Studies concerning the electrophilic amino-alkene cyclisation for the synthesis of bicyclic amines†

Johannes E. M. N. Klein, Helge Müller-Bunz and Paul Evans*

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The bromination of a series of cyclohexenyl substituted secondary amines **1a-i** has been investigated using Br_2, PHT and NBS. In the case of Br_2 and NBS the secondary amines preferentially undergo *N*-bromination. In contrast, PHT cleanly affords the products of alkene dibromination. In the case of Br_2 the *N*-bromo species then give the products of alkene dibromination, albeit less efficiently. On subsequent treatment with K_2CO_3 these dibromides form the corresponding hexahydroindoles **2a-h** and octahydroquinoline **2i**. The presence of an *N*-substituent bearing a stereogenic centre (**1h** and **1i**) was studied and the products **2h** and **2i** were isolated with no diastereoselectivity. When NBS was used a novel cyclisation, forming bromo-substituted octahydroindoles **9a,b** and **d**, was observed. In relation to this sequence it was shown that these products were not intermediates in the former Br_2/PHT processes and that the reaction only proceeded in the presence of the succinimide by-product of *N*-bromination.

Introduction

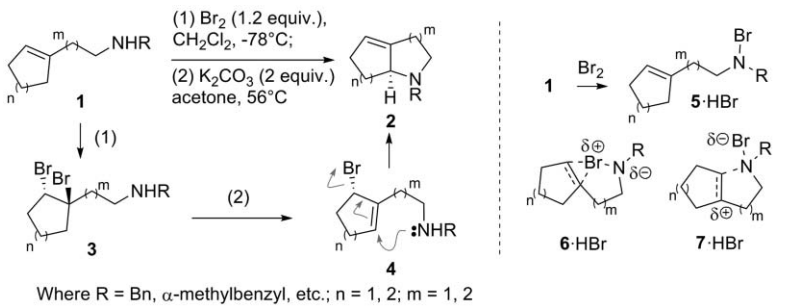
There have been several recent reports concerning the reaction of amines with alkenes not possessing electron-withdrawing groups in the presence of various catalysts and mediators. In these examples alkene functionalisation affords alkyl amino compounds.[1] However, arguably a more synthetically useful reaction is the halo-amino functionalisation of alkenes since in this instance both alkenyl carbon atoms become functionalised, thereby enabling further derivatisation. Several examples of this class of reaction have been reported using various substrates and halogen sources.[2] In relation to this general reaction type an efficient sequence caught our attention in which the cyclic alkene **1** undergoes a 2-step intramolecular conversion into **2** following its initial reaction with acid washed bromine and subsequent treatment with K_2CO_3 (Scheme 1).[3] The authors speculate that this transformation proceeds *via* initial alkene dibromination followed by a regioselective base mediated elimination and S_N2' cyclisation sequence[4] affording the products **2** of formal C–H activation.‡

Mechanistically, although this seems reasonable, it does not adequately account for the reported observation that when R represents α-methylbenzyl the bicyclic product **2** is isolated in high diastereomeric excess (>95% d.e).[3] Since the stereogenic centre is, in this instance, remote from the double bond it would appear remarkable that this group would dictate and control the stereofacial sense of the intermolecular bromonium ion formation required for the generation of **2** as a single diastereoisomer. One possible alternative mechanistic explanation for this reported diastereocontrol is that the secondary amine is directly involved in the activation of the trisubstituted alkene by initial *N*-bromination to form **5**. In turn it may be speculated that this *N*-bromo species **5** might react with the alkene in an intramolecular sense *via* a polar transition state of the type **6** or **7**. In relation to this suggestion numerous examples do exist concerning the formation of *N*-halo

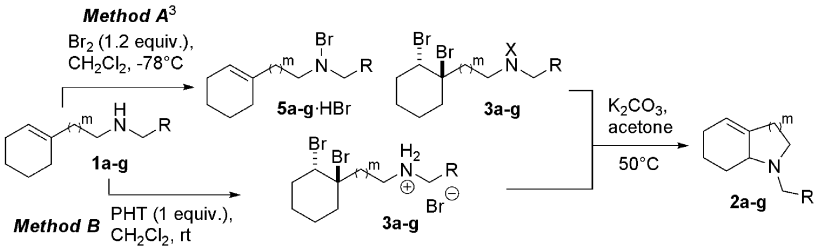
Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland. E-mail: paul.evans@ucd.ie

† Electronic supplementary information (ESI) available: General procedures for the preparation of secondary amines **1a–1f**, procedures for the synthesis of amines **1g–1i**, experimental details for the X-ray crystallography and X-ray structures of compounds **2a**, **1b**·HBr and **S6**. CCDC reference numbers 707945–707951. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b819610a

‡ Substituted cyclopentenyl and cyclohexenyl systems were not employed in this study, consequently it is not possible to state unequivocally whether this process is S_N2' rather than S_N2, although the pathway followed is crucial since the different modes of substitution lead to diastereoisomeric products when R contains a stereogenic centre.[4] The direct S_N2 displacement of **3** appears to be precluded based on stereoelectronic arguments.



Scheme 1 The bromo-amino cyclisation of alkenyl secondary amines **1**.



				Method A	Method B
Entry	Compound	R	m	Br_2	PHT
1	**2a**	Ph	1	61%	85%
2	**2b**	4-$MeOC_6H_4$	1	53%	88%
3	**2c**	2-$MeOC_6H_4$	1	-	88%
4	**2d**	(2,4,6-$Me)_3C_6H_2$	1	-	85%
5	**2e**	2-Br-(4,5-$MeO)_2C_6H_2$	1	63%	77%
6	**2f**	2-Furyl	1	65%[3a]	74%
7	**2g**	Ph	2	-	62%

Scheme 2 Synthesis of hexahydroindoles **2a–g** (X = Br, or H).

compounds from electron rich amines.[5–8] Typically such species possess limited stability and their reactivity and stability has been investigated both from a theoretical and practical standpoint. For example, their treatment with base leads to dehydrohalogenation and formation of an imine.[5] A synthetic application of this sequence has been used in order to achieve α-amino functionalisation as applied to the synthesis of perhydrohistrionicotoxin.[6] Additionally, several reports indicate that this general class of compound may effectively act as halogenating agents (*i.e.* **6**)[7] and the possibility that **5** might, alternatively, act as an electrophilic source of nitrogen was also considered.[8] Examples involving the bromination, or chlorination of double bonds in the presence of basic amino functionality (*i.e.* non-protected) are scarce.[9]

Results and discussion

Intrigued by the possibility that the functionalisation of this type of alkene (Scheme 1) might proceed *via* initial *N*-bromination followed by intramolecular bromonium ion formation (**6**), or direct cyclisation (**7**) our first approaches focussed on the use of the *N*-benzylamine derivative **1a** § following the previously described procedure.[3] Exposure of **1a** to Br_2 (1.2 equiv.) at −78 °C for 0.5 hours in dichloromethane, followed by treatment of the material thus obtained with K_2CO_3 (3 equiv.) in acetone at 50 °C, gave *N*-benzyl hexahydroindole **2a** reproducibly in 50–61% yield (see Scheme 2, Entry 1, Method A).

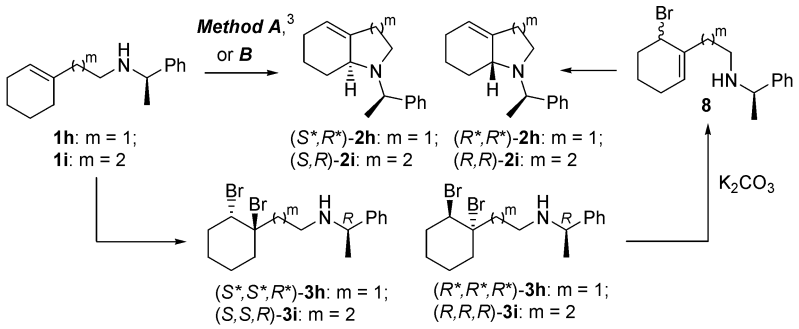
Although the desired product **2a** was obtained, several experimental observations gave further insight into the possible pathway of this reaction. Crude proton NMR spectroscopy after the initial treatment of **1a** with 1.0 equivalent of bromine ($CDCl_3$, rt, after 5 minutes) indicated significant preservation of the double bond (*ca.* 50%), which was attributed to the competitive formation of an *N*-bromoammonium compound of type **5a** (see also Scheme 5).¶ Furthermore, the formation of benzaldehyde was observed, also indicating a pathway involving *N*-bromination followed by elimination and subsequent hydrolysis of the so-formed imine. Although this evidence combined to suggest that mechanisms involving species such as **6** or **7** may indeed operate, another possibility is that the *N*-bromo species **5** releases molecular bromine, which over time leads to the formation of the dibromide (of the type **3**). Additional secondary amines **1b** (Entry 2, Method A), **1e** (Entry 5, Method A) provided the corresponding hexahydroindoles **2b** and **2e** in similarly reasonable yields following their respective treatment with bromine and subsequently K_2CO_3.

