 (s, 3H, Me-3). ^{13}C NMR (CD_3OD, 100 MHz): 144.9 (C(1)); 143.5 (C(3)); 141.8 (C(2)); 138.0 (C(4)); 134.7 (C(5)); 131.3 (C(6)); 20.3 (CH_3-3); 18.3 (CH_3-2). Anal. Calcd for $C_8H_8BBrF_4N_2{\cdot}0.5H_2O$ (307.88): C, 31.21; H, 2.95; N, 9.10. Found: C, 31.0; H, 2.7; N, 8.8.

6.3. 1,4-Dibromo-2,3-dimethylbenzene (2e)

A solution of the free base **3b** [8.69 g, 43.5 mmol, obtained by stirring a suspension of **3b** in Et_2O (20 mL) with Na_2CO_3 (5 g, 50 mmol) and H_2O (5 mL) and then filtration and evaporation of the solvent] in MeCN (100 mL) was added under Ar to a solution of $CuBr_2$ (9.71 g, 43.5 mmol, 1 equiv) and *t*BuONO (4.93 g, 5.68 ml, 47.8 mmol, 1.1 equiv) in MeCN (200 mL). The mixture was stirred at rt for 16 h, then at 82 °C for 4 h. The mixture was left at rt, diluted with AcOEt (200 mL), washed with brine (2 × 100 ml), dried ($MgSO_4$) and the solvent evaporated to give **2e** (9.79 g, 85%). Same NMR data as in lit.[15]

6.4. 4-Bromo-2,3-dimethyl-biphenyle (2d)

A solution of **4** (10.9 g, 36.3 mmol) and phenylboronic acid (5.0 g, 41.5 mmol, 1.15 equiv) in MeOH (300 mL) was refluxed under Ar with $Pd(OAc)_2$ (0.82–0.6 g, 0.1–0.07 equiv) at 65 °C for 2 h. The solution was left at rt, diluted with AcOEt (500 mL), washed with H_2O, dried (SO_4Mg) and evaporated. The residue was purified by flash chromatography (cyclohexane), to give **2d** in two crops after crystallisation in *i*PrOH (3.5–5.1 g, 34–54%).

Compound **2d**: colorless crystals, mp 56–57 °C (MeOH). IR (KBr): 2922, 1443, 1006, 823, 765, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.44 (d, 1H, H-5); 7.39 (tm, 2H, Har-m); 7.34 (tm, 1H, Har-p); 7.24 (dm, 2H, Har-o); 6.93 (d, 1H, H-6); 2.46 (s, 3H, Me-3); 2.21 (s, 3H, Me-2); J(5,6) = 8.3, J(o,m) = 7.5, J(m,p) = 7.3 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 141.8, 141.7 (C(2),C(3)); 136.5, 136.0 (C(1),C(1′)); 129.5 (C(5)); 129.3 (C(2′),C(6′)); 128.6 (C(6)); 128.1 (C(3′),C(5′)); 126.9 (C(4′)); 124.6 (C(4)); 20.2 (Me-3); 18.6 (Me-2). Anal. Calcd for $C_{14}H_{13}Br$ (261.16): C, 64.39; H, 5.02; Br, 30.60. Found: C, 64.5; H, 4.9; Br, 30.3.

7. α,α′-Dibromoxylene derivatives 5b–e,h

General procedure (a): A solution of 1,2-dimethylaryle **2b–e**,**h** (10 mmol) and finely pulverised N-bromosuccinimide (NBS 3.68 g, 21 mmol, 2.1 equiv) in CCl_4 (40–80 mL) was irradiated with HPK125 mercury lamp for 1–2 h with good stirring (tlc or ^1H NMR monitoring). The reaction mixture was diluted with CH_2Cl_2, washed with H_2O or 2 N aqueous NH_4Cl solution and dried over $MgSO_4$. The solvent was evaporated to give quantitatively **5b–e**,**h** which was used without further purification.

7.1. 1-Chloro-2,3-bis(bromomethyl)benzene (5b)

General procedure (a) with **2b** (2.0 g, 10.8 mmol) and NBS (4.04 g, 22.7 mmol, 2.1 equiv) in CCl_4 (70 mL) to give **5b**[29] (3.7 g, quant.).

Compound **5b**: yellowish oil. ^1H NMR ($CDCl_3$, 400 MHz): 7.38 (dd, 1H, H-6); 7.28 (dd, 1H, H-4); 7.24 (t, 1H, H-5); 4.81 (s, 2H, CH_2Br-2); 4.62 (s, 2H, CH_2Br-3); J(4,5) = 7.6, J(4,6) = 1.6, J(5,6) = 7.8 Hz.

7.2. 1-Bromo-2,3-bis(bromomethyl)benzene (5c)

General procedure (a) with **2c** (5 g, 27 mmol) and NBS (10.1 g, 56.7 mmol, 2.1 equiv) in CCl_4 (200 mL) to give **5c** (9.36 g, quant.).

Compound **5c**: yellowish oil. ^1H NMR ($CDCl_3$, 400 MHz): 7.57 (dd, 1H, H-6); 7.32 (dd, 1H, H-4); 7.15 (t, 1H, H-5); 4.84 (s, 2H, CH_2Br-2); 4.63 (s, 2H, CH_2Br-3); J(4,5) = 7.5, J(4,6) = 1.5, J(5,6) = 8.1 Hz. Same data as in lit.[30]

7.3. 4-Bromo-2,3-bis(bromomethyl)-biphenyle (5d)

General procedure (a) with **2d** (5.0 g, 19.1 mmol) and NBS (7.2 g, 40 mmol, 2.1 equiv) in CCl_4 (200 mL) to give **5d** (9.5 g, quant.).

Compound **5d**: colorless crystals, mp 84–86 °C (cyclohexane). IR (KBr): 556, 613, 659, 704, 759, 827, 1188, 1203, 1222, 1434, 1446, 3032 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.61 (d, 1H, J(5,6) = 8.3 Hz, H-5); 7.45 (m, 5Har); 7.09 (d, 1H, J(5,6) = 8.3 Hz, H-6); 4.97 (s, 2H, CH_2Br-3); 4.55 (s, 2H, CH_2Br-2). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.6 (2-CH_2Br); 29.9 (3-CH_2Br); 125.6 (C(4)); 128.0, 128.4, 128.7 (3 CHar); 132.0 (C(6)); 133.3 (C(5)); 136.2, 136.6 (C(1),C(1′)); 139.2 C(2)); 143.4 C(3). Anal. Calcd for $C_{14}H_{11}Br_3$ (418.96): C, 40.14; H, 2.65. Found: C, 39.9; H, 2.4.

7.4. 1,4-Dibromo-2,3-bis(bromomethyl)benzene (5e)

General procedure (a) with **2e** (1.22 g, 4.62 mmol) and NBS (1.75 g, 9.71 mmol, 2.1 equiv) in CCl_4 (70 mL) to give **5e** as orange crystals (1.83 g, 94%). Same NMR data as in lit.[31]

7.5. 1,2-Bis-bromomethyl-naphtalene (5h)

General procedure (a) with **2h** (1.0 g, 6.4 mmol) and NBS (2.39 g, 13.4 mmol, 2.1 equiv) in CCl_4 (50 mL) to give **5h** (2.0 g, quant.).

Compound **5h**: orange crystals, mp 149–150 °C (lit[32] 148.5–149.5 °C). ^1H NMR ($CDCl_3$, 400 MHz): 8.16 (dm, 1H, H-8); 7.87 (ddd, 1H, H-5); 7.84 (d, 1H, H-4); 7.65 (td, 1H, H-7); 7.55 (td, 1H, H-6); 7.45 (d, 1H, H-3); 5.12 (s, 2H, CH_2Br-1); 4.78 (s, 2H, CH_2Br-2); J(3,4) = 8.4, J(5,6) = 8.0, J(5,7) = 1.4, J(5,8) = 0.6, J(6,7) = 6.8, J(6,8) = 1.0, J(7,8) = 8.6 Hz. Data in agreement with those of lit.[33]

8. Preparation of the ketonediesters 7b–e,h by reaction with acetone-dicarboxylate 6 and decarboxylation into ketones 8b–e,h

General procedure (b), reaction with methyl acetonedicarboxylate (6): A solution of 1,2-bis-bromomethylaryle **5a–e**,**h** (10 mmol) and **6** (1.7 ml, 12 mmol, 1.2 equiv) in CH_2Cl_2 (25–40 mL) was added dropwise to a solution of NBu_4Br (2.0 g, 6 mmol, 0.6 equiv) in 1 N aqueous $NaHCO_3$ (50–80 mL) and CH_2Cl_2 (25–40 mL). The biphasic mixture was vigorously stirred at 40 °C under Argon for 6 h to overnight. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic solutions were evaporated. The residue was dissolved in AcOEt and washed with brine (3 × 50 mL), dried over $MgSO_4$ and evaporated to give a yellowish resin which was used without further purification (quantitative).

General procedure (c), decarboxylation in acidic medium: A vigorously stirred biphasic solution of **7b–e**,**h** (10 mmol) in 3 M aqueous H_2SO_4 (50 mL) and MeCN (15 mL) was refluxed at 90 °C for 16 h. The mixture was diluted with AcOEt (100 mL), neutralised with 2 M aqueous NaOH. The organic layer was separated, washed with H_2O or brine, the aqueous layer extracted with AcOEt, the combined organic phases were dried over $MgSO_4$ and evaporated to give the crude ketone **8**.

General procedure (d), decarboxylation in basic medium: A vigorously stirred biphasic solution of 1 N aqueous NaOH (70 ml) and **7b–e**,**h** (10 mmol) in MeCN solution (20 ml) was refluxed at 90 °C for 2 h. The mixture was left at rt, neutralised with concd HCl and extracted with AcOEt (2 × 50 mL). The combined organic phase was washed with brine (4 × 10 mL), dried over $MgSO_4$ and evaporated to give the ketone **8** which was purified by flash chromatography.

8.1. Dimethyl 1-chloro-7-oxo-5,6,8,9-tetrahydro-benzocycloheptene-6,8-dicarboxylate (7b) and 1-chloro-5,6,8,9-tetrahydro-benzocycloheptene-7-one (8b)

General procedure (b) with NBu_4Br (5.1 g, 16.0 mmol, 0.6 equiv) **5b** (7.6 g, 25.5 mmol), **6** (5.3 g, 30.5 mmol, 1.2 equiv) in 1 M aqueous $NaHCO_3$ (100 mL) and CH_2Cl_2 (80 mL) for 16 h to give **7b** (7.5 g, 96%) as 50/50 isomeric mixture.

General procedure (c) with crude **7b** (7.5 g, 24.2 mmol) in MeCN (20 mL) and aqueous 3 M H_2SO_4 (100 mL) to give the crude **8b** (4.5 g, 83% from **3b**).

Compound **7b**: yellowish resin. ^1H NMR ($CDCl_3$, 300 MHz): 3.0–4.0 (m, 12H); 7.0–7.4 (m, 3H). HR-MS (ESI-Q-Tof) calcd for $C_{15}H_{15}ClLiO_5$ $[M+Li]^+$: 317.0763; found: 317.0752.

Compound **8b**: yellowish resin. IR (KBr): 2956, 2945, 1699, 1450, 1349, 1187, 880, 794, 786 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.32 (m, 1H, H-2); 7.12 (m, 2H, H-4, H-3); 3.16 (m, 2H, CH_2(9)); 2.96 (m, 2H, CH_2(5)); 2.62 (m, 4H, CH_2(6), CH_2(8)). ^{13}C NMR ($CDCl_3$, 75 MHz): 210.4 (CO(7)); 142.9, 137.9 (C(9a),C(4a)), 133.7 (C(1)); 128.2, 127.7, 127.6 (C(4),C(3),C(2)); 44.4, 43.2 (C(6),C(8)); 30.9 (C(5)); 25.2 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{11}ClLiO$ $[M+Li]^+$: 201.0653; found: 201.0636.

8.2. Dimethyl 1-bromo-7-oxo-5,6,8,9-tetrahydro-benzocycloheptene-6,8-dicarboxylate (7c) and 1-bromo-5,6,8,9-tetrahydro-benzocycloheptene-7-one (8c)

General procedure (b) with NBu_4Br (5.2 g, 16.2 mmol, 0.6 equiv), **5c** (9.36 g, 27.3 mmol), **6** (5.6 g, 32.4 mmol, 1.2 equiv) in 5%

aqueous $NaHCO_3$ (120 mL) and CH_2Cl_2 (100 mL) for 6 h to give **7c** (10.9 g, quant.).

General procedure (c) with **7c** (10.9 g, 27 mmol) in MeCN (50 mL) and aqueous 3 M H_2SO_4 (100 mL). The crude product was purified by flash chromatography (cyclohexane/AcOEt 9:1) to give **8c** (4.0 g, 62% from **3c**).

Compound **7c**: yellowish resin. IR (KBr): 2953, 1744, 1719, 1653, 1437, 1333, 1305, 1226, 1161, 783 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 3.2–4.2 (m, 12H); 7.0–7.2 (m, 2H); 7.4–7.6 (m, 1H). HR-MS (ESI^+): calcd for $C_{15}H_{16}BrO_5$ $[M+H]^+$: 355.0176; found: 355.0174; calcd for $C_{15}H_{15}BrNaO_5$ $[M+Na]^+$: 376.9995; found: 376.9993.

Compound **8c**: colorless crystals, mp 32–34 °C. IR (KBr): 2952, 2907, 1702, 1561, 1448, 1344, 1184, 873, 781 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.51 (d, 1H, H-2); 7.16 (d, 1H, H-4); 7.05 (t, 1H, H-3); 3.19 (m, 2H, CH_2(9)); 2.98 (m, 2H, CH_2(5)); 2.62 (m, 4H, CH_2(6), CH_2(8)); J(1,2) = 8.1, J(2,3) = 7.4 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 210.2 (CO(7)); 142.8 (C(9a)), 139.6 (C(4a)); 131.6 (C(2)); 128.4, 128.2 (C(4),C(3)); 124.5 (C(1)); 44.4, 43.1 (C(6),C(8)); 31.1 (C(5)); 28.5 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{13}BrNaO$ $[M+Na]^+$: 260.9885 and 262.9866; found: 260.9879 and 262.9864.

8.3. Dimethyl 1-bromo-4-phenyl-7-oxo-5,6,8,9-tetrahydro-benzocyclohepten-6,8-dicarboxylate (7d) and 1-bromo-4-phenyl-5,6,8,9-tetrahydrobenzocycloheptene-7-one (8d)

General procedure (b) with NBu_4Br (1.74 g, 5.30 mmol, 0.6 equiv) **5d** (3.7 g, 8.83 mmol), **6** (2.0 mL 13.2 mmol, 1.5 equiv) in 5% aqueous $NaHCO_3$ (75 mL) and CH_2Cl_2 (50 mL) for 16 h to give **7d** (3.6 g, quant.) as 50:50 *cis/trans* isomeric mixture.

General procedure (c) with **7d** (16.9 g, 39 mmol) in MeCN (115 mL) and H_2SO_4 3.8 M (186 ml) at 100 °C for 3 days. Crude ketone was purified by flash chromatography (cyclohexane/AcOEt 9:1) then crystallised from MeOH to give pure **8d** (7.6 g, 64% from **3d**).

General procedure (d) with **7d** (3.6 g, 8.8 mmol) in MeCN (20 mL) and aqueous 1 M NaOH (60 mL) for 16 h. The crude product was purified by flash chromatography (cyclohexane/AcOEt 9:1) to give **8d** (1.20 g, 43% from **3d**).

Compound **7d**: colorless crystals, mp 146–152 °C (AcOEt). IR (KBr): 706, 765, 816, 1164, 1231, 1280, 1291, 1305, 1440, 1452, 1641, 1735, 2947 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.6–7.4 (m, 4Har); 7.25–7.15 (m, 2Har); 7.2–7.1 (m, 1Har); 3.2–4.0 (m, 12H). HR-MS (ESI^+): calcd for $C_{21}H_{19}BrNaO_5$ $[M+Na]^+$: 453.0308 and 455.0287; found: 453.0303 and 455.0287.

Compound **8d**: orange crystals; mp 117–119 °C (iPr_2O). IR (KBr): 710, 776, 819, 1175, 1451, 1693, 2943 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.54 (d, 1H, J(2,3) = 8.4 Hz, H-2); 7.45–7.36 (m, 3H, 2Har-m, Har-p); 7.23 (m, 2Har-o); 7.03 (d, 1H, J(2,3) = 8.4 Hz, H-3); 3.30 (m, 2H, 2 CH_2(9)); 2.93 (m, 2H, CH_2(6)); 2.65 (m, 2H, CH_2(8)); 2.54 (m, 2H, CH_2(6)). ^{13}C NMR ($CDCl_3$, 100 MHz): 210.2 (C(7)); 141.4, 140.9, 140.3, 140.1 ((C(9a), C(4a), C(4), Car-s); 130.7 (C(2)); 129.8 (C(3)); 129.0 (Car-o); 128.4 (Car-m); 127.4 (Car-p); 123.5 (C(1)); 44.3 (C(6)); 43.1 (C(8)); 28.8 (C(9)); 26.4 (C(5)). HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{15}BrLiO$ $[M+Li]^+$: 321.0461 and 323.0446; found: 321.0474 and 323.0461.