While the use of a conventional protecting group to obviate the apparently rapid *N*-halogenation pathway and achieve clean bromination would only serve to add steps to a synthesis, the use of hydrotribromide was attempted. In this instance it was felt that protonation (*i.e.* temporary protection) of the amine would effectively prevent *N*-bromination, ultimately leading to a cleaner process.[10] Additionally, ammonium ion formation would preclude the direct intermediacy of *N*-bromo species **5** in the reaction mechanism. In the presence of the commercially available pyrrolidone hydrotribromide (PHT)[11] smooth alkenyl dibromination could be carried out at room temperature in dichloromethane. For example, **1a** was converted into the dibromoammonium species **3a** (as its HBr salt), which was characterised by NMR spectroscopy and mass spectrometry. The dibromide **3a** was then successfully subjected to the second cyclisation step as before. Thus, **2a** was isolated following purification by flash column chromatography in 85% yield (Scheme 2, Entry 1). Notably, following this modified reaction procedure (Method B) significantly cleaner reactions were observed for all the secondary amine substrates studied (**1b–g**) and the hexahydroindole adducts (**2b–g**) were isolated in consistently higher yields than the sequence effected using molecular bromine (Method A). In the case of **2f**, no products of electrophilic aromatic substitution were detected.

With this information in hand we then investigated the diastereoselective cyclisation of α-methylbenzylamine containing substrates (±)-**1h** and (+)-**1i** (Scheme 3).§ In both cases, using either molecular bromine or the modified PHT conditions, the

§ For the synthesis of secondary amines **1a–g** and the X-ray crystallographic structure of **2a** see ESI.†

¶ Treatment of **1a** with 0.5 equiv., 1 equiv. and 2 equiv. of Br_2 indicated that complete alkenyl bromination only occurred using 2 equivalents of Br_2, while the use of sub-stoichiometric or stoichiometric amounts resulted in selective, initial *N*-bromination leading to **5a**. Evidence for this was indicated by a significant shift of the benzylic proton signal observed by NMR spectroscopy. Compound **5a** was also prepared using NBS and although it proved to be unstable, proton NMR spectra were comparable (Scheme 5).



Entry	Substrate	m	*Method*	Isolated yield	d.r
1	(±)-**1h**	1	***A***	51%	1:1
2	(±)-**1h**	1	***B***	67%	1:1
3	(+)-**1i**	2	***A***	24% 21%	1:1
4	(+)-**1i**	2	***B***	32% 33%	1:1

Method A: (a) Br_2 (1.2 equiv.), CH_2Cl_2, -78ºC, 20 min.; then (b) K_2CO_3 (3 equiv.), acetone, 50ºC, 5-8 days;
Method B: (a) PHT (1 equiv.), CH_2Cl_2, rt, 15 min.; then (b) K_2CO_3 (3 equiv.), acetone, 50ºC, 5-8 days;

Scheme 3 Investigation of diastereoselective approaches to hexahydroindole **2h** and octahydroquinoline **2i**.

corresponding hexahydroindole **2h** and octahydroquinoline **2i** were formed in moderate to good yield. However, using either Br_2 or PHT it was immediately evident from inspection of the crude proton NMR spectra that these reactions *did not* proceed in a diastereoselective fashion. Furthermore, in both cases, using either reaction conditions, formation of an approximately 1:1 mixture of diastereoisomers was evident. In the case of the racemic hexahydroindole **2h**, in our hands, the diastereoisomers proved only partially separable by flash column chromatography. The slightly faster moving diastereoisomer was separated in a small amount and its spectroscopic data proved equivalent to that reported.[3a] This material crystallised as its HCl salt and an X-ray structure was obtained, thereby demonstrating its relative stereochemistry (Fig. 1).[12] Using Br_2 (2.2 equiv.) the identity of the intermediate dibromide **3h** was subsequently investigated. Crucially, 2.2 equivalents of Br_2 were required for complete conversion and after work-up we assume that degradation of any *N*-bromo species occurs (see also above and the footnote¶). Although the proton NMR spectrum was not helpful, splitting, attributed to the presence of two diastereomeric species (*S*,S*,R**)-**3h** and (*R*,R*,R**)-**3h**, was detected in the carbon NMR spectrum. The homologated α-methylbenzylamine (+)-**1i** was also prepared for comparison and although the cyclisation proved to be slower than in the previous case, octahydroquinoline **2i** successfully formed as a mixture of two diastereoisomers.

In this instance the diastereoisomers proved to be readily separable by flash column chromatography enabling their complete spectroscopic characterisation in this enantiopure series. The slower moving diastereoisomer proved to be crystalline as its HCl salt (Fig. 1) and the relative stereochemistry of both diastereoisomers was thus deduced.[13] As observed for **2h**, spectroscopic data for the faster moving diastereoisomer (*R,R*)-**2i** matched that reported previously.[3a]

Clearly based on these results no difference in diastereoselectivity was observed between the different methods for bromination, which serves to suggest that, in our hands at least, this reaction does not proceed *via* the type of discrete intramolecular intermediate proposed in Scheme 1, which might be able to

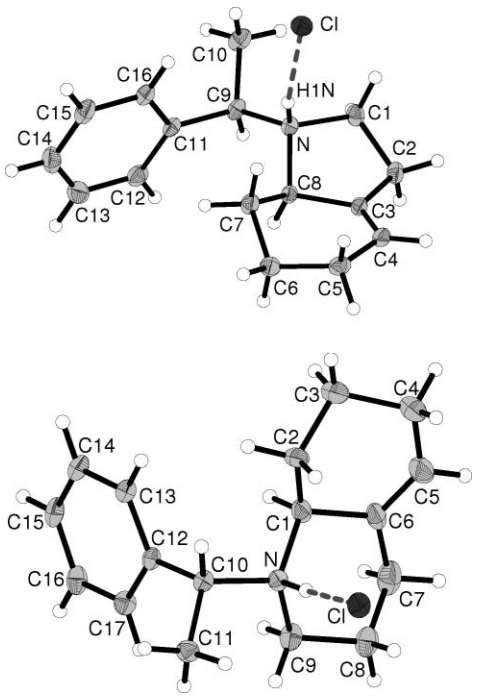
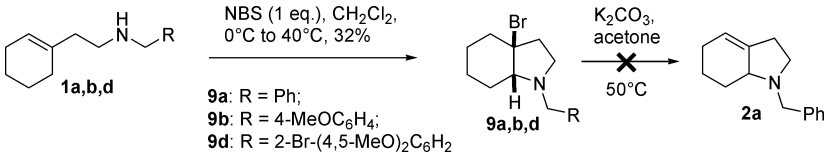


Fig. 1 X-ray crystallographic structures of (*R*,R**)-**2h**·HCl[12] and (*S,R*)-**2i**·HCl[13] (thermal ellipsoids drawn at the 15% probability level). Note that for **2h**·HCl the co-crystallised H_2O is not shown for clarity.

efficiently relay stereochemical information from the chiral centre attached to the amine to the alkene. It seems likely, therefore, that the diastereomeric mixture of dibromides **3h** and **3i** generate a diastereomeric mixture of **8** which then undergoes cyclisation to **2h** and **2i**. Evidence for the intermediacy of **8** was observed on storage of the intermediate dibromide **3h** in $CDCl_3$; within 48 hours a characteristic alkenyl signal in its ^{1}H-NMR spectrum developed, which was assigned to allylic bromide **8** (5.70 ppm).

Nevertheless, we decided to further investigate the formation of *N*-bromoamino species of the type **5** and attempted to study the reaction and hoped for cyclisation of benzylamine **1a** using



Scheme 4 NBS mediated cyclisation of cyclohexenyl amines **1a**, **1b** and **1d**.

N-bromosuccinimide (NBS). Potentially the type of tertiary amine product **9** of this reaction might be formed according to hypothetical transition states **6**, or **7** (Scheme 1). Regioselective base mediated elimination of such a species might then be expected to generate the final unsaturated products **2**. Treatment of **1a** with 1 equivalent of NBS in dichloromethane resulted in the rapid consumption of the starting material and the formation of a significantly less-polar compound. If the reaction period was prolonged and the temperature raised to 40 °C the bicyclic adduct **9a** was indeed obtained (32%) following purification by flash column chromatography (Scheme 4). Identical results were observed for alternative starting materials **1b** and **1d**. Even though the yields for this process were low the adducts formed as single diastereoisomers and the relative stereochemistry was elucidated by X-ray crystallography after formation of **9a**·HCl (Fig. 2).[14]

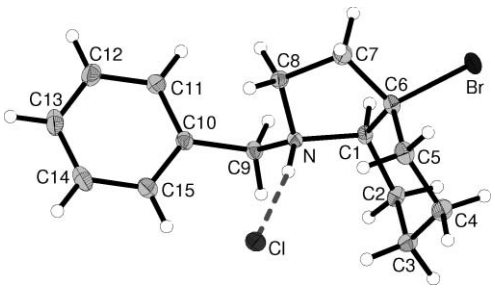
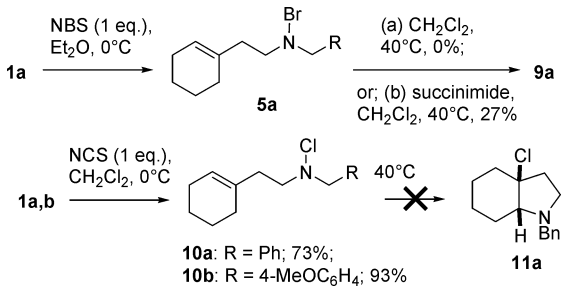


Fig. 2 X-ray crystallographic structure of **9a**·HCl (thermal ellipsoids drawn at the 50% probability level).[14]

Although the X-ray structure of **9a** indicated that the only anti-periplanar hydrogen–bromine relationship would give rise to **2a**, treatment with K_2CO_3 in acetone at 50 °C (comparable to the second step in the conversion of **1** to **2**) did not lead to elimination, which served to indicate that **9** cannot be a direct intermediate in this cyclisation process.

During attempts to further optimise this reaction we realised that on altering the solvent from dichloromethane to diethyl ether cyclisation was not observed. The sole product from this reaction was the *N*-bromo compound **5a** that could be isolated on filtration (Scheme 5). However, this species proved to be only moderately stable and over time underwent decomposition forming the hydrobromide salt of **1a**. When **5a** was prepared using 1.2 equivalents of bromine, limited stability was also observed (see discussion above).

Generally, **9a,b** and **d** proved to be stable enough to enable characterisation but, in the amino form, were found to decompose over time. We finally attempted to investigate the corresponding cyclisation using **1h**, hoping to observe a stereoselective process. However, in this instance we believe that, again, a mixture of adducts was formed in low yield although complete characterisation proved not to be possible since one of these diastereoisomers proved to decompose to several unidentified products.



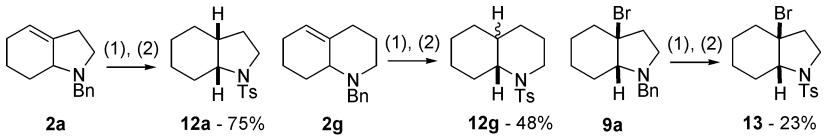
Scheme 5 Selective *N*-halogenation of amino alkenes **1a** and **1b**.

Since these results suggested the involvement of an *N*-bromo species in the formation of **9** we attempted the cyclisation of *N*-bromo compound **5a** (after the removal of succinimide) under reflux conditions as before. This, however, did not lead to formation of the cyclised product. In contrast, when **5a** was prepared in diethyl ether and the solvent was changed to dichloromethane without the prior removal of succinimide by filtration, cyclisation to **9a** was observed in comparable yield (27%). This observation serves to suggest that either, under these conditions NBS is reformed reversibly, or that protonation[15] of the *N*-bromo species **5a** is a crucial process in the intramolecular formation of **9a**.

The corresponding *N*-chloro species proved to be more stable than their bromine counterparts and **10a** and **10b** were isolated in good yield and fully characterised spectroscopically. Contrasting reactivity was also observed for **10a**; this species did not form bicycle **11a** under conditions identical to those that proved successful for the bromide **9a**. Instead **10a** was recovered unchanged, an observation that again reflects the enhanced stability of the *N*-chloro series.

N-Benzyl bicyclic adducts **2a** and **2g** were subjected to standard catalytic hydrogenation under acidic conditions, leading to both debenzylation and hydrogenation of the double bond. The secondary amino compounds were then converted into their toluene sulfonamides **12a** and **12g** to simplify purification (Scheme 6). A drastic difference was observed in terms of the diastereoselectivity for the alkenyl reduction process: whilst **2a** gave **12a** as a single diastereoisomer **2g** gave **12g** as a mixture of diastereoisomers (*ca.* 1:1).[16]

The relative stereochemistry of **12a** was uncovered by X-ray crystallography (Fig. 3)[17] which provides relevant information for previous studies concerning this compound in which the relative stereochemistry was not definitively assigned.[18] Similarly, the hydrogenation of **9a** was investigated in order to remove the benzyl group and although this process proceeded in only low yield (23%) the expected product **13** was obtained with the tertiary bromide intact.



Cond. (1) Pd/C, H_2 (1 atm.), AcOH; (2) TsCl, Et_3N (or K_2CO_3), CH_2Cl_2

Scheme 6 Debenzylation of bicycles **2a**, **2g** and **9a**.

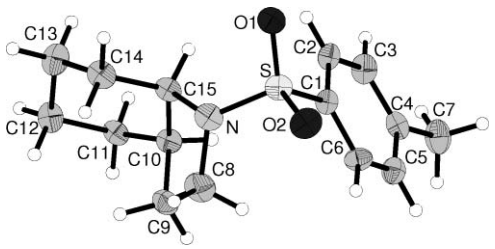


Fig. 3 X-ray crystallographic structure of **12a** (thermal ellipsoids drawn at the 50% probability level).[17]

Conclusion

In summary, while the results discussed served to demonstrate that the amino alkenes employed in this study show a strong tendency to form *N*-halo species more rapidly than reaction at the alkene (when treated with Br_2 or NBS), we cannot confirm the direct involvement of such species in the cyclisation step leading to hexahydroindoles. As such it seems that this *N*-halogenation process may be viewed as a side reaction rather than a productive element of the overall reaction pathway. The diastereoselective formation of hexahydroindoles and octahydroquinolines has been investigated following the claim that high diastereoselectivity may be achieved.[3] However, using an α-methylbenzyl substituent as a directing group we were unable to reproduce the reported results, suggesting that this work should be viewed with caution. In relation to this sequence we have demonstrated that PHT may be used to brominate a double bond in the presence of an amine featuring temporary protection through protonation, and in doing so have improved the overall yield for the aminocyclisation procedure. Finally, differences in the diastereoselectivity of the catalytic hydrogenation of hexahydroindoles and octahydroquinolines were noticed.

Experimental

Reactions with anhydrous solvents were carried out under an atmosphere of N_2. Glassware was either dried in an oven or by heat-gun before use, assembled hot and cooled to room temperature under a stream of N_2. Anhydrous dichloromethane (CH_2Cl_2) was distilled from CaH_2 prior to use. Reagents were purchased from Acros, or Aldrich, and used without further purification. Thin layer chromatography (TLC) was carried out on Merck silica gel aluminum sheets (60 F254). UV light and a $KMnO_4$ solution were used as visualising agents. Merck silica gel (60 Å, 0.040–0.063 mm) was used for flash column chromatography. Proton NMR spectra were recorded on a Varian 300 MHz, 400 MHz, 500 MHz or 600 MHz spectrometer and calibrated using the residual non-deuterated solvent signal. IR spectra were recorded on a Varian 3100 FT-IR spectrometer. High Resolution Mass Spectra (HRMS) were recorded using a Waters Corp, Micromass LCT, Electrospray Ionization (ESI) spectrometer. Melting points were determined in an open capillary on a Gallenkamp melting point apparatus and are uncorrected. The amine-hydrochloride salts were prepared as follows: the amine was dissolved in Et_2O/pentane (*ca.* 25 mg/ml) and HCl gas (generated from solid NH_4Cl by dropwise addition of conc. H_2SO_4) was bubbled through the solution *via* a Teflon cannula. The resultant precipitate was filtered, dried under vacuum and the hydrochloride salts were recrystallised from a suitable solvent. For the syntheses of secondary amines **1a-i** see ESI.†

General procedure for the amino cyclisation using molecular bromine, Method A[3a,b]

The appropriate secondary amine was dissolved in anhydrous dichloromethane (10 ml/mmol) under an atmosphere of N_2. The solution was cooled to −78 °C before Br_2 (1.2 equiv.) was added as a solution in anhydrous dichloromethane (1 ml/mmol) over a period of 15 min. The solution was stirred for a further 15 min at low temperature. Solvent was removed under reduced pressure and the residue suspended in acetone (10 ml/mmol) and K_2CO_3 (3 equiv.) was added. The suspension was heated to 50 °C for 72 h before the solvent was removed under reduced pressure and the residue partitioned between H_2O (10 ml/mmol) and dichloromethane (20 ml/mmol). The aqueous layer was further extracted with dichloromethane (2 × 10 ml/mmol) and the combined organic extracts dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure and the crude products were purified by column chromatography as indicated below.