8.4. Dimethyl 1,4-dibromo-7-oxo-5,6,8,9-tetrahydro-benzocyclohepten-6,8-dicarboxylate (7e) and 1,4-dibromo-5,6,8,9-tetrahydrobenzocycloheptene-7-one (8e)

General procedure (b) with NBu_4Br (0.84 g, 2.56 mmol, 0.6 equiv), **5e** (1.8 g, 4.27 mmol), **6** (0.92 ml, 6.40 mmol, 1.5 equiv) in 5% aqueous $NaHCO_3$ (36 mL) and CH_2Cl_2 (25 mL) for 16 h to give **7e** (1.84 g, quant.) as 50:50 *cis/trans* isomeric mixture.

General procedure (d) with **7e** (1.85 g, 4.26 mmol) in MeCN (10 mL) and aqueous 1 M NaOH (30 mL) for 2 h. The crude product was purified by flash chromatography (cyclohexane/AcOEt 9:1) to give **8e** (1.15 g, 85% from **3e**)

Compound **7e**: yellowish oil. IR (KBr): 804, 1159, 1232, 1443, 1648, 1717, 3412 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 3.40–4.20 (m, 12H); 7.26–7.40 (m, 2H). HR-MS (ESI^+IsoTof) calcd for $C_{15}H_{14}Br_2NaO_5$ $[M+Na]^+$: 454.9100, 456.9081 and 458.9063; found: 454.9107, 456.9082 and 458.9067.

Compound **8e**: orange crystals, mp 94 °C. IR (KBr): 3054, 2951, 2878, 1697, 1445, 1213, 1183, 1103, 878, 817, 527 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.36 (s, 2H, H-2, H-3); 3.28 (m, 4H, CH_2(5),CH_2(9)); 2.62 (m, 4H, CH_2(6), CH_2(8)). ^{13}C NMR ($CDCl_3$, 100 MHz): 209.3 (CO(7)); 141.7 (C(4a),C(9a)); 132.3 (C(2),C(3)); 123.3 (C(1),C(4)); 43.0 (C(6),C(8)); 29.4 (C(5),C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{14}Br_2NO$ $[M+NH_4]^+$: 333.94376, found: 333.9432.

8.5. Dimethyl 9-oxo-7,8,10,11-tetrahydro-naphthocycloheptene-8,10-dicarboxylate (7h) and 7,8,10,11-tetrahydro-cyclohepta[a]naphthalen-9-one (8h)

General procedure (b) with NBu_4Br (1.32 g, 4 mmol, 0.6 equiv), **5h** (2.0 g, 6.36 mmol), **6** (1.22 g, 1.01 ml, 7 mmol, 1.1 equiv), in 1 N $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (50 mL) for 16 h to give **7h** (2.1 g, quant.) as 50:50 *cis/trans* isomeric mixture.

General procedure (c) with **7h** (2.0 g, 6.09 mmol), in MeCN (10 mL) and aqueous 3 M H_2SO_4 (30 mL) to give **8h** (0.9 g, 75%).

Compound **7h**: yellowish resin. IR (KBr): 2953, 1743, 1711, 1648, 1436, 1354, 1293, 1231, 1211, 1166, 817, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 3.2–4.1 (m, 12H); 7.3–7.4 (m, 1H); 7.44–7.55 (m, 2H); 7.65–7.85 (m, 2H); 8.0–8.2 (m, 2H). HR-MS (ESI-Q-Tof) calcd for $C_{19}H_{18}NaO_5$ $[M+Na]^+$: 349.1046; found: 349.1057; $C_{19}H_{18}LiO_5$ $[M+Li]^+$: 333.1314; found: 333.1304.

Compound **8h**: yellowish resin. IR (KBr): 2950, 1694, 1597, 1512, 1436, 1384, 1323, 1189, 827, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.11 (d, 1H, H-1); 7.86 (dd, 1H, H-4); 7.73 (d, 1H, H-5); 7.54 (ddd, 1H, H-2); 7.47 (ddd, 1H, H-3); 7.36 (d, 1H, H-6); 3.41 (m, 2H, CH_2(11)); 3.14 (m, 2H, CH_2(7)); 2.69 (m, 4H, CH_2(10), CH_2(8)); J(1,2) = 8.6, J(1,3) = 1.0, J(2,3) = 6.8, J(2,4) = 1.4, J(3,4) = 8.0, J(5,6) = 8.4 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 211.1 (C(7)); 138.1, 135.6, 132.9, 131.4 (4Car); 128.8, 127.8, 127.2, 126.4, 125.1, 122.8 (6CHar); 44.1, 43.5 (C(8), C(10)); 30.8 (C(7)); 23.2 (C(11)). HR-MS (ESI-Q-Tof) calcd for $C_{15}H_{14}NaO$ $[M+Na]^+$: 233.0937; found: 233.0941; for $C_{15}H_{14}LiO$ $(M+Li^+)$: 217.1200; found: 217.1219.

9. Silyl enol ethers 9 or 9/9′ mixture and silyl ether ketones 10 or 10/10′ mixture

General procedure (e): To a solution of **8** (10 mmol, dried by evaporation with toluene) an dry toluene (20–50 ml) and NEt_3 (1.9 mL, 14 mmol, 1.4 equiv) was added at rt dropwise Me_3SiOTf (2.15 mL, 12 mmol, 1.2 equiv) at rt under Ar. The solution was stirred at 80 °C for 2 h, then left at rt diluted wit H_2O (10 mL) and extracted with cyclohexane (100 mL). The organic phases were washed with brine (20 mL), dried over $MgSO_4$ and evaporated to give quantitatively **9** or **9/9′** mixture as orange resin which was used without further purification.

General procedure (f): To a solution of **9** or **9/9′** mixture (10 mmol) in CH_2Cl_2 (10 mL), at 0 °C under Ar, was added portionwise *m*-CPBA (2.5 g, 15 mmol, 1.5 equiv) and stirred for 2 h (tlc monitoring). The solids were discarded by filtration and the organic phase evaporated. The solution of the residue in cyclohexane (100 mL) was washed with aqueous 1 M $NaHCO_3$ (20 mL) solution

(containing Na_2SO_3 or $Na_2S_2O_3{\cdot}5H_2O$ (10 mmol) to reduce the peracid excess) and with brine (20 mL), dried over $MgSO_4$ and evaporated to give **10** or **10/10′** mixture as yellowish resin which was used without further purification.

9.1. 1-Chloro-7-trimethylsilyloxy-6,9-dihydro-5*H*-benzocycloheptene (9b) and 4-chloro-7-trimethylsilyloxy-6,9-dihydro-5*H*-benzocycloheptene (9b′); 4-chloro-6-(trimethylsilyloxy)-5,6,8,9-tetrahydrobenzocyclohepten-7-one (10b) and 1-chloro-6-(trimethylsilyloxy)-5,6,8,9-tetrahydrobenzocyclohepten-7-one (10b′)

General procedure (e) with **8b** (4.2 g, 21.6 mmol), Et_3N (4.22 mL, 30.3 mmol, 1.4 equiv) in toluene (40 ml) and with Me_3SiOTf (4.7 mL, 26 mmol, 1.2 equiv) to give a 55:45 **9b/9b′** mixture (5.5 g, 96%).

Compound **9b**/**9b′**: brownish resin, characterised by NMR only. ^1H NMR ($CDCl_3$, 400 MHz), major isomer **9b**: 7.20 (m, 1 Har); 7.00 (m, 2Har); 5.07 (m, 1H, H-8); 3.51 (d, 2H, J = 6.6 Hz, $CH_2(9)$); 2.95 (m, 2H, $CH_2(5)$); 2.31 (m, 2H, $CH_2(6)$); 0.13 (s, 9H, $SiMe_3$). Minor isomer **9b′**: 7.20 (m, 1 Har); 7.00 (m, 2Har); 5.07 (m, 1H, H-8); 3.30 (d, 2H, J = 6.3 Hz, $CH_2(9)$); 3.15 (m, 2H, $CH_2(5)$); 2.31 (m, 2H, $CH_2(6)$); 0.14 (s, 9H, $SiMe_3$).

General procedure (f) with **9b/9b′** (5.5 g, 20.7 mmol) in CH_2Cl_2 (20 mL), *m*-CPBA (5.6 g, 32.6 mmol, 1.5 equiv) for 2 h to give a 55:45 **10b/10b′** mixture (5.2 g, 85% from ketone **8b**).

Compound **10b**/**10b′**: brownish oil characterised by NMR only. ^1H NMR ($CDCl_3$, 400 MHz) major isomer **10b**: 7.20 (m, 1H, H-3); 7.00 (m, 2Har); 4.19 (ddd, 1H, H-6); 3.31 (dd, 1H, Ha-5); 3.15 (dd, 1H, Hb-5); 3.0–2.8 (m, 3H, Ha-8, Ha-9, Hb-9); 2.40 (t, 1H, J = 11.0 Hz, Hb-C8); 0.15 (s, 9H, CMe_3); J(1,2) = 7.5, J(1,3) = 1.2, J(2,3) = 8.0 Hz, J(5a,5b) = 14.6, J(5a,6) = 3.0, J(5b,6) = 10.3, J(6,8b) = 1.0 Hz. Minor isomer **10b′**: 7.20 (m, 1H, H-2); 7.00 (m, 2Har); 4.20 (ddd, 1H, H-6); 3.17 (ddd, 1H, Ha-9); 3.14 (dd, 1H, Ha-5); 3.02 (m, 1H, Hb-9); 3.00 (m, 1H, Hb-5); 2.84 (ddd, 1H, Ha-8); 2.41 (ddt, 1H, Hb-8); 0.12 (s, 9H, CMe_3); J(2,3) = 8.0, J(2,4) = 1.2; J(3,4) = 7.4, J(5a,5b) = 14.2, J(5a,6) = 9.5, J(5b,6) = 3.2, J(6,8b) = 1.0, J(8a,8b) = 13.6, J(8a,9a) = 8.4, J(8a,9b) = 2.3, J(8b,9a) = 2.6, J(8b,9b) = 11.0, J(9a,9b) = 15.0 Hz.

9.2. 1-Bromo-7-trimethylsilyloxy-6,9-dihydro-5*H*-benzocycloheptene (9c) and 4-bromo-7-trimethylsilyloxy-6,9-dihydro-5*H*-benzocycloheptene (9c′); 4-bromo-6-(trimethylsilyloxy)-5,6,8,9-dihydrobenzocyclohepten-7-one (10c) and 1-bromo-6-(trimethylsilyloxy)-5,6,8,9-dihydrobenzocyclohepten-7-one (10c′)

General procedure (e) with **8c** (1.86 g, 7.78 mmol), Et_3N (1.63 mL, 11.7 mmol, 1.5 equiv) in toluene (20 ml) and with Me_3SiOTf (1.76 mL, 9.72 mmol, 1.25 equiv) to give a 55:45 **9c/9c′** mixture (2.35 g, quant.).

Compound **9c**/**9c′**: brownish resin, characterised by NMR only. ^1H NMR ($CDCl_3$, 400 MHz), major isomer **9c**: 7.40 (d, 1H, H-2); 7.10 (d, 1H, H-4); 6.98 (t, 1H, H-3); 5.08 (tt, 1H, H-8); 3.54 (dt, 2H, $CH_2(9)$); 2.96 (m, 2H, $CH_2(5)$); 2.31 (m, 2H, $CH_2(6)$); 0.13 (s, 9H, $SiMe_3$); J(2,3) = 8.0, J(2,4) = 1.2, J(3,4) = 7.3, J(6,8) = 1.4, J(6,9) = 1.9, J(8,9) = 6.5 Hz. Minor isomer **9c′**: 7.41 (d, 1H, H-3); 7.01 (d, 1H, H-1); 6.94 (t, 1H, H-2); 5.05 (tt, 1H, H-8); 3.31 (dt, 2H, $CH_2(9)$); 3.18 (m, 2H, $CH_2(5)$); 2.31 (m, 2H, $CH_2(6)$); 0.14 (s, 9H, $SiMe_3$); J(1,2) = 7.4, J(1,3) = 1.2, J(2,3) = 8.0, J(6,8) = 1.3, J(6,9) = 2.1, J(8,9) = 6.2 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz, **9c** M and **9c′** m isomers): 151.6 (C(7)M); 151.4 (C(7)m); 144.5, 143.1, 141.7, 139.8 (C(4a)M+m, C(9a)M+m); 130.6 (C(3)m, 130.5 (C(2)M); 127.42, 127.37, 127.3 (C(4)M, C(3)M, C(2)m); 126.8 (C(1)m); 123.7, 122.8 (C(4)m, C(1)M); 104.2 (C(8)M; 103.5 (C(8)m); 34.2 (C(6)M); 32.6 (C(6)m); 31.4 (C(5)M); 30.7 (C(5)m); 29.1 (C(9)m); 27.8 (C(9)M); 0.04 ($SiMe_3$ M+m).

General procedure (f) with **9c/9c′** (2.35 g, 7.55 mmol) in CH_2Cl_2 (20 mL), *m*-CPBA (2.04 g, 8.31 mmol, 1.1 equiv) for 3 h to give a 55:45 **10c/10c′** mixture (2.32 g, 91% from ketone **8c**).

Compound **10c**/**10c′**: brownish oil characterised by NMR only. ^1H NMR ($CDCl_3$, 400 MHz) isomer **10c**: 7.52 (dd, 1H, H-3); 7.13 (dd, 1H, H-1); 7.05 (t, 1H, H-2); 4.19 (ddd, 1H, H-6); 3.42 (dd, 1H, Ha-5); 3.21 (dd, 1H, Hb-5); 3.0–2.8 (m, 3H, Ha-8, Ha-9, Hb-9); 2.41 (td, 1H, J = 11.0, 1.0 Hz, Hb-C8); 0.15 (s, 9H, CMe_3); J(1,2) = 7.5, J(1,3) = 1.2, J(2,3) = 8.0 Hz, J(5a,5b) = 14.6, J(5a,6) = 3.0, J(5b,6) = 10.3, J(6,8b) = 1.0 Hz. Isomer **10c′**: 7.51 (dd, 1H, H-2); 7.18 (dd, 1H, H-4)); 7.06 (t, 1H, H-3); 4.20 (ddd, 1H, H-6); 3.27 (ddd, 1H, Ha-9); 3.14 (dd, 1H, Ha-5); 3.02 (m, 1H, Hb-9); 3.00 (m, 1H, Hb-5); 2.84 (ddd, 1H, Ha-8); 2.41 (ddt, 1H, Hb-8); 0.12 (s, 9H, CMe_3); J(2,3) = 8.0, J(2,4) = 1.2; J(3,4) = 7.4, J(5a,5b) = 14.2, J(5a,6) = 9.5, J(5b,6) = 3.2, J(6,8b) = 1.0, J(8a,8b) = 13.6, J(8a,9a) = 8.4, J(8a,9b) = 2.3, J(8b,9a) = 2.6, J(8b,9b) = 11.0, J(9a,9b) = 15.0 Hz.

9.3. 1-Bromo-4-phenyl-7-(trimethylsilyloxy)-6,9-dihydro-5*H*-benzocycloheptene (9d) and 4-bromo-1-phenyl-7-(trimethylsilyloxy)-6,9-dihydro-5*H*-benzocycloheptene (9d′); 4-bromo-1-phenyl-6-(trimethylsilyloxy)-5,6,8,9-tetrahydrobenzocyclohepten-7-one (10d) and 1-bromo-4-phenyl-6-(trimethylsilyloxy)-5,6,8,9-tetrahydrobenzocyclohepten-7-one (10d′)

General procedure (e) with **8d** (1.19 g, 3.78 mmol), Et_3N (0.8 mL, 5.29 mmol, 1.5 equiv) in toluene (15 ml) and with Me_3SiOTf (0.9 mL, 4.53 mmol, 1.2 equiv) for 4 h, to give a 60:40 **9d/9d′** mixture (1.39 g, 95%).

Compound **9d**/**9d′**: orange resin, characterised by NMR only ^1H NMR ($CDCl_3$, 300 MHz) major isomer **9d**: 7.45–7.33 (m, 5 Har); 7.25 (m, 1Har); 6.95 (d, 1Har, J(2,3) = 8.3 Hz, H-3); 5.11 (tt, 1H, H-8); 3.62 (dt, 2H, $CH_2(9)$); 2.90 (m, 2H, $CH_2(5)$); 2.24 (m, 2H, $CH_2(6)$); 0.15 (s, 9H, CMe_3); J(6,8) = 1.4, J(6,9) = 2.0, J(8,9) = 6.6 Hz. Minor isomer **9d′**: 7.45–7.33 (m, 5 Har); 7.25 (m, 1Har); 6.95 (2 d, 1Har, J(2,3) = 8.3 Hz, H-2); 4.95 (tt, 1H, H-8); 3.29 (m, 2H, $CH_2(5)$); 3.24 (dt, 2H, $CH_2(9)$); 2.35 (m, 2H, $CH_2(6)$); 0.15 (s, 9H, CMe_3); J(6,8) = 1.4, J(6,9) = 2.0, J(8,9) = 6.6 Hz.

General procedure (f) with **9d/9d′** (1.46 g, 3.78 mmol) in CH_2Cl_2 (25 mL), *m*-CPBA (1.03 g, 5.97 mmol, 1.5 equiv) for 3 h to give a 60/40 **10d/10d′** mixture (1.37 g, 90% from ketone **8d**).

Compound **10d**/**10d′**: yellowish oil, characterised by NMR only. ^1H NMR ($CDCl_3$, 300 MHz) major isomer **10d**: 7.55 (d, 1H, H-3); 7.46–7.36 (m, 4 Har); 7.3–7.2 (m, 1 Har); 7.04 (d, 1H, H-2); 4.22 (ddd, 1H, H-6); 3.57 (dd, 1H, Ha-5); 3.27 (dd, 1H, Hb-5); 3.16–2.75 (m, 3H, Ha-8, $CH_2(9)$); 2.33 (ddt, 1H, Hb-8); 0.18 (s, 9H, CMe_3); J(2,3) = 8.2, J(5a,6) = 3.3, J(5b,6) = 10.2, J(5a,5b) = 14.4, J(6,8b) = 1.1, J(8a,8b) = 13.5, J(8b,9a) = 3.7, J(8b,9b) = 10.8 Hz. Minor isomer **10d′**: 7.54 (d, 1H, H-2); 7.46–7.36 (m, 4 Har); 7.3–7.2 (m, 1 Har); 7.05 (d, 1H, H-3); 4.12 (ddd, 1H, H-6); 3.40 (ddd, 1H, Ha-9); 3.16–2.75 (m, 4H, $CH_2(5)$, Ha-8, Hb-9); 2.46 (ddt, 1H, Hb-8); 0.18 (s, 9H, CMe_3); J(2,3) = 8.2, J(5a,6) = 4.0, J(5b,6) = 9.0, J(6,8b) = 1.1, J(8a,8b) = 13.9, J(8a,9a) = 7.8, J(8b,9a) = 3.1, J(8b,9b) = 11.2, J(9a,9b) = 14.8 Hz.

9.4. 1,4-Dibromo-7-(trimethylsilyloxy)-8,9-dihydro-5*H*-benzocycloheptene (9e); 1,4-dibromo-6-(trimethylsilyloxy)-5,6,8,9-tetrahydrobenzocyclohepten-7-one (10e)

General procedure (e) with **8e** (6.3 g, 19.8 mmol), Et_3N (3.9 mL, 27.2 mmol, 1.4 equiv) in toluene (100 ml) and with Me_3SiOTf (4.7 mL, 23.8 mmol, 1.2 equiv) to give **9e** (7.79 g, quant.).

Compound **9e**: orange resin, characterised by NMR only. ^1H NMR ($CDCl_3$, 400 MHz): 7.25 (s, 2H, H-2, H-3); 5.04 (tt, 1H, H-8); 3.58 (dt, 2H, $CH_2(9)$); 3.24 (m, 2H, $CH_2(5)$); 2.30 (m, 2H, $CH_2(6)$); 0.14 (s, 9H, $SiMe_3$); J(6,8) = 1.4, J(6,9) = 1.9, J(8,9) = 6.6 Hz.

General procedure (f) with **9e** (7.79 g, 19.8 mmol) in CH_2Cl_2 (180 mL), *m*-CPBA (5.17 g, 29.9 mmol, 1.5 equiv) for 3 h to give **10e** (7.75 g, 96%, 90% from ketone **8e**).

Compound **10e**: brownish oil, characterised by NMR only.[1]H NMR ($CDCl_3$, 400 MHz): 0.15 (s, 9H, $SiMe_3$); 2.41 (dddd, 1H, Hb-8); 2.87 (ddd, 1H, Ha-8); 3.13 (ddd, 1H, Hb-9); 3.32 (ddd, 1H, Ha-9); 3.33 (dd, 1H, Hb-5); 3.45 (dd, 1H, Ha-5); 4.16 (ddd, 1H, H-6); 7.37 (m, 2H, H-2, H-3); *J*(5a,5b) = 14.6, *J*(5a,6) = 3.2, *J*(5b,6) = 9.8, *J*(6,8b) = 1.0, *J*(8a,8b) = 14.2, *J*(8a,9a) = 8.2, *J*(8a,9b) = 2.8, *J*(8b,9a) = 2.0, *J*(8b,9b) = 11.0, *J*(9a,9b) = 15.0 Hz.

9.5. 9-Trimethylsilyloxy-8,11-dihydro-7*H*-cyclohepta[a]naphthalene (9h) and 9-trimethylsilyloxy-10,11-dihydro-7*H*-cyclohepta-[a]naphthalene (9h′); 10-trimethylsilyloxy-7,8,10,11-tetrahydrocyclohepta[a]naphthalen-9-one (10h) and 8-trimethylsilyloxy-7,8,10,11-tetrahydro cyclohepta[*a*]naphthalen-9-one (10h′)

General procedure (e) with **8h** (0.74 g, 3.48 mmol), Et_3N (0.67 mL, 4.87 mmol, 1.4 equiv) in toluene (5 ml) and with Me_3SiOTf (0.75 mL, 4.17 mmol, 1.2 equiv) to give a 50:50 **9h/9h′** mixture (0.90 g, 91%).

Compound **9h**/**9h′**: as orange resin, characterised by NMR only. [1]H NMR ($CDCl_3$, 400 MHz, isomer **9h** M and **9h′** m mixture): 8.14 (d, *J* = 8.6 Hz, 1H M+m, Har-1); 7.85 (2d, 1H M+m, *J* = 8.2 Hz, Har-4); 7.69, 7.66 (2d, 1H M+m, *J* = 8.3 Hz, Har-5), 7.52 (m, 1H M+m); 7.42 (m, 1H M, 2H m); 7.37 (d, 1H M, *J* = 8.3 Hz, H-6); 5.23 (t, 1H M, *J* = 6.4 Hz, H-10), 5.17 (t, 1H m, *J* = 6.2 Hz, H-8 m), 3.78 (m, 2H M+m); 3.50, 3.46 (2 m, 2H M, 4H m); 3.13 (m, 2H M); 0.13 (s, 9H M+m, $SiMe_3$).

General procedure (f) with **9h/9h′** (0.90 g, 3.16 mmol) in CH_2Cl_2 (15 mL), *m*-CPBA (0.86 g, 5.0 mmol, 1.6 equiv) for 3 h to give a 50:50 **10h/10h′** mixture as (0.94 g, 96%, 90% from ketone **8h**).

Compound **10h**/**10h′**: brownish oil, characterised by NMR only. [1]H NMR ($CDCl_3$, 400 MHz) isomer **10h** M and **10h′** m mixture: 8.16–7.33 (m, 6Har M+m); 4.30, 4.27 (2dd, *J* = 3.9, 10.0 Hz, 1H M+m, H-10 M, H-8 m)); 3.34 (m, 2H M); 3.14 (m, 2H M+m); 2.93 (m, 2H m); 2.48 (m, 1H M+m); 0.15 (s, 9H M+m, $SiMe_3$).

10. Hydroxy-amides 11b–e,b′–d′,h,h′

General procedure (g): To a solution of **10** (10 mmol) in 2 M NH_3 solution in dry EtOH (50–100 mL), was added Ti(O*i*Pr)$_4$ (6.2 mL, 20 mmol, 2 equiv) and the mixture stirred for 6 h under Ar. $NaBH_4$ (0.56 g, 15 mmol, 1.5 equiv) was then added and the mixture stirred further for 2 h and evaporated. The residue was dissolved in AcOEt (50–100 mL) and vigorously stirred with aqueous 1 M NH_4OH solution (20–50 mL) for 2 h. The solids were filtered out and washed thrice with a mixture of AcOEt (20 mL) and aqueous 1 M NH_4OH solution (20 mL). The organic phase was separated, the aqueous phase extracted with AcOEt (3 × 20 mL), the combined organic phases dried over $MgSO_4$ and evaporated to give the crude amine.

A solution of the crude amine (10 mmol) in MeOH (50–100 mL) was stirred with solid $NaHCO_3$ (1.4 g, 13 mmol, 1.3 equiv) and Boc_2O (3.3 g, 15 mmol, 1.5 equiv) for 16 h at rt under Ar. The solvent was evaporated, the solution of the residue in AcOEt was washed with H_2O, dried over $MgSO_4$ and evaporated to give the crude amide, which was purified by FC (cyclohexane/AcOEt 8:2) to give the amide-alcohol **11** or regioisomer **11/11′** mixture as *cis*/*trans* mixture.

10.1. 7-*tert*-Butoxycarbonylamino-4-chloro-6,7,8,9 tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11b) and 7-*tert*-Butoxycarbonylamino-1-chloro-6,7,8,9 tetrahydro-5*H*-cyclohepten-6-ol (*cis/trans* mixture, 11b′)

General procedure (g) with **10b/10b′** (5.2 g, 18.5 mmol), in 2 M NH_3 solution in EtOH (120 mL) and with Ti(O*i*Pr)$_4$ (12.2 mL, 41.3 mmol, 2.2 equiv) for 6 h, then reduction with $NaBH_4$ (1.2 g, 31 mmol, 1.6 equiv) for 2 h to give the crude amine. Acylation with Boc_2O (5.4 g, 24.8 mmol, 1.4 equiv), $NaHCO_3$ in MeOH (100 mL) for 16 h gave the **11b/11b'** mixture (4.45 g, 78%). The isomeric mixture resolution by flash chromatography occurred badly and the *cis*/*trans* isomeric mixture of **11b′** only was obtained as pure regioisomer.

Isomeric mixture **11b/11b′**: cream crystals, mp 183–184 °C. IR (KBr): 3353, 2980, 2932, 1683, 1525, 1450, 1245, 1170, 779 cm^{-1}. HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{22}ClLiNO_3$ $[M+Li]^+$: 318.1443; found: 318.1419; calcd for $C_{16}H_{22}ClNaNO_3$ $[M+Na^+]$: 334.1180; found: 334.1159.

Cis–trans isomeric mixture **11b′**: colorless crystals, mp 165–168 °C. IR (KBr): 3362, 2982, 2933, 1682, 1665, 1525, 1448, 1391, 1367, 1324, 1248, 1169, 1079, 1042, 779 cm^{-1}. HR-MS (ESI^+IsoTof) calcd for $C_{16}H_{22}ClNaNO_3$ $[M+Na]^+$: 334.1180; found: 334.1176.

cis-**11b**, [1]H NMR ($CDCl_3$, 300 MHz): 7.26 (dd, *J* = 1.5, 7.9 Hz, H-3); 7.08 (dd, *J* = 7.5, 7.9 Hz, H-2); 7.02 (dd, *J* = 1.5, 7.5 Hz, H-1); 5.04 (d, *J* = ca. 8 Hz, NH); 4.18 (broad s, H-6); 3.77 (broad m, H-7, Ha-5); 2.88 (d, *J* = 14.6 Hz, Hb-5); 2.77 (m, CH_2(9)); 1.99 (m, Ha-8); 1.57 (m, (br m, Hb-8); 1.45 (s, CMe_3). [13]C NMR ($CDCl_3$, 75 MHz): 155.5 (NCO); 144.8 (C(4a)); 135.7 (C(9a)); 132.4 (C(4)); 128.0, 127.8, 127.4 (C(1),C(2),C(3)); 79.5 (*C*Me$_3$); 68.8 (*C*(6)); 56.6 (C(7)); 33.7 (C(5)); 32.7 (C(9)); 28.6 (C(8)); 28.4 (C*Me*$_3$).

trans-**11b**, [1]H NMR ($CDCl_3$, 300 MHz): 7.25 (dd, H-3); 7.05 (t, H-2); 6.98 (br d, H-1); 4.54 (br d, NH); 3.70 (br m, H-7); 3.64 (dd, Ha-5); 3.35 (br t, H-6); 3.08 (br s, OH); 2.86 (dd, Hb-5); 2.85 (ddd, Ha-9); 2.75 (ddd, Hb-9); 2.21 (m, Ha-8); 1.46 (s, CMe_3); 1.33 (dq, Hb-8). *J*(1.2) = 7.5, *J*(1,3) = 1.5, *J*(2,3) = 8.1, *J*(5a,5b) = 14.4, *J*(5a,6) = 1.8, *J*(5b,6) = 10.2, *J*(6,7) = 9.5, *J*(NH,7) = ca. 8, *J*(7,8a) = 4.4, *J*(7,8b) = 10.5, *J*(8a,8b) = 13.6, *J*(8a,9a) = 1.6, *J*(8a,9b) = 7.7, *J*(8b,9a) = 12.0, *J*(8b,9b) = 1.8, *J*(9a,9b) = 14.7 Hz. [13]C NMR ($CDCl_3$, 75 MHz): 155.5 (NCO); 144.6 (C(4a)); 134.6, 134.2 (C(9a), (C(4)); 127.8, 127.6, 127.1 (C(1),C(2),C(3)); 80.2 (*C*Me$_3$); 73.6 (*C*(6)); 60.0 (C(7)); 36.2 (C(5)); 32.7, 32.2 (C(8),C(9)); 28.4 (C*Me*$_3$).

cis-**11b′**, [1]H NMR ($CDCl_3$, 300 MHz): 7.28 (m, H-2); 7.06 (m, H-3, H-4); 5.04 (br d, *J* = 7.5 Hz, NH); 4.10 (br s, H-6); 3.81 (broad s, H-7); 3.36 (broad m, Ha-9); 3.06 (m, CH_2(5)); 2.55 (broad t, *J* = 12.8 Hz, Hb-9); 2.00 (ddd, *J* = 4.4, 8.2, 13.0 Hz, Ha-8); 1.45 (s, CMe_3); 1.31 (m, Hb-8). [13]C NMR ($CDCl_3$, 75 MHz): 155.3 (NCO); 139.8 (C(9a); 136.8 C(4a)); 133.5 (C(1)); 130.2, 128.7, 127.2 (C(2),C(3),(C(4)); 79.6 (*C*Me$_3$); 69.1 (C(6)); 56.7 (C(7)); 39.6 (C(5)); 28.4 (C*Me*$_3$); 27.7, 26.8 (C(8),C(9)).

trans-**11b′**, [1]H NMR ($CDCl_3$, 300 MHz): 7.23 (dd, H-2); 7.09 (dd, H-4); 7.05 (t, H-3); 4.58 (br d, NH); 3.70 (br m, H-7); 3.40 (ddd, Ha-9); 3.34 (dt, H-6); 3.12–2.96 (m, Ha-5, Hb-5); 2.62 (ddd, Hb-9); 2.20 (m, Ha-8); 1.46 (s, CMe_3); 1.29 (dq, Hb-8); *J*(2,3) = 7.6, *J*(2,4) = 1.5, *J*(3,4) = 7.6, *J*(5a,5b) = 14.0, *J*(5a,6) = ca. 9, *J*(5b,6) = 4.0, *J*(6,7) = 9.0, *J*(NH,7) = ca. 7, *J*(7,8a) = 4.3, *J*(7,8b) = 11.3, *J*(8a,8b) = 13.8, *J*(8a,9a) = 8.0, *J*(8a,9b) = 1.3, *J*(8b,9a) = 1.5, *J*(8b,9b) = 11.5, *J*(9a,9b) = 15.0 Hz. [13]C NMR ($CDCl_3$, 75 MHz): 156.8 (NCO); 139.4, 139.1 (C(4a),C(9a)); 133.1 (C(1)); 128.8, 128.0, 127.3 (C(2),C(3),(C(4)); 80.4 (*C*Me$_3$); 74.5 (C(6)); 59.9 (C(7)); 41.8 (C(5)); 31.6 (C(8)); 28.4 (C*Me*$_3$); 26.3 (C(9)).

10.2. 4-Bromo-7-*tert*-butoxycarbonylamino-5,6,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11c) and 1-bromo-7-*tert*-butoxycarbonylamino-5,6,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11c′)

General procedure (g) with **10c/10c′** (2.32 g, 7.09 mmol), in 2 M NH_3 solution in EtOH (40 mL) and with Ti(O*i*Pr)$_4$ (3.87 mL, 14.2 mmol, 2 equiv) for 16 h, then reduction with $NaBH_4$ (0.4 g, 10.6 mmol, 1.5 equiv) for 2 h to give the crude amine. Acylation with Boc_2O (2.56 g, 11.7 mmol, 1.5 equiv), Na_2CO_3 (1.24 g, 10.1 mmol, 1.3 equiv) in MeOH (25 mL) for 3 h gave the **11c/11c′**

mixture (1.63 g, 64%) after crystallisation and washing with *i*Pr_2O at 0 °C. The isomer separation occurred by semi-preparative HPLC (on C_{18} Kromasil 100, 5 μm, 4.6 × 250 mm) with MeOH/H_2O 75:25 as eluent, to give **11c** as *cis/trans* mixture (250 mg, 10%) and **11c′** as *cis/trans* mixture (1.10 g, 43%) as. The *cis*-**11c** isomer could be obtained pure.