General procedure for the amino cyclisation using pyrrolidone hydrotribromide, (PHT), Method B

The secondary amine was dissolved in dichloromethane (10 ml/mmol) under air. To the solution was added PHT (1 equiv.) in one portion. The solution was stirred for a total of 15 min and the solvent subsequently removed under reduced pressure. The residue was dissolved in acetone (10 ml/mmol) and K_2CO_3 (3 equiv.) was added in one portion. The suspension was heated to 50 °C for 67–70 h before the solvent was removed under reduced pressure and the residue partitioned between H_2O (10 ml/mmol) and dichloromethane (20 ml/mmol). The aqueous layer was re-extracted with dichloromethane (2 × 10 ml/mmol). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by column chromatography as indicated below.

1-Benzyl-2,3,5,6,7,7a-hexahydro-1*H*-indole (2a)

The *title compound* was purified by column chromatography (EtOAc-cyclohexane; 1:12) which gave **2a** as a yellow oil [Method A: 62%; Method B: 85%]. The purified product solidified upon storage in the fridge to give X-ray quality crystals (see ESI†). M.pt. 28–30 °C; R_f = 0.45 (EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.33 (d, J = 7.5 Hz, 2H) 7.29 (t, J = 7.5 Hz, 2H) 7.22 (t, J = 7.5 Hz, 1H) 5.43 (bs, 1H) 4.06 (d, J = 13.0 Hz, 1H) 3.22 (d, J = 13.0 Hz, 1H) 2.92–2.97 (m, 1H) 2.57–2.63 (m, 1H) 2.32–2.38 (m, 2H) 2.02–2.13 (m, 4H) 1.81–1.88 (m, 1H) 1.43–1.54 (m, 1H) 1.54 (q, J = 12.0 Hz, 1H); ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ (ppm) 140.3 (C) 138.9 (C) 129.1 (CH) 128.1 (CH) 126.8 (CH) 118.5 (CH) 64.4 (CH) 58.8 (CH_2) 52.0 (CH_2) 28.1 (CH_2) 27.9 (CH_2) 25.1 (CH_2) 20.5 (CH_2); IR (neat) 3377, 3030, 2927, 2851, 2785, 2723, 2348, 1651, 1609 cm^{-1}; HRMS (ES$^+$) calcd. for $[C_{15}H_{20}N]^+$ 214.1596; found 214.1586.

1-(4-Methoxybenzyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2b)

The *title compound* was purified by flash column chromatography (EtOAc-cyclohexane; 1:7) to give **2b** as a clear oil [Method A: 53%; Method B: 88%]. R_f = 0.30 (EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.24 (d, J = 8.5 Hz, 2H) 6.83 (d, J = 8.5 Hz, 2H) 5.42 (bs, 1H) 3.99 (d, J = 12.7 Hz, 1H) 3.79 (s, 3H) 3.17 (d, J = 12.7 Hz, 1H) 2.90–2.95 (m, 1H) 2.54–2.60 (m, 1H) 2.31–2.37 (m, 2H) 2.02–2.13 (m, 4H) 1.81–1.87 (m, 1H) 1.42–1.53 (m, 1H) 1.12–1.21 (m, 1H); ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ (ppm) 158.6 (C) 140.4 (C) 131.0 (C) 130.2 (CH) 118.5 (CH) 113.5 (CH) 64.3 (CH) 58.1 (CH_2) 55.2 (CH_3) 51.9 (CH_2) 28.1 (CH_2) 27.9 (CH_2) 25.1 (CH_2) 20.5 (CH_2); IR (neat) 3061, 2998, 2930, 2834, 2780, 2718, 2542, 2483, 2278, 2065, 1995, 1882, 1756, 1692, 1612, 1586, 1513 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{22}NO]^+$ 244.1701; found 244.1693.

1-(2-Methoxybenzyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2c)

Purification by column chromatography (EtOAc-cyclohexane; 1:7) gave the *title compound* **2c** as a clear yellow oil [Method B: 88% yield]. R_f = 0.40 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (dd, J = 1.5 Hz, J = 7.5 Hz, 1H) 7.22 (dt, J = 1.5 Hz, J = 8.0 Hz, 1H) 6.91 (t, J = 7.5 Hz, 1H) 6.81 (d, J = 8.0, 1H) 5.42 (bs, 1H) 4.04 (d, J = 13.5 Hz, 1H) 3.83 (s, 3H) 3.40 (d, J = 13.5 Hz, 1H) 3.03–3.08 (m, 1H) 2.62–2.69 (m, 1H) 2.34–2.40 (m, 2H) 2.12–2.22 (m, 2H) 2.03–2.08 (m, 2H) 1.83–1.90 (m, 1H) 1.44–1.56 (m, 1H) 1.14–1.24 (m, 1H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 157.6 (C) 140.6 (C) 130.8 (CH) 127.9 (CH) 127.1 (C) 120.2 (CH) 118.4 (CH) 110.3 (CH) 64.2 (CH) 55.3 (CH_3) 52.0 (CH_2) 51.8 (CH_2) 28.1 (CH_2) 28.0 (CH_2) 25.2 (CH_2) 20.6 (CH_2); IR (neat) 3441, 3000. 2930 2857, 2835, 2789, 2721, 1690, 1601, 1589 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{22}NO]^+$ 244.1701; found 244.1700.

1-(2,4,6-Trimethylbenzyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2d)

The *title compound* was purified by flash column chromatography (EtOAc-cyclohexane; 1:19) to give **2d** as a white solid [Method B: 85%]. M.pt. 35–37 °C; R_f = 0.55 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83 (s, 2H) 5.40 (bs, 1H) 3.91 (d, J = 12.5 Hz, 1H) 3.33 (d, J = 12.5 Hz, 1H) 2.81–2.81 (m, 1H) 2.59–2.66 (m, 1H) 2.39 (s, 6H) 2.27 (s, 3H) 2.23–2.36 (m, 2H) 2.11–2.22 (m, 2H) 2.03–2.10 (m, 2H) 1.82–1.91 (m, 1H) 1.45–1.60 (m, 1H) 1.16–1.26 (m, 1H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 141.3 (C) 137.6 (C) 136.0 (C) 132.8 (C) 128.9 (CH) 117.8 (CH) 65.4 (CH) 52.0 (CH_2) 51.8 (CH_2) 28.2 (CH_2) 27.9 (CH_2) 25.2 (CH_2) 20.9 (CH_3) 20.6 (CH_2) 20.3 (CH_3); IR (neat) 3441, 3004, 2923, 2836, 2782, 2716, 1689, 1613, 1580 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{18}H_{26}N]^+$ 256.2065; found 256.2072.

1-(2-Bromo-4,5-dimethoxybenzyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2e)

Purification by flash column chromatography (EtOAc-cyclohexane; 1:12) gave **2e** as a light tan solid [Method A: 63%; Method B: 77%]. M.pt. 84–86 °C; R_f = 0.40 (EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.03 (s, 1H) 6.99 (s, 1H) 5.44 (bs, 1H) 3.99 (d, J = 13.5 Hz, 1H) 3.86 (s, 3H) 3.85 (s, 3H) 3.40 (d, J = 13.5 Hz, 1H) 3.00–3.05 (m, 1H) 2.67–2.73 (m, 1H) 2.35–2.43 (m, 2H) 2.19 (q, J = 9.0 Hz, 1H) 2.07–2.13 (m, 1H) 2.02–2.07 (m, 2H) 1.82–1.88 (m, 1H) 1.44–1.55 (m, 1H) 1.13–1.23 (m, 1H); ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ (ppm) 148.4 (C) 148.3 (C) 140.3 (C) 130.4 (C) 118.5 (CH) 115.2 (CH) 114.0 (C) 113.6 (CH) 64.7 (CH) 57.6 (CH_2) 56.1 (CH_3) 56.0 (CH_3) 52.3 (CH_2) 28.1 (CH_2) 28.0 (CH_2) 25.0 (CH_2) 20.4 (CH_2); IR (CH_2Cl_2) 3376, 3000, 2932, 2936, 2796, 1648, 1603, 1506 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{17}H_{23}NO_2Br]^+$ 352.0912; found 352.0918.

1-(Furan-2-ylmethyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2f)[3a]

Compound **2f** was purified by column chromatography (EtOAc-cyclohexane; 1:19) to give a yellow oil [Method A: 65%;[3] Method B: 74%]. R_f = 0.60 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35–7.36 (m, 1H) 6.30 (dd, J = 2.0 Hz, J = 3.0 Hz, 1H) 6.19 (d, J = 3.0 Hz, 1H) 5.41 (bs, 1H) 3.94 (d, J = 14.0 Hz, 1H) 3.46 (d, J = 14.0 Hz, 1H) 3.01–3.06 (m, 1H) 2.53–2.60 (m, 1H) 2.34–2.42 (m, 2H) 2.21–2.28 (m, 1H) 1.99–2.10 (m, 3H) 1.80–1.87 (m, 1H) 1.40–1.52 (m, 1H) 1.10–1.20 (m, 1H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 152.4 (C) 141.8 (CH) 140.0 (C) 118.6 (CH) 110.0 (CH) 108.0 (CH) 63.5 (CH) 51.9 (CH_2) 49.8 (CH_2) 27.9 (CH_2) 27.7 (CH_2) 25.0 (CH_2) 20.5 (CH_2); IR (neat) 3437, 3114, 3062, 2922, 2858, 2788, 2660, 1642, 1599, 1504 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{13}H_{18}NO]^+$ 204.1388; found 204.1380.