Isomeric mixture **11c/11c′**: cream solid, mp 179–184 °C. IR (KBr): 3358, 2978, 2934, 1681, 1667, 1523, 1446, 1367, 1248, 1166, 1043, 777 cm^{-1}. HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{22}BrLiNO_3$ $[M+Li]^+$: 362.0938 and 364.0919; found: 362.0849 and 364.0829.

trans-**11c**: ^1H NMR ($CDCl_3$, 400 MHz): 7.44 (dd, 1H, H-3); 7.01 (br d, 1H, H-1); 6.97 (t, 1H, H-2); 4.53 (br d, 1H, NH); 3.69 (br m, 1H, H-7); 3.63 (dd, 1H, Ha-5); 3.35 (br t, 1H, H-6); 3.08 (br s, 1H, OH); 2.95 (dd, 1H, Hb-5); 2.87 (ddd, 1H, Ha-9); 2.76 (ddd, 1H, Hb-9); 2.21 (m, 1H, Ha-8); 1.46 (s, 9H, CMe_3); 1.32 (dq, 1H, Hb-8); *J*(1.2) = 7.4, *J*(1,3) = 1.6, *J*(2,3) = 8.0, *J*(5a,5b) = 14.2, *J*(5a,6) = 1.6, *J*(5b,6) = 10.0, *J*(6,7) = 9.0, *J*(NH,7) = 8.2, *J*(7,8a) = 4.2, *J*(7,8b) = 11.3, *J*(8a,8b) = 13.8, *J*(8a,9a) = 1.8, *J*(8a,9b) = 7.5, *J*(8b,9a) = 11.0, *J*(8b,9b) = 2.0, *J*(9a,9b) = 14.7 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 156.9 (NCO); 144.6 (C(4a)); 136.2 (C(9a)); 131.4 (C(3)); 128.2, 128.0 (C(1), C(2)), 125.7 (C(4)); 80.5 (*C*Me_3); 73.7 (C(6)); 60.1 (C(7)); 39.7 (C(5)); 32.7 (C(8)); 28.5 (C(9)); 28.5 (C*Me*$_3$).

cis-**11c**: colorless crystals, mp 183–184 °C. IR (KBr): 775, 1014, 1043, 1085, 1164, 1251, 1367, 1390, 1453, 1524, 1665, 2981, 2933, 3375, 3471 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.46 (d, 1H, *J* = 8.0 Hz, H-3); 7.06 (d, 1H, *J* = 7.3 Hz, H-1); 7.01 (dd, 1H, *J* = 7.3, 8.0 Hz, H-2); 5.04 (br d, 1H, *J* = 8.5 Hz, NH); 4.19 (br s, 1H, H-6); 3.77 (br s, 2H, H-7, Ha-5); 2.98 (d, 1H, *J* = 14.3 Hz, Hb-5); 2.79 (m, 2H, CH_2(9)); 1.99 (br m, 1H, Ha-8); 1.50 (br m, 1H, Hb-8); 1.45 (s, 9H, CMe_3). ^{13}C NMR ($CDCl_3$, 100 MHz): 155.7 (NCO); 145.0 (C(4a)); 134.7 (C(9a)); 131.5 (C(3)); 128.6, 128.3 (C(1),C(2)), 127.1 (C(4)); 79.7 (*C*Me_3); 69.1 (*C*(6)); 57.0 (C(7)); 37.4 (C(5)); 33.2 (C(9)); 28.9 (C(8)); 28.7 (C*Me*$_3$). HR-MS (ESI^+) calcd for $C_{16}H_{22}BrNNaO_3$ $[M+Na]^+$: 378.0675; found: 378.0665.

trans-**11c′**: ^1H NMR ($CDCl_3$, 400 MHz): 7.43 (dd, 1H, H-2); 7.14 (br d, 1H, H-4); 6.98 (t, 1H, H-3); 4.52 (br d, 1H, NH); 3.70 (br m, 1H, H-7); 3.40 (ddd, 1H, Ha-9); 3.35 (dt, 1H, H-6); 3.06, 3.02 (m, 2H, Ha-5,Hb-5); 2.71 (ddd, 1H, Hb-9); 2.20 (m, 1H, Ha-8); 1.46 (s, 9H, CMe_3); 1.31 (dq, 1H, Hb-8); *J*(2,3) = 8.0, *J*(2,4) = 1.0, *J*(3,4) = 7.4, *J*(5a,5b) = 14.0, *J*(5a,6) = 10,4, *J*(5b,6) = 3.2, *J*(6,7) = 9.0, *J*(NH,7) = ca 7, *J*(7,8a) = 4.4, *J*(7,8b) = 11.2, *J*(8a,8b) = 13.8, *J*(8a,9a) = 8.2, *J*(8a,9b) = 1.6, *J*(8b,9a) = 1.6, *J*(8b,9b) = 11.2, *J*(9a,9b) = 15.0 Hz.

cis-**11c′**: ^1H NMR ($CDCl_3$, 400 MHz, 330 K): 7.47 (dd, 1H, H-2); 7.09 (br d, 1H, H-4); 6.98 (t, 1H, H-3); 4.91 (br d, 1H, NH); 4.11 (t, 1H, H-6); 3.81 (m, 1H, H-7); 3.39 (ddd, 1H, Ha-9); 3.12, 3.07 (m, 2H, Ha-5, Hb-5); 2.67 (dd, 1H, Hb-9); 2.00 (ddd, 1H, Ha-8); 1.47 (dq, 1H, Hb-8); 1.46 (s, 9H, CMe_3); 1.28 (br s, 1H, OH). *J*(2,3) = 8.0, *J*(2,4) = 1.0, *J*(3,4) = 7.4, *J*(5a,5b) = 14.4, *J*(5a,6) = 1.8, *J*(5b,6) = 7.2, *J*(6,7) = 2.2, *J*(OH,6) = 7.6; *J*(NH,7) = 8.0, *J*(7,8a) = 4.2, *J*(7,8b) = 11.6, *J*(8a,8b) = 14.0, *J*(8a,9a) = 8.4, *J*(8a,9b) = 1.2, *J*(8b,9a) = 1.5, *J*(8b,9b) = 11.6, *J*(9a,9b) = 14.8 Hz.

10.3. 4-Bromo-7-(*tert*-butoxycarbonylamino)-1-phenyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11d) and 1-bromo-7-(*tert*-butoxycarbonylamino)-4-phenyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11d′)

General procedure (g) with **10d/10d′** (1.52 g, 3.77 mmol) in 2 M NH_3 solution in EtOH (10 mL) and with Ti(O*i*Pr)$_4$ (2.3 mL, 7.54 mmol, 2 equiv) for 6 h, then reduction with $NaBH_4$ (213 mg, 5.65 mmol, 1.5 equiv) for 3 h to give the crude amine (945 mg, 76%). Acylation with Boc_2O (940 mg, 4.27 mmol, 1.5 equiv), $NaHCO_3$ (392 mg, 3.70 mmol, 1.3 equiv) in MeOH (20 mL) for 16 h gave the 60:40 mixture of **11d/11d′** (518 mg, 32%) inseparable isomers.

Isomeric mixture **11d/11d′**: colorless crystals, mp 174–176 °C. IR (KBr): 3487, 3362, 2979, 2932, 1664, 1530, 1252, 1168 cm^{-1}. HR-MS (ESI-Q-Tof) calcd for $C_{22}H_{26}BrLiNO_3$ $[M+Li]^+$: 438.1251 and 440.1233; found: 438.1237 and 440.1221.

cis-**11d** or **11d′**, ^1H NMR ($CDCl_3$, 400 MHz): 7.49 (d, *J* = 8.3 Hz, 1Har); 7.45–7.2 (m, 5Har); 7.00 (d, *J* = 8.3 Hz, 1Har); 5.03 (br s, 1H, NH); 4.24 (br s, 1H, H-6); 3.79 (br s, 2H); 3.06 (br s, 1H); 2.94 (br s, 1H); 2.50 (br s, 1H); 1.90 (br s, 1H); 1.44 (s, 10H).

cis-**11d′** or **11d**, ^1H NMR ($CDCl_3$, 400 MHz): 7.51 (d, *J* = 8.3 Hz, 1Har); 7.45–7.2 (m, 5Har); 6.98 (d, *J* = 8.3 Hz, 1Har); 4.96 (br d, *J* = 8.8 Hz, 1H, NH); 4.02 (br s, 1H, H-6); 3.79 (br s, 2H); 3.50 (br s, 1H); 3.28 (br s, 1H); 2.84 (br d, *J* = 15 Hz, 1H); 2.04 (br s, 1H); 1.44 (br s, 10H).

trans-**11d**, ^1H NMR ($CDCl_3$, 400 MHz): 7.48 (d, 1H, H-3); 7.42–7.33 (m, 3 Har); 7.19 (m, 2Har); 6.96 (d, 1H, H-2); 4.54 (br s, 1H, NH); 3.69 (br d, 2H, H-7, Ha-5); 3.43 (br t, 1H, H-6); 3.20 (br s, 1H, OH); 3.05 (dd, 1H, Hb-5); 2.93 (dd, 1H, Ha-9); 2.61 (dd, 1H, Hb-9); 2.10 (m, 1H, Ha-8); 1.44 (s, 9H, CMe_3); 1.29 (br q, 1H, Hb-8); *J*(2,3) = 8.2, *J*(5a,5b) = 14.2, *J*(5a,6) = 1.6, *J*(5b,6) = 10.2, *J*(6,7) = 8.6, *J*(7,8a) = 4.4, *J*(7,8b) = 11.4, *J*(8a,8b) = 13.6, *J*(8a,9a) = 8.0, *J*(8a,9b) = 1.2, *J*(8b,9a) = 1.6, *J*(8b,9b) = 11.0, *J*(9a,9b) = 14.8 Hz.

trans-**11d′**: ^1H NMR ($CDCl_3$, 400 MHz): 7.47 (d, 1H, H-2); 7.44–7.33 (m, 3Har); 7.25 (m, 2Har); 6.98 (d, 1H, H-3); 4.56 (br s, 1H, NH); 3.70 (br q, 1H, H-7); 3.50 (dd, 1H, Ha-9); 3.40 (br t, 1H, H-6); 3.19 (br s, 1H, OH); 3.14 (dd, 1H, Ha-5); 2.82 (dd, 1H, Hb-5); 2.78 (dd, 1H, Hb-9); 2.25 (m, 1H, Ha-8); 1.45 (s, 9H, CMe_3); 1.37 (br q, 1H, Hb-8); *J*(2,3) = 8.2, *J*(5a,5b) = 14.4, *J*(5a,6) = 1.8, *J*(5b,6) = 10.2, *J*(6,7) = 10.8, *J*(7,8a) = 4.6, *J*(7,8b) = 11.8, *J*(8a,8b) = 13.6, *J*(8a,9a) = 8.0, *J*(8a,9b) = 1.0, *J*(8b,9a) = 1.6, *J*(8b,9b) = 11.4, *J*(9a,9b) = 15.0 Hz.

10.4. 1,4-Dibromo-7-(*tert*-butoxycarbonylamino)-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ol (*cis/trans* mixture, 11e)

General procedure (g) with **10e** (7.75 g, 19.1 mmol) in 2 M NH_3 solution in EtOH (60 mL) and with Ti(O*i*Pr)$_4$ (22.6 mL, g, 76.3 mmol, 4 equiv) for 6 h, then reduction with $NaBH_4$ (1.08 g, 28.6 mmol, 1.5 equiv) for 3 h to give the crude amine (10.3 g, quant.). Acylation with Boc_2O (6.48 g, 29.7 mmol, 1.5 equiv), $NaHCO_3$ (2.73 g, 25.7 mmol, 1.3 equiv) in MeOH (100 mL) for 16 h gave **11e** (1.20 g, 15%) after purification by flash chromatography (cyclohexane/AcOEt 8/2). The *trans*-**11e** isomer could be obtained pure.

cis-**11e**: cream resin. IR (KBr): 3450, 3355, 1667, 1529, 1367, 1168 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.32, 7.31 (2 d, *J* = 8.6 Hz, 2H, H-2,H-3); 4.92 (br s, 1H, NH); 4.22 (d, 1H, H-6); 3.75 (m, 1H, H-7); 3.70 (m, 1H, Ha-9); 3.43 (m, 1H, Ha-5); 3.09 (m, 1H, Hb-5); 2.77 (m, 1H, Hb-9); 2.01 (m, 1H, Ha-8); 1.53 (m, 1H, Hb-8); 1.53 (s, 9H, CMe_3). ^{13}C NMR ($CDCl_3$, 100 MHz): 27.1 (C(9)); 28.4 (C*Me*$_3$); 31.2 (C(8)); 37.9 (C(5)); 56.1 (C(7)); 68.3 (C(6)); 79.6 (*C*Me_3); 123.8, 124.6 (C(1),C(4)); 131.8, 132.4 (C(2),C(3)); 141.7, 143.3 (C(4a),C(9a)); 155.2 (NCO).

trans-**11e**: cream crystals, mp 175–180 °C. IR (KBr): 3360, 2980, 1677, 1521, 1368, 1324, 1173, 1045 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.29, 7.28 (2 d, 2H, *J* = 8.4 Hz, H-2,H-3); 4.54 (br s, 1H, NH); 3.70 (br s, 1H, H-7); 3.64 (dd, 1H, Ha-5); 3.42 (ddd, 1H, Ha-9); 3.34 (ddd, IH, H-6); 3.02 (dd, 1H, Hb-5); 2.80 (ddd, 1H, Hb-9); 2.22 (dddt, 1H, Ha-8); 1.27 (dq, 1H, Hb-8); 1.45 (s, 9H, CMe_3); *J*(5a,5b) = 14.5, *J*(5a,6) = 1.8, *J*(5b,6) = 10.2, *J*(6,7) = 8.6, *J*(6,8a) = 1.0, *J*(7,8a) = 4.5, *J*(7,8b) = 11.0, *J*(8a,8b) = 13.7, *J*(8a,9a) = 8.0, *J*(8a,9b) =1.8, *J*(8b,9a) = 1.0, *J*(8b,9b) = 11.5, *J*(9a,9b) = 14.8 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 28.3 (C*Me*$_3$); 30.7 (C(9)); 31.3 (C(8)); 40.4 (C(5)); 59.7 (C(7)); 73.5 (C(6)); 80.4 (*C*Me_3); 122.9, 124.5 (C(4),C(1)); 131.9, 132.1 (C(2),C(3)); 138.2, 143.2 (C(4a),C(9a)); 156.8 (NCO). HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{21}Br_2NNaO_3$ $[M+Na]^+$: 457.9761; found: 457.9753.

10.5. 9-*tert*-Butoxycarbonylamino-8,9,10,11-tetrahydro-7-*H*-cyclohepta[*a*]naphthalen-10-ol (*cis*/*trans* mixture, 11h) and 9-*tert*-butoxycarbonylamino-8,9,10,11-tetrahydro-7-*H*-cyclohepta[*a*]naphthalen-8-ol (*cis*/*trans* mixture, 11h′)

General procedure (g) with **10h/10h′** (0.9 g, 3.02 mmol) in 2 M NH_3 solution in EtOH (15 mL) and with $Ti(OiPr)_4$ (1.8 mL, 6.03 mmol, 2 equiv) for 6 h, then reduction with $NaBH_4$ (171 mg, 4.5 mmol, 1.2 equiv) for 2 h to give the crude amine (560 mg, 81%). Acylation of the crude amine (1.2 g, 5.15 mmol) with Boc_2O ((1.7 g, 7.73 mmol, 1.5 equiv), $NaHCO_3$ (562 mg, 6.69 mmol 1.3 equiv) in MeOH (20 mL) for 16 h gave the 50:50 mixture of **11h/11h′** (0.70 g, 41%) which was resolved by chromatography (AcOEt/cyclohexane/Et_2O) in the order *cis*-**11h**, *cis*-**11h′**, *trans*-**11h**, *trans*-**11h′**.

cis-**11h**: obtained impur and characterised by NMR only. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.17 (d, 1H, Har-1); 7.83 (d, 1H, Har-4); 7.72 (d, 1H, Har-5); 7.53 (td, 1H, Har-2); 7.44 (dt, 1H, Har-3); 7.30 (dd, 1H, Har-6); 5.07 (d, 1H, J = 8.3 Hz, NH), 4.27 (dt, 1H, J = 1.6, 8.4 Hz, 1H); 3.95 (m, 2 H); 3.14 (d, 1H, J = 14.9 Hz, Hb-11); 2.95 (m, 2H, CH_2(7)); 2.08 (m, 1H, Ha-8); 1.46 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); J(1,2) = 8.6, J(1.3) = 1.4, J(2,3) = 6.8, J(2,4) = 1.2, J(3,4) = 8.0, J(5,6) = 8.2 Hz.

cis-**11h′**: colorless crystals, mp 195–196 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.12 (d, 1H, Har-1); 7.85 (d, 1H, Har-4); 7.70 (d, 1H, Har-5); 7.51 (dt, 1H, Har-2); 7.42 (dt, 1H, Har-3); 7.70 (d, 1H, Har-6); 5.06 (d, 1H, J = 8.5 Hz, NH), 4.17 (br t, 1H, J = 8.0 Hz, H-8); 3.93 (br s, 1H, H-9); 3.64 (dd, 1H, J = 8.0, 14.8 Hz, Ha-11); 3.34 (d, 1H, J = 14.5 Hz, Ha-7); 3.24 (dd, 1H, J = 7.4, 14.5 Hz, Hb-7); 2.78 (dd, 1H, J = 11.4, 14.8 Hz, Hb-11); 2.15 (ddd, 1H, J = 4.2, 8.0, 13.4 Hz, Ha-10); 1.45 (m, 1H, Hb-10); 1.46 (s, 9H, CMe_3); J(1,2) = 8.6, J(1.3) = 1.2, J(2,3) = 6.8, J(2,4) = 1.4, J(3,4) = 8.0, J(5,6) = 8.1 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 155.4 (N*C*O); 138.4 (C(6a)); 133.3, 131.5, 131.2 (C(4a),C(11a),C(11b)); 130.0 128.7, 126.6 (C(4),C(5),C(6)); 126.3 (C(2)); 125.2 (C(3)); 123.1 (C(1)); 79.5 (*C*Me$_3$); 69.0 (C(8)); 56.9 (C(9)); 39.6 (C(7)); 28.5 (C*Me*$_3$); 27.8 (C(10)); 24.4 (C(11)). HRMS (ESI$^+$) calcd for $C_{20}H_{25}NNaO_3^+$ [M+Na]$^+$: 350.1727; found: 350.1720.

trans-**11h**: colorless crystals, mp 178–179 °C. IR (KBr): 3367, 2979, 2932, 1681, 1522, 1370, 1316, 1245, 1172, 1001, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.23 (d, 1H, Har-1); 7.82 (d, 1H, Har-4); 7.67 (d, 1H, Har-5); 7.52 (td, 1H, Har-2); 7.46 (t, 1H, Har-3); 7.25 (d, 1H, Har-6); 4.53 (d, 1H, NH), 3.81 (d, 2H, Ha-11, H-9); 3.37 (m, 2H, H-10, OH); 3.10 (dd, 1H, Hb-11); 3.07 (dt, 1H, Ha-7); 2.87 (ddd, 1H, Hb-7); 2.25 (m, 1H, Ha-C(8)); 1.47 (s, 9H, CMe_3); 1.33 (dq, 1H, Hb-8); J(1,2) = 8.6, J(1.3) = 1.0, J(2,3) = 6.8, J(2,4) = 1.4, J(3,4) = 8.0, J(5,6) = 8.3, J(7a,7b) = 14.9, J(7a,8a) = 1.6, J(7a,8b) = 11.6, J(7b,8a) = 7.5, J(7b,8b) = 1.6, J(8a,8b) = 13.5, J(8a,9) = 4.2, J(8b,9) = 11.6, J(9,NH) = 8.5, J(9,10) not determined, J(10,11a) = 1.6, J(10,11b) = 10.2, J(11a,11b) = 14.8 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 157.0 (N*C*O); 140.0 (C(6a)); 132.8, 132.1, 131.9 (C(4a),C(11a),C(11b)); 128.6 127.5, 127.0 (C(4),C(5),C(6)); 126.3 (C(2)); 124.9 (C(3)); 123.3 (C(1)); 80.3 (*C*Me$_3$); 74.1 (C(10); 60.3 (C(9)); 34.1 (C(11)); 32.9, 32.2 (C(7), C(8)); 28.4 (C*Me*$_3$). HRMS (ESI$^+$) calcd for $C_{20}H_{25}NNaO_3^+$ [M+Na]$^+$: 350.1727; found: 350.1720.

trans-**11h′**: colorless crystals, mp 174–175 °C. IR (KBr): 740, 815, 1007, 1172, 1244, 1317, 1366, 1523, 1682, 2930, 2982, 3357 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.08 (d, 1H, Har-1); 7.83 (dd, 1H, Har-4); 7.68 (d, 1H, Har-5); 7.50 (td, 1H, Har-2); 7.44 (dt, 1H, Har-3); 7.36 (d, 1H, Har-6); 4.55 (br d, 1H, NH), 3.77 (br q, 1H, H-9); 3.62 (dd, 1H, Ha-11); 3.39 (dt, 1H, H-8); 3.28 (dd, 1H, Ha-7, OH-8); 3.13 (dd, 1H, Hb-7); 2.87 (dd, 1H, Hb-11); 2.33 (m, 1H, Ha-10); 1.47 (s, 1H, CMe_3); 1.34 (q, 1H, Hb-10); J(1,2) = 8.4, J(1.3) = 1.0, J(2,3) = 6.8, J(2,4) = 1.4, J(3,4) = 8.0, J(5,6) = 8.2, J(9,NH) = ca. 8.5, J(7a,7b) = 14.0, J(7a,8) = 10.2, J(7b,8) = 2.0, J(8,9) = 9.0, J(9,10a) = 4.4, J(9,10b) = 11.4, J(10a,10b) =13.4, J(10a,11a) = 8.0, J(10a,11b) = 1.2, J(10b,11a) = 1.0, J(10b,11b) = 11.2, J(11a,11b) = 15.0 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 156.9 (N*C*O); 137.6 (C(6a)); 134.2, 132.9, 131.0 (C(4a),C(11a),C(11b)); 128.8, 128.7 (C(4), C(6)); 126.7, 126.3 (C(5),C(2)); 125.0 (C(3)); 122.8 (C(1)); 80.3 (*C*Me$_3$); 74.4 (C(8)); 60.1 (C(9)); 42.0 (C(7)); 32.1(C(10)); 28.3 (C*Me*$_3$); 23.9 (C(11)). HRMS (ESI$^+$) calcd for $C_{20}H_{25}NNaO_3^+$ [M+Na]$^+$: 350.1727; found: 350.1718.

11. Preparation and reduction of the oximes 13c,c′,d,d′

11.1. 4-Bromo-6-hydroxy-5,6,8,9-tetrahydrobenzocyclohepten-7-hydroxyimine (13c) and 1-bromo-6-hydroxy-5,6,8,9-tetrahydrobenzocyclohepten-8-hydroxyimine (13c′)

A solution of **10c/10ĉ** (780 mg, 2.38 mmol) in pyridine (4 ml) with $NH_2OH{\cdot}HCl$ (199 mg, 2.86 mmol, 1.2 equiv) was stirred under Ar for 5 h at rt. The solvent was evaporated and the residue dissolved in MeCN (1–2 mL) and AcOEt (10 mL) with $NBu_4NF{\cdot}3H_2O$ (0.15 g, 0.5 mmol, 0.2 equiv). The solution was stirred for 1 h at rt, then washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The isomer **13c′** crystallised partially by triturating in AcOEt/cyclohexane and was isolated by filtration and washing with MeCN then with Et_2O. A chromatography of the mother liquor cyclohexane/AcOEt 6:4 (**13c** R_f = 0.43, **13c′** R_f = 0.31) gave **13c** (210 mg, 33%) and the remaining **13c′**. Global yield of **13c′**: 230 mg, 35%.

Compound **13c**: colorless crystals, mp 142–143 °C. IR (KBr): 3530, 3441, 3209, 2882, 1448, 1062, 943, 922, 841, 782, 705 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.43 (dd, 1H, H-1); 7.14 (dd, 1H, H-3); 7.02 (t, 1H, H-2); 4.39 (dd, 1H, H-6); 3.39 (dd, 1H, Ha-5); 3.34 (dd, 1H, Hb-5); 3.20 (dddd, 1H, Ha-8); 3.04 (ddd, 1H, Ha-9); 2.83 (ddd, 1H, Hb-9); 2.45 (ddd, 1H, Hb-8); J(1,2) = 7.4, ^4J(1,3) = 1.3, J(2,3) = 8.0, J(5a,5b) = 14.3, J(5a,6) = 8.2, J(5b,6) = 4.5, J(8a,8b) = 14.3, J(8a,9a) = 8.2, J(8a,9b) = 4.8, J(8b,9a) = 5.0, J(8b,9b) = 7.9, J(9a,9b) = 14.4 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 161.6 (C=N); 144.9, 137.1 (C(4a),C(9a)); 132.2 (C(3)); 129.4 (C(1)); 128.9 (C(2)); 126.7 (C(4)); 71.4 (C(6)); 40.0 (C(5)); 32.7 (C(9)); 22.9 (C(8)). HR-MS (ESI$^+$) calcd for $C_{11}H_{13}BrNO_2$ [M+H]$^+$: 270.0124 and 272.0103; found: 270.0122 and 272.0105.

Compound **13c′**: colorless crystals, mp 176–177 °C. IR (KBr): 3496, 3213, 2919, 1466, 1447, 1057, 1010, 950, 904, 777, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.45 (dd, 1H, H-2); 7.16 (dd, 1H, H-4); 7.01 (t, 1H, H-3); 4.41 (m, 1H, H-6); 3.33 (ddd, 1H, Ha-9); 3.24 (ddd, 1H, Ha-8); 3.15 (d, 2H, CH_2(5)); 2.93 (ddd, 1H, Hb-9); 2.31 (ddd, 1H, Hb-8); J(2,3) = 8.0, ^4J(2,4) = 1.2, J(3,4) = 7.8, J(6,8) = 1.0, J(8a,8b) = 14.0, J(8a,9a) = 8.8, J(8a,9b) = 3.3, J(8b,9a) = 3.2, J(8b,9b) = 8.8, J(9a,9b) = 14.0 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 161.8 (C=N), 141.5, 140.2 (C(9a),C(4a)), 132.4 (C(2)), 131.4 (C(4)), 128.7 (C(3)), 125.0 (C(1)), 71.8 (C(6)), 42.5 (C(5)), 30.6 (C(9)), 22.1 (C(8)). HR-MS (ESI$^+$) calcd for $C_{11}H_{13}BrNO_2$ [M+H]$^+$: 270.0124 and 272,0103; found: 270.0122 and 272,0105. Anal. Calcd for $C_{11}H_{12}BrNO_2$ (270.12): C, 48.91; H, 4.48; N, 5.19. Found: C, 48.9; H, 4.5; N, 5.2.

11.2. 4-Bromo-6-hydroxy-1-phenyl-5,6,8,9-tetrahydrobenzocyclohepten-7-hydroxyimine (13d) and 1-bromo-6-hydroxy-4-phenyl-5,6,8,9-tetrahydrobenzocyclohepten-8-hydroxyimine (13d′)

A solution of **10d/10d′** (8.6 g, 21 mmol) in pyridine (86 mL) was stirred with $NH_2OH{\cdot}HCl$ (1.8 g, 25 mmol, 1.2 equiv) at rt for 16 h. Same work-up as for **13c/13c′**. The crude oxime mixture (7.4 g, quant.) was purified by flash chromatography (cyclohexane/AcOEt 6:4) to give a 60:40 mixture of **13d/13d′** (90:10 *E*/*Z* mixtures, 5.4 g, 73%).

Compound **13d**/**13d′**: colorless crystals, mp 50–52 °C. IR (KBr): 704, 770, 821, 924, 946, 1028, 1064, 1454, 1705, 2918, 3058, 3327 cm^{-1}. HR-MS (ESI^+) calcd for $C_{17}H_{17}BrNO_2$ $[M+H]^+$: 346.0437 and 348.0418; found: 346.0424 and 348.0400.

Compound **13d**: ^1H NMR ($CDCl_3$, 400 MHz) major oxime *E*: 7.30–7.45 (m, 4Har); 7.24 (m, 2Har); 6.95 (d, *J* = 8.4 Hz, 1Har); 4.44 (dd, 1H, H-6); 3.52 (dd, 1H, Ha-5); 3.34 (dd, 1H, Hb-5); 2.67–2.97 (m, 4H); *J*(5a,5b) = 14.4, *J*(5a,6) = 4.0, *J*(5b,6) = 8.8 Hz. Oxime *Z*, partial data: 5.46 (dd, 1H, *J* = 3.9, 8.9 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz) major oxime *E*: 161.2 (C(7)); 141.1 (C(9a)); 140.9 (Car-s); 140.5 (C(1)); 135.7 (C(4a)); 130.4 (C(3)); 129.8 (C(2)); 129.0 (CHar-m); 128.2 (CHar-o); 127.2 (CHar-p); 124.8 (C(4)); 70.0 (C(6)); 38.9 (C(5)); 26.9 (C(9)); 22.8 (C(8)).

Compound **13d′**: ^1H NMR ($CDCl_3$, 400 MHz) major oxime *E*: 7.30–7.45 (m, 4Har); 7.24 (m, 2Har); 6.95 (d, *J* = 8.4 Hz, 1Har); 4.32 (dd, 1H, H-6); 3.16 (m, 2H, CH_2(9)); 3.10 (dd, 1H, Ha-5); 3.04 (dd, 1H, Hb-5); 2.67–2.97 (m, 2H, CH_2(8)); *J*(5a,5b) = 14.4, *J*(5a,6) = 4.4, *J*(5b,6) = 8.4 Hz. Oxime *Z*, partial data: 5.35 (dd, 1H, *J* = 4.2, 8.5 Hz, H-6). ^{13}C NMR ($CDCl_3$, 100 MHz) major oxime *E*: 161.6 (C(7)); 142.6 (C(4a)); 140.8 (Car-s); 140.5 (C(4)); 135.5 (C(9a)); 130.7 (C(2)); 129.6 (C(3)); 129.2 (Car-m); 128.1 (Car-o); 127.2 (Car-p); 123.2 (C(1)); 70.8 (C(6)); 36.6 (C(5)); 29.4 (C(9)); 22.2 (C(8)).

11.3. Reduction of 13c

A solution of **13c** (1.01 g, 3.75 mmol) in EtOH (30 mL) and concentrated aqueous NH_4OH solution (12 ml, 180 mmol, 50 equiv) was hydrogenolysed at rt over wet Raney-nickel (1.8–2.0 g) at rt for 30–50 min with NMR monitoring. When the reduction was complete, the catalyst was discarded by centrifugation or filtration over Celite. The solution was evaporated to give crude amine (0.95 g, ca. 95%) which was directly N-protected. A solution od the crude amine in MeOH (10 ml) was stirred with Boc_2O (1.22 g, 5.65 mmol, 1.5 equiv) and Na_2CO_3 (0.5 g, 4.81 mmol, 1.3 equiv) for 16 h at rt. AcOEt was added (50 mL) and the solution washed with brine, dried ($MgSO_4$) and evaporated to give **11c** (1.12 g, 85%) as 50:50 *cis/trans* isomeric mixture.

11.4. Reduction of 13c′

Same procedure as for **13c** with **13c′** (0.47 g, 1.75 mmol) in EtOH (10 mL), wet Raney-nickel (0.85 g) and aqueous concentrated NH_4OH solution (6 ml, 90 mmol, 50 equiv). Same work-up and N-protection with Boc_2O (0.57 g, 2.6 mmol, 1.5 equiv) and Na_2CO_3 (0.24 g, 2.26 mmol, 1.3 equiv) gave **11c′** (0.61 g, 98%) as 50:50 *cis/trans* isomeric mixture.

11.5. Reduction of 13d,d′

Same procedure as for **13c** with the mixture **13d**,**d′** (468 mg, 1.35 mmol) in EtOH (19 ml), aqueous concentrated NH_4OH solution (5.6 ml, 79 equiv) and wet Raney-nickel (0.9 g) for 1 h at rt. Same work-up and N-protection with Boc_2O (0.46 g, 2.1 mmol, 1.5 equiv) and $NaHCO_3$ (0.15 g, 1.8 mmol, 1.3 equiv) in MeOH (7 mL) gave the 60:40 isomeric mixture **11d/11d′** (508 mg, 87%), mp 174–176 °C.

12. Keto-amides 12c–e,b′–d′,h,h′

General procedure (h): To a solution of **11** or **11′** (10 mmol) in wet CH_2Cl_2 (50 mL) was added Dess–Martin periodinane (DMP) (6–9 g, 15–20 mmol, 1.5–2 equiv) and the mixture stirred at rt for 2 h (tlc monitoring). After dilution with Et_2O (100 mL), the solution was vigorously stirred with aqueous 1 M $NaHCO_3$ solution (50 mL, containing Na_2SO_3 (2.5 g, 20 mmol), or $Na_2S_2O_3{\cdot}5H_2O$ (15 g, 60 mmol)) for 20 min, the organic phase was washed with aqueous 1 M $NaHCO_3$ solution (50 mL) and then with brine (50 mL), dried over $MgSO_4$ and evaporated to give the crude amide **12** which was crystallised from iPr_2O.

12.1. 7-*tert*-Butoxycarbonylamino-1-chloro-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12b′)

General procedure (h) with *cis/trans*-**11b′** (0.25 g, 0.80 mmol) in CH_2Cl_2 (6 mL) and with DMP (510 mg, 1.2 mmol, 1.5 equiv) for 3 h to give **12b′** (0.23 g, 92%).

Compound **12b′**: colorless crystals, mp 132–134 °C. IR (KBr): 2963, 2924, 1724, 1489, 1447, 1447, 1147, 1046, 989, 782 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): 7.31 (dd, 1H, *J* = 1.8, 7.5 Hz, H-2); 7.10 (m, 2H, H-3,H-4); 5.36 (d, 1H, *J* = 7.5 Hz, NH), 4.49 (dt, 1H, *J* = 11.1, 7.5 Hz, H-7), 3.87 (d, 1H, *J* = 16.0 Hz, Ha-5); 3.67 (d, 1H, *J* = 16.0 Hz, Hb-5); 3.14 (m, 2H, CH_2(9)); 2.61 (m, 1H, Ha-8); 1.48 (m, 1H, Hb-8); 1.41 (s, 9H, CMe_3). ^{13}C NMR ($CDCl_3$, 75 MHz): 205.0 (CO(6)); 155.0 (NCO); 137.3 (C(9a)); 134.7, 133.8 (C(4a), C(1)); 129.0, 128.3, 128.0 (C(2), (C(3), (C(4)); 79.9 (*C*Me_3); 59.7 (C(7)); 48.2 (C(5)); 32.9 (C(8)); 28.3 (C*Me*$_3$); 26.0 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{22}ClLiNO_3$ $[M+Li]^+$: 318.1443; found: 318.1381; calcd for $C_{16}H_{22}ClNaNO_3$ $[M+Na]^+$: 334.1180; found: 334.1124.

12.2. 4-Bromo-7-*tert*-Butoxycarbonylamino-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12c)

General procedure (h) with *cis/trans*-**11c** (1.10 g, 3.08 mmol) in CH_2Cl_2 (10 mL) and with DMP (2.61 g, 6.16 mmol, 2 equiv) for 3 h to give **12c** (816 mg, 75%).