1-Benzyl-1,2,3,4,6,7,8,8a-octahydroquinoline (2g)

The *title compound* was isolated following purification by flash column chromatography (EtOAc-cyclohexane; 2:23) as a clear oil [Method B: 62%]. R_f = 0.30 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27–7.33 (m, 4H) 7.19–7.24 (m, 1H) 5.51 (bs, 1H) 4.16 (d, J = 13.5 Hz, 1H) 3.11 (d, J = 13.5 Hz, 1H) 2.82–2.88 (m, 1H) 2.7–2.76 (m, 1H) 2.19–2.32 (m, 2H) 1.90–2.12 (m, 4H) 1.73–1.83 (m, 1H) 1.42–1.60 (m, 4H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 139.6 (C) 136.8 (C) 129.2 (CH) 128.1 (CH) 126.7 (CH) 122.6 (CH) 61.0 (CH) 58.3 (CH_2) 53.3 (CH_2) 34.5 (CH_2) 29.6 (CH_2) 26.3 (CH_2) 25.5 (CH_2) 21.6 (CH_2); IR (neat) 3084, 3061, 3026, 2931, 2856, 2836, 2784, 2746, 2724, 2651, 1602 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{22}N]^+$ 228.1752; found 228.1743.

1-(1-Phenylethyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2h)

Following the general procedures **2h** was prepared albeit after 5 d for the second, K_2CO_3, operation [Method A: 51%; Method B: 67% as a 1:1 mixture of diastereoisomers (determined by ^{1}H-NMR spectroscopy of crude reaction products)]. The two diastereoisomers proved to be very difficult to separate by flash column chromatography. However, partial purification proved to be possible (EtOAc-cHex; 2:23) enabling characterisation of both diastereoisomers. The relative stereochemistry of the faster moving diastereoisomer was determined by X-ray crystallography after formation of the hydrochloride salt. X-ray quality crystals were obtained by slow evaporation from EtOAc. **(*R**)-1-((*R**)-1-Phenylethyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2h)**:[3a] viscous oil; R_f = 0.20 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37 (d, *J* = 7.5 Hz, 2H) 7.28 (t, *J* = 7.5 Hz, 2H) 7.21 (t, *J* = 7.5 Hz, 1H) 5.39 (bs, 1H) 3.64 (q, *J* = 6.5 Hz, 1H) 3.02–3.07 (m, 1H) 2.68–2.74 (m, 1H) 2.31–2.42 (m, 3H) 1.94 (bs, 2H) 1.57–1.66 (m, 1H) 1.39 (d, *J* = 6.5 Hz, 3H) 1.23–1.38 (m, 2H) 0.83 (q, *J* = 12.0 Hz, 1H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 145.6 (C) 141.0 (C) 128.0 (CH) 127.7 (CH) 126.7 (CH) 118.5 (CH) 63.7 (CH) 62.1 (CH) 48.5 (CH_2) 29.6 (CH_2) 27.7 (CH_2) 25.0 (CH_2) 20.9 (CH_2) 18.6 (CH_3); IR (neat) 3061, 3026, 2971, 2930, 2836, 2783, 2727, 2666, 1945, 1874, 1806, 1749, 1600 cm^{-1}; HRMS (ES$^+$): calcd for $[C_{16}H_{22}N]^+$ 228.1752; found 228.1741. **(*S**)-1-((*R**)-1-Phenylethyl)-2,3,5,6,7,7a-hexahydro-1*H*-indole (2h)**: R_f = 0.20 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.19–7.38 (m, 5H) 5.38 (bs, 1H) 4.06 (q, *J* = 7.0 Hz, 1H) 2.96–3.06 (m, 1H) 2.45–2.54 (m, 1H) 2.26–2.34 (m, 2H) 2.16–2.26 (m, 2H) 1.97–2.06 (m, 2H) 1.80–1.88 (m, 1H) 1.53 (d, *J* = 7.0 Hz, 3H) 1.40–1.50 (m, 1H) 1.13–1.23 (m, 1H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 140.3 (C) 139.5 (C) 128.5 (CH) 127.6 (CH) 126.9 (CH) 118.5 (CH) 60.1 (CH) 57.7 (CH) 44.9 (CH_2) 28.5 (CH_2) 27.5 (CH_2) 25.2 (CH_2) 20.6 (CH_2) 19.8 (CH_3); IR (neat) 3083, 3060, 3026, 2972, 2931, 2858, 2836, 2783, 2727, 2666 cm^{-1}; HRMS (ES$^+$): calcd for $[C_{16}H_{22}N]^+$ 228.1752; found 228.1745. Data obtained from mixture of both diastereiosmers.

(*S*)- and (*R*)-1-((*R*)-1-Phenylethyl)-1,2,3,4,6,7,8,8a-octahydroquinoline (2i)

Following the general procedure apart from conducting the second, cyclisation, step for 8 d. The two diastereoisomers were separated by flash column chromatography (EtOAc-cHex; 1:19) to give the *title compounds* as clear oils [Method A: 45%; **(*R*,*R*)-2i**: 24%, **(*S*,*R*)-2i**: 21%; Method B: 65%; **(*R*,*R*)-2i**: 32%, **(*S*,*R*)-2i**: 33%]. The relative stereochemistry was determined for the slower moving (*S*,*R*)-diastereoisomer by X-ray crystallography after formation of the hydrochloride salt and recrystallisation from CH_2Cl_2. **(*R*)-1-((*R*)-1-phenylethyl)-1,2,3,4,6,7,8,8a-octahydroquinoline (2i)**:[3a] $[\alpha]_D$ = –46.1 (c 0.2, $CHCl_3$); R_f = 0.40 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, *J* = 7.5 Hz, 2H) 7.29 (t, *J* = 7.5 Hz, 2H) 7.19 (t, *J* = 7.5 Hz, 1H) 5.48 (bs, 1H) 4.39 (q, *J* = 7.0 Hz, 1H) 3.04–3.10 (m, 1H) 2.43–2.51 (m, 1H) 2.13–2.25 (m, 3H) 1.91–2.10 (m, 3H) 1.78–1.86 (m, 1H) 1.44–1.60 (m, 3H) 1.29–1.38 (m, 1H) 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 144.7 (C) 137.7 (C) 127.9 (CH) 127.8 (CH) 126.1 (CH) 121.6 (CH) 57.6 (CH) 53.8 (CH) 45.1 (CH_2) 34.7 (CH_2) 29.0 (CH_2) 26.7 (CH_2) 25.5 (CH_2) 21.7 (CH_2) 7.7 (CH_3); IR (neat) 3085, 3059, 3028, 2929, 2855, 2837, 2795, 2750, 2717, 1947, 1875, 1805, 1710, 1672, 1601 cm^{-1}; HRMS (ES$^+$): calcd for $[C_{17}H_{24}N]^+$ 242.1909; found 242.1903. **(*S*)-1-((*R*)-1-Phenylethyl)-1,2,3,4,6,7,8,8a-octahydroquinoline (2i)**: $[\alpha]_D$ = +248 (c 0.2, $CHCl_3$); R_f = 0.20 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33 (t, *J* = 7.5 Hz, 2H) 7.23–7.28 (m, 3H) 5.47 (bs, 1H) 4.41 (q, *J* = 7.0 Hz, 1H) 3.10–3.16 (m, 1H) 2.66–2.73 (m, 1H) 2.45–2.53 (m, 1H) 2.12–2.19 (m, 1H) 1.98–2.10 (m, 1H) 1.84–1.95 (m, 2H) 1.73–1.84 (m, 2H) 1.61–1.68 (m, 1H) 1.34–1.58 (m, 3H) 1.47 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 139.4 (C) 137.1 (C) 128.6 (CH) 127.7 (CH) 126.8 (CH) 122.7 (CH) 58.0 (CH) 55.0 (CH) 46.2 (CH_2) 34.6 (CH_2) 29.3 (CH_2) 26.9 (CH_2) 25.5 (CH_2) 21.7 (CH_2) 19.4 (CH_3); IR (neat) 3059, 3028, 2928, 2855, 2800, 2762, 2718, 1944, 1871, 1802, 1740, 1671, 1601; HRMS (ES$^+$): calcd for $[C_{17}H_{24}N]^+$ 242.1909; found 242.1899.