Compound **12c**: colorless crystals, mp 164–166 °C. IR (KBr): 3297, 2978, 1724, 1682, 1542, 1442, 1365, 1298, 1276, 1255, 1187, 1171, 1091, 1056, 1010, 782 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.49 (d, 1H, H-3); 7.12 (d, 1H, H-1); 7.06 (t, 1H, H-2); 5.41 (d, 1H, NH); 4.49 (m, 1H, H-7); 4.15 (d, 1H, Ha-5); 3.99 (d, 1H, Hb-5); 2.97 (m, 1H, Ha-9); 2.89 (ddd, 1H, Hb-9); 2.62 (m, 1H, Ha-8); 1.53 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); *J*(1,2) = 7.8, *J*(1,3) = 1.2, *J*(2,3) = 7.4, *J*(5a,5b) = 16.5, *J*(NH,7) = 7.0, *J*(7,8a) = 7.6, *J*(7,8b) = 10.8, *J*(8a,8b) = 12.6, *J*(8a,9a) = 4.8, *J*(8a,9b) = 10.2, *J*(8b,9a) = 6.4, *J*(8b,9b) = 4.6, *J*(9a,9b) = 14.6 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.2 (C(6)); 153.3 (NCO_2); 142.4 (C(9a)); 132.7 (C(4a)); 132.2 (C(3)); 129.5, 128.9 (C(1),C(2)); 125.4 (C(4)); 80.3 (*C*Me_3); 59.7 (C(7)); 47.0 (C(5)); 34.5 (C(8)); 31.9 (C(9)); 28.7 (C*Me*$_3$). HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{20}BrLiNO_3$ $(M+Li)^+$: 360.0781 and 362.0763; found: 360.0740 and 362.0736.

12.3. 1-Bromo-7-*tert*-Butoxycarbonylamino-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12c′)

General procedure (h) with *cis/trans*-**11c′** (250 mg, 0.7 mmol) in CH_2Cl_2 (4 mL) and with DMP (0.60 g, 1.4 mmol, 2 equiv) for 3 h to give **12c′** (164 mg, 66%).

Compound **12c′**: colorless crystals, mp 114–116 °C. IR (KBr): 3422, 2969, 2928, 1684, 1654, 1446, 1264, 1166, 1113 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.50 (d, 1H, H-2); 7.12 (d, 1H, H-4); 7.04 (dd, 1H, H-3); 5.35 (br d, 1H, NH); 4.49 (dt, 1H, H-7); 3.88 (d, 1H, Ha-5); 3.70 (d, 1H, Hb-5); 3.21 (ddd, 1H, Ha-9); 3.15 (ddd, 1H, Hb-9); 2.62 (m, 1H, Ha-8); 1.50 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); *J*(2,3) = 8.0, *J*(2,4) = 1.2, *J*(3,4) = 7.4, *J*(5a,5b) = 16.1, *J*(NH,7) = 7.4, *J*(7,8a) = 7.6, *J*(7,8b) = 11.0, *J*(8a,8b) = 13.2, *J*(8a,9a) = 4.4, *J*(8a,9b) = 10.4, *J*(8b,9a) = 6.4, *J*(8b,9b) = 4.2, *J*(9a,9b) = 14.8 Hz. ^{13}C NMR ($CDCl_3$, 75 MHz): 205.2 (CO(6)); 155.1 (NCO); 139.1 (C(9a)); 134.8 (C(4a)); 132.5 (C(2)); 129.2 (C(4)); 128.5 (C(3)); 124.7 (C(1)); 80.0 (*C*Me_3); 59.6 (C(7)); 48.6 (C(5)); 32.9 (C(8)); 29.4 (C(9)); 28.4

(CMe_3). HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{20}BrLiNO_3$ $[M+Li]^+$: 360.0781 and 362.0763; found: 360.0781 and 362.0767.

12.4. 4-Bromo-7-(*tert*-butoxycarbonylamino)-1-phenyl-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12d) and 1-bromo-7-(*tert*-butoxycarbonylamino)-4-phenyl-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12d′)

General procedure (h) with the isomeric mixture **11d/11d′** (364 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) and with DMP (1.07 g, 2.53 mmol, 3 equiv) for 2 h to give **12d/12d′** (198 mg, 54%) which were separated by par HPLC (MeOH/H_2O 7:3) to give **12d** (137 mg, 38%) and **12d′** (61 mg, 17%).

Compound **12d**: colorless crystals, mp 148–154 °C. IR (KBr): 3332, 2984, 2930, 1725, 1678, 1529, 1451, 1371, 1333, 1300, 1274, 1252, 1170, 1051, 1008, 764, 701 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.52 (d, 1H, H-3); 7.44–7.35 (m, 3Har); 7.27–7.24 (m, 2Har); 7.05 (d, 1H, H-2); 5.43 (d, 1H, NH); 4.54 (m, 1H, H-7); 4.30 (d, 1H, Ha-5); 3.97 (d, 1H, Hb-5); 2.88 (dt, 1H, Ha-9); 2.77 (ddd, 1H, Hb-9); 2.51 (m, 1H, Ha-8); 1.48 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); J(5a,5b) = 17.6, J(2,3) = 8.3; J(7,NH) = 7.0; J(7,8a) = 8.0, J(7,8b) = 11.0, J(8a,8b) = 13.2, J(8a,9a) = 5.0; J(8a,9b) = 11.2; J(8b,9a) = 5.2; J(8b,9b) = 5.2; J(9a,9b) = 14.7 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.2 (C(6)); 154.9 (NCO); 141.7 (C(9a)); 140.4, 139.1 (C(1),Car-s); 132.6 (C(4a)); 131.0 (C(3)); 130.7 (C(2)); 129.0 (Car-o); 128.3 (Car-m); 127.4 (Car-p); 124.1 (C(4)); 79.8 (CMe_3); 58.5 (C(7)); 47.1 (C(5)); 33.8 (C(8)); 28.3 (CMe_3); 27.2 (C(9)). Anal. Calcd for $C_{22}H_{24}BrNO_3$ (430.33): C, 61.40; H, 5.62; N, 3.25; Br, 18.57. Found: C, 61.2; H, 5.4; N, 3.1; Br, 18.5.

Compound **12d′**: colorless crystals, mp 144–150 °C. IR (KBr): 3301, 2977, 2934, 1725, 1704, 1702, 1675, 1542, 1453, 1366, 1183, 1170, 703. ^1H NMR ($CDCl_3$, 400 MHz): 7.54 (d, 1H, H-2); 7.45–7.34 (m, 3Har); 7.29 (d, 2Har, J = 7.2 Hz); 7.05 (d, 1H, H-3); 5.37 (d, 1H, NH); 4.48 (m, 1H, H-7); 3.85 (d, 1H, Ha-5); 3.72 (d, 1H, Hb-5); 3.30 (ddd, 1H, Ha-9); 3.17 (ddd, 1H, Hb-9); 2.68 (m, 1H, Ha-8); 1.54 (m, 1H, Hb-8); 1.43 (s, 9H, CMe_3); J(2,3) = 8.2 Hz, J(5a,5b) = 17.0, J(7,NH) = 7.2, J(7,8a) = 7.9, J(7,8b) = 10.8, J(8a,8b) = 13.0, J(8a,9a) = 4.5, J(8a,9b) = 11.0, J(8b,9a) = 6.0, J(8b,9b) = 4.4, J(9a,9b) = 14.7 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.6 (C(6)); 154.8 (NCO); 142.0 (C(9a)); 139.8, 139.1 (C(4),Car-s); 132.3 (C(4a)); 131.6, 130.1, 129.5, 128.4, 127.5 (C(2),C(3), 3Car); 123.6 (C(1)); 79.8 (CMe_3); 59.1 (C(7)); 44.6 (C(5)); 32.5 (C(8)); 29.8 (C(9)); 28.3 (CMe_3). HR-MS (ESI^+) calcd for $C_{22}H_{24}BrNO_3Li$ $[M+Li]^+$: 436.1095 and 438.1077; found: 436.1086 and 438.1065.

12.5. 1,4-Dibromo-7-(*tert*-butoxycarbonylamino)-5,7,8,9-tetrahydrobenzocyclohepten-6-one (12e)

General procedure (h) with *cis/trans*-**11e** (901 mg, 2.07 mmol) in CH_2Cl_2 (20 mL) and with DMP (1.14 g, 2.69 mmol, 1.3 equiv) for 2 h to give **12e** (710 mg, 79%).

Compound **12e**: yellowish crystals, mp 185–186 °C. IR (KBr): 3277, 2974, 1731, 1675, 1540, 1439, 1365, 1272, 1164, 1052, 978, 808 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.38, 7.36 (2 d, 2H, H-2, H-3); 5.36 (d, 1H, NH); 4.41 (q, 1H, H-7); 4.27 (d, 1H, Ha-5); 3.92 (d, 1H, Hb-5); 3.32 (ddd, 1H, Ha-9); 3.02 (ddd, 1H, Hb-9); 2.62 (m, 1H, Ha-8); 1.54 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); J(2,3) = 8.4, J(5a,5b) = 18.0, J(7,NH) = 7.8, J(7,8a) = 7.8, J(7,8b) = 10.4, J(8a,8b) = 12.2, J(8a,9a) = 5.0, J(8a,9b) = 12.2, J(8b,9a) = 4.8, J(8b,9b) = 5.0, J(9a,9b) = 14.7 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 204.9 (CO(6)); 154.9 (NCO); 140.6 (C(9a)); 134.3 (C(4a)); 133.2, 132.5 (C(2),C(3)); 124.1, 123.5 (C(1),C(4)); 80.0 (CMe_3); 58.1 (C(7)); 47.6 (C(5)); 32.2 (C(8)); 30.4 (C(9)); 28.3 (CMe_3). HR-MS (ESI-Q-Tof) calcd for $C_{16}H_{19}Br_2NNaO_3$ $[M+Na]^+$: 455.9604; found: 455.9610.

12.6. 9-*tert*-Butoxycarbonylamino-7,8,9,11-tetrahydro-cyclohepta[*a*]naphthalen-10-one (12h)

General procedure (h) with *cis*- or *trans*-**11h** (50 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) and with DMP (97 mg, 0.23 mmol, 1.5 equiv) for 3 h to give **12h** (50 mg, quant.).

Compound **12h**: colorless crystals, mp 152–153 °C. IR (KBr): 3352, 2971, 2931, 1720, 1682, 1514, 1367, 1247, 1163, 1058, 982, 819, 743 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.12 (d, 1H, H-1); 7.84 (d, 1H, H-4); 7.74 (d, 1H, H-5); 7.55 (dt, 1H, H-2); 7.46 (dt, 1H, H-3); 7.31 (d, 1H, H-6); 5.43 (d, 1H, NH), 4.63 (dt, 1H, H-9); 4.27 (d, 1H, Ha-11); 4.23 (d, 1H, Hb-11); 3.20 (ddd, 1H, Ha-7); 3.05 (ddd, 1H, Hb-7); 2.73 (m, 1H, Ha-8); 1.58 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); J(1,2) = 8.4, J(1.3) = 1.2, J(2,3) = 6.8, J(2,4) = 1.4, J(3,4) = 8.0, J(5,6) = 8.2, J(9,NH) = 7.0, J(7a,7b) = 14.6, J(7a,8a) = 3.4, J(7a,8b) = 8.5, J(7b,8a) = 9.2, J(7b,8b) = 3.5, J(8a,9) = 7.2, J(8b,9) = 11.2, J(8a,8b) = 13.0, J(11a,11b) = 15.0 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 204.8 (CO(10)); 155.0 (NCO); 138.4 (C(6a)); 133.1, 131.5 (C(4a),C(11b)); 128.7 (C(4)); 128.1 (C(5)); 127.7 (C(6)); 127.6 (C(11a)); 126.8 (C(2)); 125.3 (C(3)); 123.2 (C(1)); 79.8 (CMe_3); 60.8 (C(9)); 41.6 (C(11)); 35.4 (C(8)); 31.6 (C(7)); 28.3 (CMe_3). HR-MS (ESI-Q-Tof) calcd for $C_{20}H_{23}LiNO_3$ $[M+Li]^+$: 332.1833; found: 332.1813.

12.7. 9-*tert*-Butoxycarbonylamino-7,8,9,11-tetrahydro-cyclohepta[*a*]naphthalen-8-one (12h′)

General procedure (h) with *cis*- or *trans*-**11h′** (90 mg, 0.27 mmol) in CH_2Cl_2 (6 mL) and with DMP (174 mg, 0.40 mmol, 1.5 equiv) for 3 h to give **12h′** (80 mg, 90%).

Compound **12h′**: colorless crystals, mp 128–129 °C. IR (KBr): 3352, 2971, 2931, 1720, 1682, 1514, 1367, 1246, 1163, 1057, 981, 818, 743 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.09 (d, 1H, H-1); 7.85 (d, 1H, H-4); 7.72 (d, 1H, H-5); 7.53 (dt, 1H, H-2); 7.48 (dt, 1H, H-3); 7.31 (d, 1H, H-6); 5.39 (d, 1H, NH), 4.55 (dt, 1H, H-9); 4.03 (d, 1H, Ha-7); 3.88 (d, 1H, Hb-7); 3.43 (m, 1H, Ha-11); 3.35 (m, 1H, Hb-11); 2.75 (m, 1H, Ha-10); 1.64 (m, 1H, Hb-10); 1.40 (s, 9H, CMe_3); J(1,2) = 8.7, J(1.3) = 1.2, J(2,3) = 6.8, J(2,4) = 1.2, J(3,4) = 8.1, J(5,6) = 8.3, J(7a,7b) = 16.3, J(9,NH) = 7.2, J(9,10a) = 7.6, J(9,10b) = 10.8, J(10a,10b) = 12.8, J(10a,11a) = 4.4, J(10a,11b) = 10.8, J(10b,11a) = 6.4, J(10b,11b) = 4.2, J(11a,11b) = 14.8 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.7 (CO(8)); 154.9 (NCO); 135.5 (C(6a)); 133.3, 131.3 (C(4a),C(11b)); 130.0 (C(11a)); 128.8 (C(4)); 127.7(C(5)); 127.4 (C(6)); 126.5 (C(2)); 125.5 (C(3)); 122.9 (C(1)); 79.7 (CMe_3); 59.6 (C(9)); 48.5 (C(7)); 33.9 (C(10)); 28.3 (CMe_3); 23.9 (C(11)). HR-MS (ESI-Q-Tof) calcd for $C_{20}H_{23}NaNO_3$ $[M+Na]^+$: 348.1570; found: 348.1530.

13. Keto-amines 1c–e,b′–d′,h,h′

General procedure (i) a solution of **12** or **12′** (1 mmol) in dry dioxane (1–2 mL) with 2 N HCl in dry Et_2O (5 mL) was stirred at rt for 2–4 days. The amine hydrochloride **1** was isolated by filtration or centrifugation and washing with dry Et_2O (1 mL).

13.1. 7-Amino-1-chloro-5,7,8,9-tetrahydro-benzocyclohepten-6-one, hydrochloride (1b′)

General procedure (i) with **12b′** (80 mg, 0.26 mmol) in dioxane (3 mL) and 2 N HCl in Et_2O (3 mL) for 2 d to give **1b′** (50 mg, 79%) after recrystallisation in MeOH/Et_2O.

Compound **1b′**: colorless crystals, mp 240 °C (dec). IR (KBr): 3432, 2962, 2903, 1725, 1582, 1582, 1573, 1509, 1446, 1048,

989, 778 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 7.39 (m, 1H, H-2); 7.22 (m, 1H, H-3, H-4); 4.33 (dd, 1H, H-7); 4.21 (d, 1H, Ha-5); 3.76 (d, 1H, Hb-5); 3.46 (ddd, 1H, Ha-9); 3.30 (ddd, 1H, Hb-9); 2.57 (m, 1H, Ha-8); 1.71 (m, 1H, Hb-8); *J*(5a,5b) = 15.0, *J*(7,8a) = 7.4, *J*(7,8b) = 11.8, *J*(8a,8b) = 13.0, *J*(8a,9a) = 9.3, *J*(8a,9b) = 3.4, *J*(8b,9a) = 3.4, *J*(8b,9b) = 8.6, *J*(9a,9b) = 15.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.1 (CO(6)); 138.4 (C(9a)); 136.0 (C(4a)); 134.8 C(1)); 130.2 (C(2)); 129.8, 129.7 (C(3),C(4)); 60.1 (C(7)); 48.2 (C(5)); 31.5 (C(8)); 26.1 (C(9). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{13}ClNO$ $[M+H]^+$: 210.0680; found: 210.0690.

13.2. 7-Amino-4-bromo-5,7,8,9-tetrahydro-benzocyclohepten-6-one, hydrochloride (1c)

General procedure (i) with **12c** (164 mg, 0.46 mmol) in dioxane (1 mL) and 2 N HCl in Et_2O (5 mL) for 3 d to give **1c** (107 mg, 80%) after recrystallisation in *i*PrOH/ Et_2O.