2*R-((1*R**,2*S**)-1,2-Dibromocyclohexyl)-*N*-(1-phenylethyl)-ethylamine and 2*R**-((1*S**,2*R**)-1,2-dibromocyclohexyl)-*N*-(1-phenylethyl)ethylamine (3h)**

2-Cyclohex-1-enyl-*N*-(1-phenylethyl)ethylamine **1h** (230 mg, 1.0 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (30 ml) and $NaHCO_3$ (168 mg, 2.0 mmol, 2 equiv.) added. The mixture was cooled to –78 °C. Br_2 (113 µl, 2.2 mmol, 2.2 equiv.) was added as a solution in anhydrous CH_2Cl_2 (10 ml) in a dropwise fashion. The mixture was stirred for 10 min at –78 °C and subsequently slowly warmed to room temperature (approx. 1 h). The mixture was poured into a saturated Na_2SO_3 solution (20 ml) and was extracted with CH_2Cl_2 (3 × 40 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude material was directly subjected to flash column chromatography (EtOAc-cyclohexane; 1:9 to 3:7) and the *title compound* (162 mg, 42%) was isolated as a clear oil. R_f = 0.25 (EtOAc); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31–7.34 (m, 4H) 7.21–7.25 (m, 1H) 4.52–4.57 (bs/m, 1H) 3.82 (bq, *J* = 6.5 Hz, 1H) 2.74–2.87 (m, 2H) 2.45–2.55 (m, 1H) 2.08–2.29 (m, 2H) 1.90–2.04 (m, 2H) 1.76–1.89 (m, 3H) 1.70 (bs, 1H) 1.50–1.65 (m, 2H) 1.37 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 145.35 (C) 145.3 (C) 128.45 (CH) 128.4 (CH) 126.9 (CH) 126.5 (CH) 126.45 (CH) 74.25 (C) 74.2 (C) 59.5 (CH) 59.4 (CH) 58.3 (CH) 58.2 (CH) 45.1 (CH_2, broad) 43.35 (CH_2) 43.3 (CH_2) 35.85 (CH_2) 35.8 (CH_2) 31.75 (CH_2) 31.7 (CH_2) 24.4 (CH_3) 24.3 (CH_3) 22.05 (CH_2) 22.0 (CH_2) 20.4 (CH_2) 20.35 (CH_2).

***N*-Benzyl-[2-((1*R**,2*S**)-1,2-dibromocyclohexyl)ethyl]amine (3a)**

N-Benzyl-2-cyclohex-1-enylethylamine **1a** (215 mg, 1.0 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (30 ml) under an atmosphere of N_2, $NaHCO_3$ (168 mg, 2.0 mmol, 2 equiv.) added in one portion and the solution cooled to –78 °C. Br_2 (113 µl, 2.2 mmol, 2.2 equiv.) was added dropwise as a solution in anhydrous CH_2Cl_2 (10 ml). The mixture was stirred for 10 min. The cooling bath was then removed and the mixture slowly warmed to room temperature before pouring into a saturated $Na_2S_2O_3$ solution (20 ml). Extraction with CH_2Cl_2 (2 × 25 ml), drying of the combined organic layers over Na_2SO_4, filtration and solvent removal under reduced pressure afforded the crude product. Immediate purification by flash column chromatography (EtOAc-cHex; 1:9) gave **3a** as a clear oil (48 mg, 13%). Note: the product

thus obtained was observed to undergo slow decomposition. R_f = 0.25 (EtOAc); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.25–7.39 (m, 5H) 4.64 (bs, 1H) 3.86 (s, 2H) 2.96–3.05 (m, 2H) 2.54–2.61 (m, 1H) 2.20–2.24 (m, 2H) 1.98–2.10 (m, 2H) 1.81–1.94 (m, 3H) 1.75 (bs, 1H) 1.57–1.70 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm) 140.1 (C) 128.4 (CH) 128.1 (CH) 127.0 (CH) 74.3 (C) 59.5 (CH) 54.0 (CH_2) 45.1 (CH_2) 44.9 (CH_2) 35.9 (CH_2) 31.8 (CH_2) 22.1 (CH_2) 20.4 (CH_2); IR (neat) 3323, 3030, 2935, 2856, 1652, 1611 cm^{-1}; HRMS (ES$^+$): calcd for $[C_{15}H_{22}N^{79}Br_2]^+$ 374.0119; found 374.0107.

General procedure for the synthesis of bromooctahydroindoles 9

The secondary cyclohex-1-enyl-amine **1** was dissolved in dichloromethane (5 ml/mmol). The solution was cooled to 0 °C and solid NBS (1 equiv.) was added in one portion. The mixture was stirred at 0 °C for 30 min, then warmed to room temperature over a period of 30 min and subsequently heated to reflux for 1 h. The volatiles were removed under reduced pressure and the residue suspended in pentane (5 ml/mmol), filtered through a sintered funnel, washed with pentane (2 × 5 ml/mmol) and the combined filtrates concentrated *in vacuo*. Flash column chromatography (EtOAc-cyclohexane; 1:19) gave the products as indicated below.

(3a*S,7*aR*)-1-Benzyl-3a-bromooctahydroindole (9a)**

The *title compound* **9a** (32%) was isolated as a viscous colourless oil. X-ray crystals of the corresponding HCl salt were formed from CH_2Cl_2. R_f = 0.60 (EtOAc-cyclohexane; 1:4); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.28–7.33 (m, 4H) 7.21–7.26 (m, 1H) 4.05 (d, J = 13.5 Hz, 1H) 3.22 (d, J = 13.5 Hz, 1H) 2.92–2.98 (m, 1H) 2.86–2.89 (m, 1H) 2.33–2.42 (m, 2H) 2.08–2.18 (m, 2H) 1.95–2.01 (m, 1H) 1.84–1.91 (m, 1H) 1.75–1.81 (m, 1H) 1.58–1.69 (m, 2H) 1.51–1.58 (m, 1H) 1.37–1.43 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm) 139.5 (C) 128.4 (CH) 128.2 (CH) 126.8 (CH) 69.4 (CH) 68.8 (C) 57.6 (CH_2) 50.6 (CH_2) 40.9 (CH_2) 38.7 (CH_2) 23.6 (CH_2) 23.1 (CH_2) 19.8 (CH_2); IR (neat) 3108, 3085, 3063, 3028, 2933, 2879, 2858, 2803, 1655, 1606, 1586, 1561 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{15}H_{21}N^{79}Br]^+$ 294.0857; found 294.0865.

(3a*S,7a*R**)-3a-Bromo-1-(4-methoxybenzyl)octahydroindole (9b)**

The *title compound* **9b** (32%) was isolated as a viscous colourless oil. R_f = 0.50 (EtOAc-cyclohexane; 1:4); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21 (d, J = 8.5 Hz, 2H) 6.84 (d, J = 8.5 Hz, 2H) 3.96 (d, J = 13.0 Hz, 1H) 3.78 (s, 3H) 3.17 (d, J = 13.0 Hz, 1H) 2.89–2.96 (m, 1H) 2.82–2.87 (m, 1H) 2.29–2.43 (m, 2H) 2.04–2.18 (m, 2H) 1.93–2.02 (m, 1H) 1.74–1.87 (m, 2H) 1.48–1.69 (m, 3H) 1.32–1.46 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 158.5 (C) 131.4 (C) 129.5 (CH) 113.6 (CH) 69.3 (CH) 68.9 (C) 56.9 (CH_2) 55.2 (CH_3) 50.4 (CH_2) 40.9 (CH_2) 38.7 (CH_2) 23.6 (CH_2) 23.1 (CH_2) 19.8 (CH_2); IR (neat) 3061, 3031, 2996, 2933, 2858, 2833, 2806, 2727, 2685, 1668, 1612, 1586, 1512 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{23}N^{79}BrO]^+$ 324.0963; found 324.0974.

(3a*S,7a*R**)-3a-Bromo-1-(2-bromo-4,5-dimethoxybenzyl)-octahydroindole (9d)**

According to the procedure described **9d** (32%) was obtained as a viscous colourless oil. R_f = 0.40 (EtOAc-cHex; 1:4); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.05 (s, 1H) 6.98 (s, 1H) 3.91 (d, J = 14.0 Hz, 1H) 3.85 (s, 3H) 3.84 (s, 3H) 3.47 (d, J = 14.0 Hz, 1H) 2.96–3.03 (m, 2H) 2.52–2.60 (m, 1H) 2.35–2.45 (m, 1H) 2.15–2.24 (m, 1H) 1.99–2.11 (m, 2H) 1.80–1.91 (m, 1H) 1.47–1.73 (m, 4H) 1.34–1.43 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 148.4 (C) 148.3 (C) 130.7 (C) 115.4 (CH) 113.4 (C) 113.1 (CH) 69.7 (CH) 69.2 (C) 56.6 (CH_2) 56.1 (CH_3) 56.0 (CH_3) 50.8 (CH_2) 40.6 (CH_2) 38.8 (CH_2) 23.9 (CH_2) 23.1 (CH_2) 20.4 (CH_2); IR (neat) 3080, 2933, 2838, 2256, 1681, 1603 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{17}H_{24}N^{79}Br_2O_2]^+$ 432.0174; found 432.0159.