Compound **1c**: colorless crystals, mp 212 °C (sublimation). IR (KBr): 2955, 2935, 2204, 2123, 1722, 1444, 1081, 986, 779 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 8:2 mixture with an hemi-acetal): 7.55 (d, 1H, H-3); 7.26 (d, 1H, H-1); 7.15 (t, 1H, H-2); 4.33 (dd, 1H, H-7); 4.28 (d, 1H, Ha-5); 4.20 (d, 1H, Hb-5); 3.09 3.27 (ddd, 1H, Ha-9); 3.09 (ddd, 1H, Hb-9); 2.55 (m, 1H, Ha-8); 1.74 (m, 1H, Hb-8); *J*(1,2) = 7.6, *J*(2,3) = 8.0, *J*(5a,5b) = 15.2, *J*(7,8a) = 7.2, *J*(7,8b) = 11.8, *J*(8a,8b) = 12.8, *J*(8a,9a) = 3.3, *J*(8a,9b) = 8.9, *J*(8b,9a) = 8.8, *J*(8b,9b) = 3.6, *J*(9a,9b) = 14.7 Hz. Hemiacetal, partial data: ca. 1.70 (m, Hb-8); 2.07 (m, Ha-8); 2.94 (m, CH_2(9)); 7.07 (t, H-2); ca. 7.15 (d, H-1); 7.48 ((d, H-3); *J*(1,2) = 7.6, *J*(2,3) = 8.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.0 (CO(6)); 143.8 (C(9a)); 133.5 (C(3)); 133.1 (C(4a)); 130.8, 130.2 (C(1),C(2)); 125.8 (C(1)); 60.6 (C(7)); 46.5 (C(5)); 32.8 (C(8)), 31.8 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0175 and 256.0155; found: 254.0178 and 256.0156.

13.3. 7-Amino-1-bromo-5,7,8,9-tetrahydro-benzocyclohepten-6-one, hydrochloride (1c′)

General procedure (i) with **12c′** (816 mg, 2.3 mmol) in dioxane (3 mL) and 2 N HCl in Et_2O (15 mL) for 3 d to give **1c′** (535 mg, 80%) after recrystallisation in *i*PrOH/Et_2O.

Compound **1c′**: colorless crystals, mp 260–270 °C (sublimation). IR (KBr): 2963, 2924, 1724, 1491, 1443, 1147, 1047, 986, 779 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 8:2 mixture with an hemi-acetal): 7.57 (d, 1H, H-2); 7.25 (d, 1H, H-4); 7.14 (t, 1H, H-3); 4.30 (dd, 1H, H-7); 4.20 (d, 1H, Ha-5); 3.79 (d, 1H, Hb-5); 3.46 (ddd, 1H, Ha-9); 3.35 (ddd, 1H, Hb-9); 2.54 (m, 1H, Ha-8); 1.71 (m, 1H, Hb-8); *J*(2,3) = 8.1, *J*(2,4) = 1.0, *J*(3,4) = 7.6, *J*(5a,5b) = 15.2, *J*(7,8a) = 7.2, *J*(7,8b) = 11.7, *J*(8a,8b) = 13.0, *J*(8a,9a) = 9.6, *J*(8a,9b) = 3.5, *J*(8b,9a) = 3.6, *J*(8b,9b) = 8.2, *J*(9a,9b) = 15.1 Hz. Hemiacetal, partial data: ca. 1.70 (m, 1H, Hb-8); 2.07 (m, 1H, Ha-8); 2.89 (m, 1H, Hb-9); 3.16 (d, 1H, Hb-5); 3.24 (d, 1H, Ha-5); 7.05 (t, 1H, H-3); 7.20 (d, 1H, H-4); 7.48 ((d, 1H, H-2); *J*(2,3) = 8.1, *J*(3,4) = 7.4, *J*(5a,5b) = 15.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.2 (CO(6)); 140.1 (C(9a)); 136.0 (C(4a)); 133.6 (C(2)); 130.5, 130.1 (C(3),C(4)); 125.3 (C(1)); 60.2 (C(7)); 48.4 (C(5)); 31.3 (C(8)); 29.4 (C(9). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0175 and 256.0155; found: 254.0151 and 256.0130.

13.4. 7-Amino-4-bromo-1-phenyl-5,7,8,9-tetrahydrobenzocyclohepten-6-one, hydrochloride (1d)

General procedure (i) with **12d** (70 mg, 0.16 mmol) in dioxane (2 mL) and 2 N HCl in Et_2O (4 mL) for 2 d to give **1d** (57.5 mg, 96%) after recrystallisation in *i*PrOH/ Et_2O.

Compound **1d**: colorless crystals, mp >250 °C. IR (KBr): 3028, 2866, 1730, 1578, 1507, 1452, 772, 705 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 7.61 (d, 1H, H-3); 7.49–7.38 (m, 3 Har); 7.29–7.21 (m, 2 Har); 7.12 (d, 1H, H-2); 4.39 (d, 1H, Ha-5); 4.32 (dd, 1H, H-7); 4.25 (d, 1H, Hb-5); 3.06 (t, 2H, CH_2(9); 2.38 (m, 1H, Ha-8); 1.73 (m, 1H, Hb-8); *J*(2,3) = 8.2, *J*(5a,5b) = 15.9, *J*(7,8a) = 7.6, *J*(7,8b) = 11.8, *J*(8a,8b) = 13.6, *J*(8a,9) = *J*(8b,9) = 6.1 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.0 (CO(6)); 143.5, 141.8, 140.6 (C(9a),C(1), Car-s); 133.6 (C(4a)); 132.5 (C(3)); 132.1 (C(2)); 130.1 (Car-o); 129.6 (Car-m); 128.8 (Car-p); 124.8 (C(4)); 59.9 (C(7)); 46.9 (C(5)); 32.1 (C(8)); 27.5 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{17}BrNO$ $[M+H]^+$: 330.0488 and 332.0469; found: 330.0453 and 332.0436.

13.5. 7-Amino-1-bromo-4-phenyl-5,7,8,9-tetrahydrobenzocyclohepten-6-one, hydrochloride (1d′)

General procedure (i) with **12d′** (61 mg, 0.14 mmol) in dioxane (1.5 mL) and 2 N HCl in Et_2O (3 mL) for 2 d to give **1d′** (49.4 mg, 95%) after recrystallisation in *i*PrOH/ Et_2O.

Compound **1d′**: colorless crystals, mp 185–190 °C (dec). IR (KBr): 3424, 2923, 2891, 1722, 1582, 1579, 1513, 1454, 821, 769, 705 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 7.63 (d, 1H, H-2); 7.48–7.34 (m, 5 Har); 7.12 (d, 1H, H-3); 4.33 (dd, 1H, H-7); 4.03 (d, 1H, Ha-5); 3.86 (d, 1H, H-5); 3.54 (ddd, 1H, Ha-9); 3.43 (ddd, 1H, Hb-9); 2.59 (m, 1H, Ha-8); 1.77 (m, 1H, Hb-8); *J*(2,3) = 8.3, *J*(5a,5b) = 15.3, *J*(7,8a) = 7.6, *J*(7,8b) = 11.8, *J*(8a,8b) = 12.8, *J*(8a,9a) = 9.6, *J*(8a,9b) = 3.6, *J*(8b,9a) = 3.6, *J*(8b,9b) = 8.2, *J*(9a,9b) = 15.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.6 (CO(6)); 143.8, 141.2, 140.5 (C(9a),C(1), Car-s); 133.4 (C(4a)); 133.0 (C(3)); 131.8 (C(2)); 130.8 (Car-o); 129.5 (Car-m); 128.8 (Car-p); 124.5 (C(4)); 60.4 (C(7)); 44.4 (C(5)); 31.1 (C(8)); 30.0 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{17}BrNO$ $[M+H]^+$: 330.0488 and 332.0469; found: 330.0458 and 332.0433.

13.6. 7-Amino-1,4-dibromo-5,7,8,9-tetrahydrobenzocyclohepten-6-one, hydrochloride (1e)

General procedure (i) with **12e** (60 mg, 0.14 mmol) in dioxane (1.5 mL) and 2 N HCl in Et_2O (1.5 mL) for 2 d to give **1e** (32 mg, 63%) after recrystallisation in MeOH/ Et_2O.

Compound **1e**: colorless crystals, mp >250 °C. IR (KBr): 3420, 2920, 1728, 1438, 1141, 1445, 809 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 7.49, 7.47 (2 d, 2H, H-2, H-3) 4.39 (d, 1H, H-5); 4.26 (dd, 1H, H-7); 4.21 (d, 1H, H-5); 3.43 (m, 2H, CH_2(9)); 2.54 (m, 1H, Ha-8); 1.75 (m, 1H, Hb-8); *J*(2,3) = 8.7, *J*(7,8a) = 7.9, *J*(7,8b) = 11.2, *J*(5a,5b) = 16.3 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 201.6 (CO(6)); 142.1 (C(9a); 135.4 (C(4a)); 134.6, 134.2 (C(2), C(3)); 125.0 124.6 (C(1),C(4)); 59.6 (C(7)); 47.4 (C(5)); 30.5 (C(9)); 30.6 (C(8)). HR-MS (ESI-Q-Tof) calcd for $C_{11}H_{12}Br_2NO$ $[M+H]^+$: 331.9280, 333. 9259 and 335.9239; found: 331.9279, 333.9259 and 335.9238.

13.7. 9-Amino-7,8,9,11-tetrahydro-cyclohepta[*a*]naphthalen-10-one, hydrochloride (1h)

General procedure (i) with **12h** (40 mg, 0.12 mmol) in Et_2O (2 mL) and 2 N HCl in Et_2O (1 mL) for 2 d to give **1h** (27 mg, 84%).

Compound **1h**: colorless crystals, mp 240 °C (dec). IR (KBr): 3440, 2936, 1730, 1719, 1509, 1498, 1114, 1082, 1056, 820, 744 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 8.22 (d, 1H, H-1); 7.87 (d, 1H, H-4); 7.80 (d, 1H, H-5); 7.58 (dt, 1H, H-2); 7.49 (dt, 1H, H-3); 7.40 (d, 1H, H-6); 4.49 (dd, 1H, H-9); 4.46 (d, 1H, Ha-11); 4.40 (d, 1H, Hb-11); 3.49 (m, 1H, Ha-7); 3.19 (ddd, 1H, Hb-7); 2.67 (m, 1H, Ha-8); 1.80 (m, 1H, Hb-8); *J*(1,2) = 8.4, *J*(1.3) = 1.0, *J*(2,3) = 6.8, *J*(2,4) = 1.3, *J*(3,4) = 8.1, *J*(5,6) = 8.4, *J*(7a,7b) = 14.8, *J*(7a,8a) = 2.6, *J*(7a,8b) = 10.2, *J*(7b,8a) = 8.0, *J*(7b,8b) = 2.8, *J*(8a,9) = 7.2, *J*(8b,9) = 12.0, *J*(8a,8b) = 12.9, *J*(11a,11b) = 14.2 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.6 (C(10)); 140.2 (C(6a)); 135.3, 133.2 (C(4a), C(11b)); 130.2 (C(4)); 129.9 (C(5)); 129.0 (C(6)); 128.9 (C(11a));

128.3 (C(2)); 127.0 (C(3)); 124.8 (C(1)); 61.6 (C(9)); 41.6 (C(11)); 34.5 (C(8)); 34.0 (C(7)). HR-MS (ESI-Q-Tof) calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226; found: 226.1221.

13.8. 9-Amino-7,9,10,11-tetrahydro-cyclohepta[*a*]naphthalen-8-one, hydrochloride (1h′)

General procedure (i) with **12h′** (50 mg, 0.15 mmol) in Et_2O (2 mL) and 2 N HCl in Et_2O (1 mL) for 2 d to give **1h′** (30 mg, 77%).

Compound **1h′**: colorless crystals, mp 232 °C (dec.). IR (KBr): 3422, 2971, 2224, 1721, 1512, 1488, 1458, 818, 772, 737 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 8.22 (d, 1H, H-1); 7.89 (d, 1H, H-4); 7.79 (d, 1H, H-5); 7.58 (dt, 1H, H-2); 7.50 (dt, 1H, H-3); 7.39 (d, 1H, H-6); 4.34 (dd, 1H, H-9); 4.33 (d, 1H, Ha-7); 3.92 (d, 1H, Hb-7); 3.67 (ddd, 1H, Ha-11); 3.57 (ddd, 1H, Hb-11); 2.70 (m, 1H, Ha-10); 1.84 (m, 1H, Hb-10); *J*(1,2) = 8.5, *J*(1.3) = 1.2, *J*(2,3) = 6.8, *J*(2,4) = 1.4, *J*(3,4) = 8.0, *J*(5,6) = 8.4, *J*(7a,7b) = 15.4, *J*(9,10a) = 7.5, *J*(9,10b) = 11.6, *J*(10a,10b) = 12.6, *J*(10a,11a) = 9.5, *J*(10a,11b) = 3.5, *J*(10b,11a) = 3.6, *J*(10b,11b) = 7.8, *J*(11a,11b) = 15.2 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.8 (C(8)); 136.7 (C(6a)); 135.0, 132.6 (C(4a),C(11b)); 131.1 (C(11a)); 129.9 (C(4)); 129.0 (C(5)); 128.1 (C(6)); 127.9 (C(2)); 126.8 (C(3)); 124.0 (C(1)); 60.3 (C(9)); 48.4 (C(7)); 32.6 (C(10)); 23.9 (C(11)). HR-MS (ESI-Q-Tof) calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226; found: 226.1206.

14. Preparation of 12f,f′g by Suzuki coupling

General procedure (j) a mixture of bromocetoamide (1 mmol), phenylboronic acid (140 mg, 1.13 mmol, 1.1 equiv), CsF (0.34 g, 2.26 mmol, 2.2 equiv) and $Pd(PPh_3)_4$ (120 mg, 0.1 mmol) in dry 1,2-dimethoxyethane (DME, 12 mL) was stirred under Ar at 85 °C for 5 h. The reaction mixture was diluted with AcOEt, washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue purified by flash chromatography (cyclohexane/AcOEt 9/1).

General procedure (k) same procedure with K_2CO_3 (0.2 g, 1.5 mmol, 1.5 equiv) as base and in DME (12 mL) and H_2O (3 mL) as reaction solvent.

14.1. 7-*tert*-Butoxycarbonylamino-4-phenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (12f)

General procedure (j) with **12c** (90 mg, 0.256 mmol), phenylboronic acid (35 mg, 0.28 mmol), CsF (86 mg, 0.56 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) in DME (3 mL) was heated at 85 °C for 5 h. The work-up gave **12f′** (70 mg, 78%).

Compound **12f**: colorless crystals, mp 173–174 °C. IR (KBr): 3277, 2978, 1725, 1706, 1677, 1554, 1366, 1279, 1189, 1005, 762, 705 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.40 (m, 5 Har); 7.21 (m, 3 Har); 5.44 (d, 1H, NH); 4.55 (m, 1H, H-7); 3.80 (d, 1H, Ha-5); 3.71 (d, 1H, Hb-5); 3.06 (m, 1H, Ha-9); 2.97 (ddd, 1H, Hb-9); 2.67 (m, 1H, Ha-8); 1.54 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); *J*(5a,5b) = 15.0, *J*(NH,7) = 7.0, *J*(7,8a) = 7.2, *J*(7,8b) = 10.0, *J*(8a,8b) = 13.0, *J*(8a,9a) = 3.6, *J*(8a,9b) = 9.0, *J*(8b,9a) = 8.0, *J*(8b,9b) = 3.7, *J*(9a,9b) = 14.6 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.6 (C(6)); 155.1 (NCO_2); 142.7 (C(9a)); 140.9, 140.8 (3Car); 130.0 C(4a)); 130.0, 129.5, 128.6, 128.4, 127.4, 127.3 (6CHar); 79.8 (*C*Me_3); 60.8 (C(7)); 43.6 (C(5)); 34.7 (C(8)); 31.6 (C(9)); 28.5 (*CMe*$_3$). HR-MS (ESI-Q-Tof) calcd for $C_{22}H_{25}LiNO_3$ $[M+Li]^+$: 358.1989; found: 358.1899; $C_{22}H_{25}NaNO_3$ $[M+Na]^+$: 374.1727; found: 374.1635.

14.2. 7-*tert*-Butoxycarbonylamino-1-phenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (12f′)

General procedure (j) with **12c′** (90 mg, 0.26 mmol), phenylboronic acid (35 mg, 0.28 mmol), CsF (86 mg, 0.56 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol) in DME (3 mL) at 85 °C for 5 h. The work-up gave **12f′** (75 mg, 83%).

Compound **12f′**: colorless crystals, mp 187–188 °C. IR (KBr): 3348, 2981, 2931, 1720, 1682, 1524, 1365, 1295, 1253, 1171, 1052, 761, 705 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.38 (m, 3 Har); 7.27 (m, 2 Har); 7.20 (m, 2 Har); 5.41 (d, 1H, NH); 4.58 (dt, 1H, H-7); 3.95 (d, 1H, Ha-5); 3.72 (d, 1H, Hb-5); 2.85 (m, 2H, CH_2(9)); 2.53 (m, 1H, Ha-8); 1.46 (m, 1H, Hb-8); 1.42 (s, 9H, CMe_3); *J*(5a,5b) = 15.6, *J*(NH,7) = 7.2, *J*(7,8a) = 7.2, *J*(7,8b) = 11.2 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 205.7 (C(6)); 155.1 (NCO_2); 142.4, 141.4 (2 Car); 137.5 (C(9a)); 133.3 (C(4a)); 129.9, 129.4, 129.2, 128.3, 127.2, 126.8 (6CHar); 79.9 (*C*Me_3); 60.0 (C(7)); 48.5 (C(5)); 34.5 (C(8)); 28.5 (*CMe*$_3$); 26.3 (C(9)). HR-MS (ESI-Q-Tof): calcd for $C_{22}H_{25}NaNO_3$ $[M+Na]^+$: 374.1727; found: 374.1720.