***N*-Benzyl-*N*-chloro-2-cyclohex-1-enylethylamine (10a)**

N-Benzyl-2-cyclohex-1-enylethylamine **1a** (215 mg, 1.0 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 ml) and the solution cooled to 0 °C. Solid NCS (134 mg, 1.0 mmol, 1 equiv.) was added in one portion and the mixture stirred for 15 min. The solvent was removed under reduced pressure and the residue suspended in pentane (5 ml) and filtered through a sintered funnel. The solid was washed with pentane (2 × 5 ml) and the combined filtrate concentrated under reduced pressure. The crude product was immediately subjected to column chromatography (pentane-Et_2O; 9:1) to give **10a** (183 mg, 73%) as a clear oil. R_f = 0.70 (EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30–7.42 (m, 5H) 5.48 (bs, 1H) 4.14 (s, 2H) 3.08 (t, J = 7.5 Hz, 2H) 2.38 (t, J = 7.5 Hz, 2H) 1.98–2.07 (m, 2H) 1.89–1.98 (m, 2H) 1.53–1.70 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 137.1 (C) 134.8 (C) 129.1 (CH) 128.3 (CH) 127.7 (CH) 122.6 (CH) 68.1 (CH_2) 61.9 (CH_2) 36.2 (CH_2) 28.8 (CH_2) 25.2 (CH_2) 22.9 (CH_2) 22.4 (CH_2); IR (neat) 3040, 2918, 2847, 2665, 1659, 1604 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{15}H_{21}{}^{35}ClN]^+$ 250.1363; found 250.1351.

***N*-Chloro-2-cyclohex-1-enyl-*N*-(4-methoxybenzyl)ethylamine (10b)**

As above, 2-cyclohex-1-enyl-*N*-(4-methoxybenzyl)ethylamine **1b** (245 mg, 1.0 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 ml) cooled to 0 °C and solid NCS (134 mg, 1.0 mmol, 1 equiv.) added. After stirring for 15 min the solvent was removed and the residue suspended in pentane (10 ml). After filtration the resultant solid was washed with pentane (2 × 10 ml) and the combined filtrate concentrated under reduced pressure. The crude product was purified by flash column chromatography (pentane-Et_2O; 9:1) which gave **10b** (260 mg, 93%) as a clear oil. R_f = 0.75 (EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (d, J = 8.5 Hz, 2H) 6.86 (d, J = 8.5 Hz, 2H) 5.43 (bs, 1H) 4.04 (s, 2H) 3.79 (s, 3H) 3.00 (t, J = 7.5 Hz, 2H) 2.32 (t, J = 7.5 Hz, 2H) 1.93–2.02 (m, 2H) 1.85–1.93 (m, 2H), 1.48–1.62 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 159.2 (C) 134.9 (C) 130.4 (CH) 129.2 (C) 122.5 (CH) 113.6 (CH) 67.5 (CH_2) 61.5 (CH_2) 55.2 (CH_3) 36.2 (CH_2) 28.5 (CH_2) 25.2 (CH_2) 22.9 (CH_2) 22.3 (CH_2); IR (neat) 3036, 2998, 2927, 2835, 1668, 1613, 1586, 1514 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{23}{}^{35}ClNO]^+$ 280.1468; found 280.1458.

2-Cyclohex-1-enyl-*N*-(4-methoxybenzyl)ethylammonium bromide (1b·HBr)

2-Cyclohex-1-enyl-*N*-(4-methoxybenzyl)ethylamine **1b** (245 mg, 1 mmol, 1 equiv.) was dissolved in Et_2O (5 ml) and the solution cooled to 0 °C. To the solution was added solid NBS (178 mg,

1 mmol, 1 equiv.) in one portion. The suspension was stirred for 30 min at room temperature before the solid was removed by filtration, which was washed with pentane (2 × 5 ml). The filtrate was immediately concentrated under reduced pressure to give *N*-bromo-2-cyclohex-1-enyl-*N*-(4-methoxybenzyl)ethylamine **5b** as a clear oil (324 mg, 100%). This *N*-halogenated species was directly subjected to NMR analysis. Due to the instability of the compound only a ^{1}H-NMR spectrum was obtained. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (d, J = 8.5 Hz, 2H) 6.86 (d, J = 8.5 Hz, 2H) 5.43 (bs, 1H) 4.05 (s, 2H) 3.78 (s, 3H) 2.98 (t, J = 7.0 Hz, 2H) 2.32 (t, J = 7.0 Hz, 2H) 1.93–2.01 (m, 2H) 1.85–1.93 (m, 2H) 1.48–1.64 (m, 4H). A crystalline solid formed from $CDCl_3$ which was subjected to X-ray analysis and was identified as **1b·HBr** (yield not determined). M.pt. 148 °C (decomp.); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 9.11 (bs, 2H) 7.53 (d, J = 8.5 Hz, 2H) 6.91 (d, J = 8.5 Hz, 2H) 5.49 (bs, 1H) 4.04 (s, 2H) 3.76 (s, 3H) 2.88 (t, J = 8.0 Hz, 2H) 2.47 (t, J = 8.0 Hz, 2H) 1.92–2.01 (m, 2H) 1.77–1.85 (m, 2H) 1.47–1.62 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5 (C) 132.1 (C) 132.0 (CH) 125.3 (CH) 121.6 (C) 114.5 (CH) 55.2 (CH_3) 50.0 (CH_2) 44.1 (CH_2) 33.9 (CH_2) 28.0 (CH_2) 25.2 (CH_2) 22.6 (CH_2) 22.0 (CH_2); IR (CH_2Cl_2) 3433, 2929, 2795, 2700, 2396, 1613, 1516 cm^{-1}; Anal. Calcd. for $C_{16}H_{24}BrNO$: C (58.90) H (7.41) N (4.29) Br (24.49), Found: C (58.61) H (7.20) N (4.26) Br (24.37).

N-Benzyl-2-((1*R**,2*S**)-1,2-dibromocyclohexyl)ethylammonium bromide (3a·HBr)

N-Benzyl-2-cyclohex-1-enylethylamine **1a** (46 mg, 0.21 mmol, 1 equiv.) was dissolved in $CDCl_3$ (2 ml). PHT (106 mg, 0.21 mmol, 1 equiv.) was added in one portion and the mixture stirred for 15 min. Complete conversion was observed by NMR spectroscopy and the title compound was characterized as its HBr salt. ^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm) 9.74 (bs, 2H) 7.57–7.59 (m, 2H) 7.32–7.38 (m, 3H) 4.38 (s, 1H) 4.16 (t, J = 5.5 Hz, 2H) 3.15–3.27 (m, 2H) 2.53–2.63 (m, 2H) 2.40–2.46 (m, 1H) 1.98–2.02 (m, 1H) 1.89–1.94 (m, 1H) 1.82–1.86 (m, 1H) 1.70–1.78 (m, 2H) 1.59–1.65 (m, 1H) 1.48–1.55 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm) 130.2 (CH) 129.9 (C) 129.4 (CH) 129.0 (CH) 71.3 (C) 58.4 (CH) 50.5 (CH_2) 42.6 (CH_2) 39.7 (CH_2) 35.5 (CH_2) 31.5 (CH_2) 21.8 (CH_2) 20.3 (CH_2); HRMS (ES$^+$): calcd. for $[C_{15}H_{22}N^{79}Br_2]^+$ 374.0119; found 374.0104.

(3a*R**,7a*R**)-1-(Toluene-4-sulfonyl)octahydroindole (12a)[18]

1-Benzyl-2,3,5,6,7,7a-hexahydro-1*H*-indole **2a** (107 mg, 0.5 mmol, 1 equiv.) was dissolved in glacial acetic acid (10 ml) and the solution degassed for 30 min with a steady stream of N_2. Pd/C (10% Pd on carbon, w/w, 53 mg, 0.05 mmol, 0.1 equiv.) was added and the flask purged with H_2 and subsequently equipped with a H_2 balloon. The reaction mixture was stirred for 24 h at room temperature. Filtration through celite and washing with glacial acetic acid (2 × 10 ml) followed by concentration of the combined filtrates under reduced pressure gave the crude secondary amine. The residue was dissolved in CH_2Cl_2 (10 ml) and K_2CO_3 (691 mg, 5 mmol, 10 equiv.) added. The suspension was cooled to 0 °C before TsCl (95 mg, 0.5 mmol, 1 equiv.) was added in one portion. The mixture was stirred at 0 °C for 1 h followed by 6 h at room temperature. The mixture was poured into H_2O (10 ml) and the aqueous layer was acidified using 1 M HCl (pH ~ 2). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml) and the combined organic layers were washed with brine (10 ml), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude material was subjected to flash column chromatography (EtOAc-cyclohexane; 1:19) which gave **12a** (103 mg, 74%) as a colourless solid. X-ray quality crystals were obtained by slow evaporation from EtOH. M.pt. 50–52 °C (EtOH); R_f = 0.25 (EtOAc-cyclohexane; 1:9); ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.71 (d, J = 8.0 Hz, 2H) 7.30 (d, J = 8.0 Hz, 2H) 3.48–3.56 (m, 2H) 3.18 (q, J = 9.0 Hz, 1H) 2.42 (s, 3H) 1.76–1.92 (m, 3H) 1.49–1.65 (m, 5H) 1.29–1.41 (m, 2H) 1.17–1.27 (m, 1H); ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ (ppm) 142.9 (C) 135.3 (C) 129.5 (CH) 127.2 (CH) 59.5 (CH) 47.2 (CH_2) 37.7 (CH) 29.8 (CH_2) 27.6 (CH_2) 26.2 (CH_2) 23.1 (CH_2) 21.4 (CH_3) 21.3 (CH_2); IR (CH_2Cl_2) 3625, 3549, 3064, 3029, 2929, 2859, 1922, 1813, 1598, 1339, 1161 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{15}H_{22}NO_2S]^+$ 280.1371; found 280.1368.