14.3. 7-*tert*-Butoxycarbonylamino-1,4-diphenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (12g)

1. General procedure (k): A solution of **12e** (30 mg, 0.07 mmol), phenylboronic acid (34 mg, 0.28 mmol, 4 equiv), K_2CO_3 (38 mg, 0.28 mmol, 4 equiv) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol) in DME (2 mL) and H_2O (0.1 mL) were heated under Argon in a microwave heather (for 25 min at 300 W/125 °C/3 bar). The work-up gave **12g** (23 mg, 79%).

2. *General procedure (k)* with **12d** (100 mg, 0.23 mmol), phenylboronic acid (42 mg, 0.34 mmol, 1.5 equiv), K_2CO_3 (48 mg, 0.34 mmol) and $Pd(PPh_3)_4$ (26.5 mg, 0.023 mmol) in DME (3.3 mL) and H_2O (0.7 mL) for 3 h at 85 °C. The work-up gave **12g** (88 mg, 89%) after washing with iPr_2O.

Compound **12g:** colorless crystals, mp 192–196 °C (iPr_2O). IR (KBr): 3410, 2972, 2930, 1705, 1492, 1365, 1159, 705 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 1.42 (s, 9H, CMe_3); 1.51 (m, 1H, Hb-8); 2.57 (m, 1H, Ha-8); 2.91 (m, 2H, Hb-9, Ha-9); 3.75 (d, 1H, Hb-5); 3.89 (d, 1H, Ha-5); 4.6 (td, 1H, H-7); 5.43 (d, 1H, NH-7); 7.23 (s, 2H, H-2, H-3); 7.33–7.47 (m, 10 Har); *J*(5a,5b) = 16.4, *J*(7,NH) = 7.6, *J*(7,8a) = 7.6, *J*(7,8b) = 11.2, *J*(8a,8b) = 13.2 Hz. ^{13}C NMR ($CDCl_3$, 100 MHz): 26.7 (C(9)); 28.3 (*CMe*$_3$); 34.1 (C(8)); 44.0 (C(5)); 59.6 (C(7)); 79.6 (*C*Me_3); 127.1, 127.2 (2 CHar-p); 128.2 (2 CHar-m); 128.5 (C(3)); 129.0 (C(2)); 129.2, 129.8 (2 CHar-o); 130.7 (C(4a)); 137.8 (C(9a)); 140.8; 141.4; 141.8 (3 Car); 154.9 (NCO-7); 206.0 (CO(6)). HR-MS (ESI-Q-Tof): calcd for $C_{28}H_{29}NO_3$ $[M+Na]^+$: 450.2045; found: 450.2035.

15. Keto-amines 1f,f′,g

15.1. 7-Amino-4-phenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (1f)

General procedure (i) with **12f** (50 mg, 0.14 mmol) in dioxane (1 mL) and 2 N HCl in Et_2O (1 mL) for 48 h to give **1f** (30 mg, 73%).

Compound **1f:** colorless crystals, mp 255–260 °C (dec) (MeOH/Et_2O). IR (KBr): 3450, 2898, 2890, 2157, 1715, 1463, 1170, 763, 707 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz, 9:1 mixture with an hemiacetal). Ketone: 7.41 (m, 5Har); 7.28 (m, 2Har); 7.20 (dd, 1H, *J* = 3.1, 5.9 Hz, 1 Har); 4.39 (dd, 1H, H-7); 3.99 (d, 1H, Ha-5); 3.77 (d, 1H, Hb-5); 3.32 (m, 1H, Ha-9)); 3.13 (ddd, 1H, Hb-9)); 2.60 (m, 1H, Ha-8); 1.76 (m, 1H, Hb-8); *J*(5a,5b) = 13.8, *J*(7,8a) = 7.0, *J*(7,8b) = 12.0, *J*(8a,8b) = 12.6, *J*(8a,9a) = 2.8, *J*(8a,9b) = 8.1, *J*(8b,9a) = 10.0, *J*(8b,9b) = 3.1, *J*(9a,9b) = 15.0 Hz. Hemi-acetal, partial data: ca. 1.75 (m, 1H, Hb-8); 2.06 (m, 1H, Ha-8); 2.96 (m, 2H, CH_2(9)). ^{13}C NMR (CD_3OD, 100 MHz): 202.9 (CO(6)); 144.1 (C(9a)); 142.1 (2Car); 131.0, 130.7 (2 CHar); 130.6 (C(4a)); 129.8, 129.3 128.7, 128.4 (4CHar); 61.3 (C(7)); 43.3 (C(5)); 33.1 (C(8)); 31.6 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1383; found: 252.1366.

15.2. 7-Amino-1-phenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (1f′)

General procedure (i) with **12f′** (35 mg, 0.1 mmol) in dioxane (1 mL) and 2 N HCl in Et_2O (1 mL) for 48 h to give **1f′** (22 mg, 76%).

Compound **1f′**: colorless crystals, mp >250 °C (MeOH/Et_2O). IR (KBr): 3422, 2966, 1722, 1484, 1459, 762, 704 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 7.43 (m, 3Har); 7.28 (m, 4Har); 7.21 (m, 1Har); 4.35 (dd, 1H, H-7); 4.22 (d, 1H, Ha-5); 3.77 (d, 1H, Hb-5); 3.06 (m, 1H, Ha-9); 3.02 (m, 1H, Hb-9); 2.40 (m, 1H, Ha-8); 1.70 (m, 1H, Hb-8); J(5a,5b) = 14.7, J(7,8a) = 7.2, J(7,8b) = 11.8, J(8a,8b) = 13.2, J(8a,9a) = ca. 8.2, J(8a,9b) = ca. 4.2, J(8b,9a) = ca. 4.2, J(8b,9b) = ca. 7.6, J(9a,9b) = 15.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 202.7 (CO(6)); 143.8, 142.6 (2Car); 138.3 (C(9a)); 134.2 (C(4a)); 130.8, 130.2, 130.2 129.4, 128.4 128.2 (6CHar); 60.5 (C(7)); 48.3 (C(5)); 32.7 (C(8)); 26.4 (C(9)). HR-MS (ESI-Q-Tof) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1383; found: 252.1363.

15.3. 7-Amino-1,4-diphenyl-5,7,8,9-tetrahydro-benzocyclohepten-6-one (1g)

General procedure (i) with **12g** (30 mg, 0.07 mmol) in 4 N HCl in Et_2O (1 mL) and dioxane (1 mL) for 16 h to give **1g** (23 mg, 88%).

Compound **1g**: colorless crystals, mp >200 °C. IR (KBr): 3408, 2923, 2867, 1725, 1509, 1467, 762, 702 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): 1.77 (m, 1H, Hb-8); 2.44 (m, 1H, Ha-8); 3.07 (ddd, 1H, Hb-9); 3.14 (ddd, 1H, Ha-9); 3.85 (d, 1H, Hb-5); 4.04 (d, 1H, Ha-5); 4.38 (dd, 1H, H-7); 7.25 (s, 2H, H-2,H-3); 7.32 (d, 2Har-o); 7.39–7.49 (m, 8Har); J(5a,5b) = 14.8, J(7,8a) = 7.2, J(7,8b) = 12.0, J(8a,8b) = 12.4, J(8a,9a) = 8.8, J(8a,9b) = 4.0, J(8b,9a) = 4.0, J(8b,9b) = 8.0, J(9a,9b) = 15.0 Hz. ^{13}C NMR (CD_3OD, 100 MHz): 26.9 (C(9)); 32.4 (C(8)); 43.8 (C(5)); 60.6 (C(7)); 128.4, 128.5 (2CHar-p); 129.4, 129.5 (2CHar-m); 129.9 (C(3)); 130.2 (C(2), CHar-o); 130.9 (CHar-o); 131.6 (C(4a)); 139 (C(9a)); 142.2, 142.7, 143.1, 143.4 (4CHar); 203.1 (C(6)).

HR-MS (ESI-Q-Tof) calcd for $C_{23}H_{22}NO$ $[M+H]^+$: 328.1701; found: 328.1656.

16. Enzyme assays

16.1. Enzyme source

Porcine kidney APN and *Aeromonas proteolitica* aminopeptidase were purchased from Sigma Chemical Co. Porcine kidney LAPc was purified according to a published procedure.[26] Human recombinant LTA_4H was provided by our collaborator J. Z. Haeggström.[25c]

16.2. Assay conditions[25c]

(a) All enzymes: Kinetic data were collected with an HP/Agilent UV–Visible, diode array, spectrophotometer 8453 using the software 'HP chemstation' provided with the machine. Typically, spectrophotometric assays were performed with L-leucine-*p*-nitroanilide as the substrate for APN (K_m = 0.2 mM), LAPc (K_m = 2 mM) and APaero (K_m = 0.02 mM). All kinetic studies were performed at 30 °C and the reactions were started by addition of the enzyme in 1 ml assay medium. (b) APN: 1 mUnits per assay, in 0.02 M Tris·HCl pH 7.5. (c) LAPc: 20 Units per assay in 0.1 M Tris·HCl, 0.1 mM $ZnCl_2$, 5 mM $MnCl_2$, 1 M KCl, pH 8.0 and (d) APaero 2 mUnits per assays in 0.05 M Tris·HCl pH 7.5.

The release of p-nitroanilide (ε = 10,800 M^{-1} cm^{-1}) at 405 nm was measured continuously during 30 min to determine initial velocities. Assays were performed in semi microcuvettes (1 cm path). K_i were determined using Dixon plots.[34]

For the specific evaluation of compound **1d′**, the concentration of APN used in the assay was decreased to 0.1 mUnits (12 pM) per assay and the linear reaction was monitored during at least 5–6 h in order to measure significant velocities. The K_i value was also determined from a Dixon plot.

Acknowledgments

The support of the *École Nationale Supérieure de Chimie de Mulhouse* and the *Université de Haute-Alsace* is gratefully acknowledged. We also wish to thank the *Ligue contre le Cancer* for financial support. We thank Professor Patrick Pale for his scientific and material assistance, Dr. Cécile Joyeux for the HR-MS measurements and the students Azely Mirre, Julien Debray, Arnaud Mignatelli and Meral Ilhan for their participation to this work.

References and notes

1. Barret, A. J.; Rawling, N. D.; Woessner, J. F., 2nd ed. In *Handbook of Proteolytic Enzymes*; Elsevier Academic Press: Oxford, 2004; Vol. 2, p 233sq.
2. Mina-Osorio, P. *Trends Mol. Med.* **2008**, *14*, 361.
3. (a) Bhagwat, S. V.; Lahdenranta, J.; Giordano, R.; Arap, W.; Pasqualini, R. *Blood* **2001**, *97*, 652; (b) Bhagwat, S. V.; Petrovic, N.; Okamoto, Y.; Shapiro, L. H. *Blood* **2003**, *101*, 1818; (c) Petrovic, N.; Schacke, W.; Gahagan, J. R.; O'Conor, C. A.; Winnicka, B.; Conway, R. E.; Mina-Osorio, P.; Shapiro, L. H. *Blood* **2007**, *110*, 142.
4. (a) Terauchi, M.; Kajiyama, H.; Shibata, K.; Ino, K.; Nawa, A.; Mizutani, S.; Kikkawa, F. *BMC Cancer* **2007**, *7*, 140; (b) Langner, J.; Mueller, C.; Riemann, D.; Löhn, M. *Immunol. Lett.* **1997**, *56*, 62.
5. (a) Yamashita, M.; Kajiyama, H.; Terauchi, M.; Shibata, K.; Ino, K.; Nawa, A.; Mizutani, S.; Kikkawa, F. *Int. J. Cancer* **2007**, *120*, 2243; (b) Fukasawa, K.; Fujii, H.; Saitoh, Y.; Koizumi, K.; Aozuka, Y.; Sekine, K.; Yamada, M.; Saiki, I.; Nishikawa, K. *Cancer Lett.* **2006**, *243*, 135.
6. Rangel, R.; Sun, Y.; Guzman-Rojas, L.; Ozawa, M. G.; Sun, J.; Giordano, R. J.; Van Pelt, C. S.; Tinkey, P. T.; Behringer, R. R.; Sidman, R. L.; Arap, W.; Pasqualini, R. *Proc. Natl. Acad. Sci.* **2007**, *104*, 4588.
7. (a) Riemann, D.; Kehlen, A.; Langner, J. *Immunol. Today* **1999**, *20*, 83; (b) Bank, U.; Heimburg, A.; Helmuth, M.; Stefin, S.; Lendeckel, U.; Reinhold, D.; Faust, J.; Fuchs, P.; Sens, B.; Neubert, K.; Täger, M.; Ansorge, S. *Int. Immunopharmacol.* **2006**, *6*, 1925; (c) Matteo, P. D.; Arrigoni, G. L.; Alberici, L.; Corti, A.; Gallo-Stampino, C.; Traversari, C.; Doglioni, C.; Rizzardi, G.-P. *J. Histochem. Cytochem.* **2011**, *59*, 47.
8. Reinhold, D.; Biton, A.; Pieper, S.; Lendeckel, U.; Faust, J.; Neubert, K.; Bank, U.; Täger, M.; Ansorge, S.; Brocke, S. *Int. Immunopharmacol.* **2006**, *6*, 1935.
9. (a) Mucha, A.; Drąg, M.; Dalton, J. P.; Kafarski, P. *Biochimie* **2010**, *92*, 1509; (b) Bauvois, B.; Dauzonne, D. *Med. Chem. Rev.* **2006**, *26*, 88.
10. Jacobsen, F. E.; Lewis, J. A.; Cohen, S. M. *Chem. Med. Chem.* **2007**, *2*, 152.
11. Albrecht, S.; Al-Lakkis-Wehbe, M.; Orsini, A.; Defoin, A.; Pale, P.; Salomon, E.; Tarnus, C.; Weibel, J.-M. *Bioorg. Med. Chem.* **2011**, *19*, 1434.
12. Hopkins, A. L.; Groom, C. R.; Alex, A. *Drug Discovery Today* **2004**, *9*, 430.
13. Matsui, M.; Fowler, J. H.; Walling, L. L. *Biol. Chem.* **2006**, *387*, 1535.
14. Barret, A. J.; Rawling, N. D.; Woessner, J. F., 2nd ed. In *Handbook of Proteolytic Enzymes*; Elsevier Academic Press: Oxford, 2004; Vol. 2, p 253 sq.
15. Lai, Y.-H.; Yap, A. H.-T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1373.
16. Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405.
17. Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Nakamura, H.; Fujikawa, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4187.
18. Simchen, G.; Kober, W. *Synthesis* **1976**, 259.
19. Taniguchi, Y.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *154*, 3229.
20. (a) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427; (b) Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.
21. Miriyala, B.; Bhattacharyya, S.; Williamson, J. *Tetrahedron* **2004**, *60*, 1463.
22. (a) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141; (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. www.SyntheticPages.org/pages/51.
23. Auffinger, P.; Hays, F. A.; Westhof, E.; Shing, H. P. *Proc. Natl. Acad. Sci.* **2004**, *101*, 16789.
24. Harnandes, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; de Azevedo, W. F., Jr.; Leite, A. C. L. *Curr. Drug Targets* **2010**, *11*, 303.
25. (a) Schalk, C.; d'Orchymont, H.; Jauch, M.-F.; Tarnus, C. *Arch. Biochem. Biophys.* **1994**, *311*, 42; (b) d'Orchymont, H.; Tarnus, C. Eur. Patent 0378456 A1, 1990.; (c) Albrecht, S.; Defoin, A.; Salomon, E.; Tarnus, C.; Wetterholm, A.; Haeggström, J. Z. *Bioorg. Med. Chem.* **2006**, *14*, 7241.
26. Himmelhoch, R.; Peterson, S. A. *Biochemistry* **1968**, *7*, 2085.
27. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3.
28. Skinner-Adams, T. S.; Stack, C. M.; Trenholme, K. R.; Brown, C. L.; Grembecka, J.; Lowther, J.; Mucha, A.; Drąg, M.; Kafarski, P.; McGowan, S.; Whisstock, J. C.; Gardiner, D. L.; Dalton, J. P. *Trends Biochem. Sci.* **2010**, *35*, 53.
29. Dey, A. S.; Rosowsky, A.; Modest, E. J. *J. Org. Chem.* **1970**, *35*, 536.

30. (a) McCauley, J. A.; McIntyre, C. J.; Rudd, M. T.; Nguyen, K. T.; Romano, J. J.; Butcher, J. W.; Gilbert, K. F.; Bush, K. J.; Holloway, M. K.; Swestock, J.; Wan, B.-L.; Carroll, S. S.; DiMuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Mao, S.-S.; Stahlhut, M. W.; Fandozzi, C. M.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *J. Med. Chem.* **2010**, *53*, 2443; (b) Tsue, H.; Nakashima, S.; Goto, Y.; Tatemitsu, H.; Misumi, S.; Abraham, R. J.; Asahi, T.; Tanaka, Y.; Okada, T.; Mataga, N.; Sakata, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3067.
31. Wu, A.; Chakraborty, A.; Witt, D.; Lagona, J.; Damkaci, F.; Ofori, M. A.; Chiles, J. K.; Fettinger, J. C.; Isaacs, L. *J. Org. Chem.* **2002**, *67*, 5817.
32. Ried, W.; Bodem, H. *Liebigs Ann. Chem.* **1954**, *589*, 55.
33. Ohkawa, S.; DiGiacomo, B.; Larson, D. L.; Takemori, A. E.; Portoghese, P. S. *J. Med. Chem.* **1997**, *40*, 1720.
34. Segel, I. H. *Enzyme Kinetics*; John Wiley & Son: New-York, 1993.