(4a*R**,8a*R**)- and (4a*S**,8a*R**)-1-(Toluene-4-sulfonyl)-decahydroquinoline (12g)

As above, a mixture of 1-benzyl-1,2,3,4,6,7,8,8a-octahydroquinoline **2g** (70 mg, 0.31 mmol, 1 equiv.), Pd/C (10% Pd on carbon, w/w, 33 mg, 0.031 mmol, 0.1 equiv.) in glacial acetic acid (6 ml) was stirred under an atmosphere of H_2 (1 atm.) at room temperature for 24 h. The crude amine was dissolved in CH_2Cl_2 (6 ml) and TsCl (65 mg, 0.34 mmol, 1.1 equiv.) and K_2CO_3 (428 mg, 3.1 mmol, 10 equiv.) were added. The suspension was stirred for 14 h at room temperature. Work up as above gave the crude product which was subjected to column chromatography (cyclohexane-EtOAc; 19:1) to give **12g** (44 mg, 48%—approximately a 1:1 mixture of *cis* and *trans* diastereoisomers) as a clear oil. R_f = 0.30 (EtOAc-cyclohexane; 1:9); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.64–7.73 (m, 4H) 7.22–7.31 (m, 4H) 4.03–4.12 (m, 1H) 3.92–4.02 (m, 1H) 3.65–3.73 (m, 1H) 2.91 (t, J = 13.0 Hz, 1H) 2.69–2.79 (m, 1H) 2.42–2.50 (m, 1H) 2.41 (s, 6H) 2.21–2.29 (m, 1H) 1.48–1.80 (m, 14H) 1.07–1.47 (m, 9H) 0.87–1.02 (m, 2H); ^{13}C-NMR (100.5 MHz, $CDCl_3$) δ (ppm) 142.8 (C) 142.6 (C) 139.0 (C) 137.9 (C) 129.6 (CH) 129.5 (CH) 127.1 (CH) 126.9 (CH) 65.1 (CH) 55.3 (CH) 48.6 (CH_2) 41.1 (CH) 40.3 (CH_2) 35.0 (CH) 33.5 (CH_2) 31.8 (CH_2) 31.7 (CH_2) 31.6 (CH_2) 26.0 (CH_2) 25.6 (CH_2) 25.5 (CH_2) 25.4 (CH_2) 25.3 (CH_2) 24.0 (CH_2) 23.5 (CH_2) 21.5 (CH_3, 2x) 20.0 (CH_2); IR (neat) 3064, 3028, 2927, 2855, 1920, 1689, 1656, 1599, 1337, 1323, 1169, 1152 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{16}H_{24}NO_2S]^+$ 294.1528; found 294.1541.

(3a*S**,7a*R**)-3a-Bromo-1-(toluene-4-sulfonyl)octahydroindole (13)

As above, *rac*-(3a*S*,7a*R*)-1-benzyl-3a-bromooctahydro-1*H*-indole **9a** (200 mg, 0.68 mmol, 1 equiv.) and Pd/C (10% Pd on carbon, w/w, 72 mg, 0.068 mmol, 0.1 equiv.) in glacial acetic acid (13 ml) was stirred under H_2 (1 atm.) for 13.5 h at room temperature. The crude amine was dissolved in CH_2Cl_2 (7 ml) and treated with triethylamine (105 µl, 0.75 mmol, 1.1 equiv.) and TsCl (129 mg, 0.68 mmol, 1 equiv.). After work up as detailed above the crude product was purified by column chromatography (EtOAc-cyclohexane; 1:19). Thus, the *title compound* (55 mg, 23%) was obtained as a white gum. R_f = 0.25 (EtOAc-cyclohexane; 1:4);

^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) 7.75 (d, J = 8.0 Hz, 2H) 7.30 (d, J = 8.0 Hz, 2H) 3.84 (dd, J = 6.5, 10.0 Hz, 1H) 3.65 (dt, J = 2.0, 9.5 Hz, 1H) 3.47 (dt, J = 7.5, 9.5 Hz, 1H) 2.43–2.49 (m, 1H) 2.41 (s, 3H) 2.36–2.41 (m, 1H) 2.20–2.30 (m, 2H) 2.04 (dd, J = 7.0, 14.0 Hz, 1H) 1.67–1.75 (m, 1H) 1.49–1.60 (m, 2H) 1.28–1.39 (m, 2H); ^{13}C-NMR (125.6 MHz, $CDCl_3$) δ (ppm) 143.2 (C) 134.7 (C) 129.4 (CH) 127.7 (CH) 71.4 (C) 68.4 (CH_2) 46.2 (CH_2) 39.5 (CH_2) 37.8 (CH_2) 33.7 (CH_2) 23.7 (CH_2) 22.8 (CH_2) 21.5 (CH_3); IR (CH_2Cl_2) 3030, 2940, 2890, 2863, 1642, 1599, 1343, 1160, 667 cm^{-1}; HRMS (ES$^+$): calcd. for $[C_{15}H_{21}{}^{79}BrNO_2S]^+$ 358.0476; found 358.0473.

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12 Compound **2h**·HCl; Molecular formula: $C_{16}H_{22}ClN{\cdot}H_2O$; Formula weight: 281.81 gmol^{-1}; Crystal system: Monoclinic; Unit cell dimensions: a = 10.3845(9) Å, α = 90°; b = 14.8703(13) Å, β = 107.902(2)°; c = 10.5114(9) Å, γ = 90°; Volume: 1544.6(2) Å^3; Temperature: 293(2) K; Space group: $P2_1/n$; Number of formula units in unit cell (Z): 4; Reflections collected: 26250; Independent reflections: 3029 [R(int) = 0.0178]; Final R indices [I>2sigma(I)]: R1 = 0.0501, wR2 = 0.1499; R indices (all data): R1 = 0.0533, wR2 = 0.1540.

13 Compound **2i**·HCl; Molecular formula: $C_{17}H_{24}NCl$; Formula weight: 277.82 gmol^{-1}; Crystal system: Monoclinic; Unit cell dimensions: a = 16.115(2) Å, α = 90°; b = 10.4898(13) Å, β = 121.095(3)°; c = 10.9685(14) Å, γ = 90°; Volume: 1587.7(4) Å^3; Temperature: 293(2) K; Space group: C2; Number of formula units in unit cell (Z): 4; Reflections collected: 4287; Independent reflections: 1664 [R(int) = 0.0327]; Final R indices [I>2sigma(I)]: R1 = 0.0432, wR2 = 0.1006; R indices (all data): R1 = 0.0517, wR2 = 0.1045; Flack parameter: –0.02(10).

14 Compound **9a**·HCl; Molecular formula: $C_{15}H_{21}NClBr$; Formula weight: 330.69 gmol^{-1}; Crystal system: Monoclinic; Unit cell dimensions: a = 26.387(5) Å, α = 90°; b = 6.8937(12) Å, β = 122.455(3)°; c = 19.161(3) Å, γ = 90°; Volume: 2941.0(9) Å^3; Temperature: 100(2) K; Space group: C2/c; Number of formula units in unit cell (Z): 8; Reflections collected: 28702; Independent reflections: 3626 [R(int) = 0.0271]; Final R indices [I>2sigma(I)]: R1 = 0.0267, wR2 = 0.0686; R indices (all data): R1 = 0.0297, wR2 = 0.0700.

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17 Compound **12a**; Molecular formula: $C_{15}H_{21}NO_2S$; Formula weight: 279.39 gmol^{-1}; Crystal system: Orthorhombic; Unit cell dimensions: a = 6.237(2) Å, α = 90°; b = 12.419(4) Å, β = 90°; c = 17.923(6) Å, γ = 90°; Volume: 1388.2(8) Å^3; Temperature: 100(2) K; Space group: $P2_12_12_1$; Number of formula units in unit cell (Z): 4; Reflections collected: 5752; Independent reflections: 1710 [R(int) = 0.0877]; Final R indices [I>2sigma(I)]: R1 = 0.0554, wR2 = 0.1326; R indices (all data): R1 = 0.0640, wR2 = 0.1371.

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