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A new approach towards 2-amino-1-aryloxy-3-methoxypropanes from 1-arylmethyl-2-(bromomethyl)aziridines

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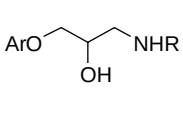
Abstract—1-Arylmethyl-2-(bromomethyl)azirdines were converted into the corresponding 2-(aryloxymethyl)aziridines upon treatment with the appropriate potassium phenoxides in DMF/acetone in excellent yields, followed by regioselective ring opening towards *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines using benzyl bromide in acetonitrile. Treatment of the latter β-bromoamines with sodium methoxide afforded the desired 2-amino-1-aryloxy-3-methoxypropanes as the major compounds (49–58%) besides the isomeric 3-amino-1-aryloxy-2-methoxypropanes in minor quantities (9–15%).

1. Introduction

Many important pharmaceutical compounds contain a 1,2,3-trisubstituted three-carbon unit in their structure, and the synthesis of drugs based on this moiety has become a key issue in academic research as well as in pharmaceutical industry. Especially aryloxypropanolamines **1** constitute a very popular class of target compounds in organic synthesis due to the pronounced physiological activities ascribed to many representatives of this class of compounds. Propranolol, atenolol and metoprolol are frequently cited β-blockers containing an aryloxypropanolamine moiety **1**, used for the treatment of hypertension, angina pectoris, glaucoma, obesity, and arrhythmia.[1] Furthermore, aryloxypropanolamines with a 4-aminopiperidine scaffold exhibit antidiabetic activity[2] and those containing a xanthone unit have been reported as antihypertensive and vasorelaxing agents.[3] Synthetic efforts towards 2-amino-1,3-dioxypropane derivatives, however, are much more scarce then those towards the structurally related aryloxypropanolamines, despite of the biological relevance of the former class of compounds. Sphingolipids **2**, membrane compounds of essentially all eukaryotic cells, comprise a 2-amino-1,3-dihydroxypropane subunit as a part of a longer (unsaturated) carbon chain.[4] Also 2-[*N*-(arylmethyl)amino]propane-1,3-diols **3** (AMAP's) have been reported as new antitumor DNA intercalators with promising prospects in medicine.[5] Moreover, compounds containing a 2-amino-1,3-propanediol subunit are important constituents of broad-spectrum antibiotics such as thiamphenicol and the fluorine-containing florfenicol.[6]



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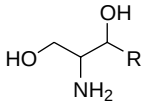

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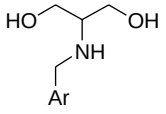

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Due to the general biological interest in 2-amino-1,3-dioxypropanes and the lack of synthetic methods for the preparation of 2-amino-1-aryloxy-3-alkoxypropanes, a new approach towards derivatives containing this moiety is reported here. This communication comprises the first report of the synthesis of 2-(di(arylmethyl)amino)-1-aryloxy-3-methoxypropanes as a new class of 1,2,3-trisubstituted propane derivatives with promising potential in medicinal chemistry, starting from 1-arylmethyl-2-(bromomethyl)aziridines.

Although several examples of the synthesis of 2-amino-1,3-propanediols are known,[7] these strategies are less suitable when aryloxypropane derivatives are contemplated, since an additional transformation of a hydroxyl group into an aryloxy group is required. Ring opening reactions of aziridines bearing an electron-withdrawing group at nitrogen (activated aziridines) have been well-covered in the literature, but only a minor part are dealing with the synthesis of 2-amino-1,3-dioxypropane derivatives,[8] for example, the synthesis of 2-amino-1,3-diaryloxypropane

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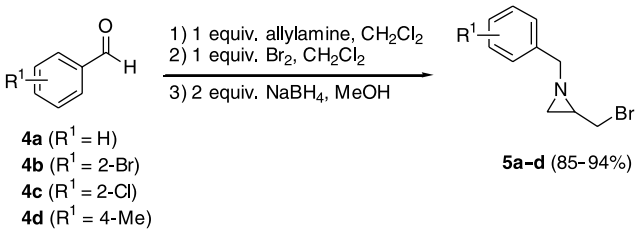
derivatives from 1-arenesulfonyl-2-(bromomethyl)aziridines upon treatment with a substituted phenol in water in the presence of potassium carbonate and silica.[8k] These procedures require the removal of the *N*-activating group in a final stage of the synthesis in order to obtain the corresponding amines. Up to now, only one type of ring opening reaction of unactivated aziridines, namely 1-alkyl-2-(alkoxymethyl)aziridines, towards 2-amino-1,3-dioxypropanes has been reported in the literature.[9] This transformation involves activation of the aziridine ring by means of an organic acid (e.g., AcOH or TFA), followed by ring opening of the aziridinium ion by the nucleophilic carboxylate anion. Hydrolysis of the resulting ester then affords the desired 2-amino-1-alkoxy-3-hydroxypropanes.

2. Results and discussion

1-Arylmethyl-2-(bromomethyl)aziridines **5** are very easily accessible substrates suitable for various applications in organic synthesis, although the synthetic potential of these β-haloamines has been scarcely evaluated in the literature. Condensation of benzaldehydes **4a–d** with 1 equiv of allylamine in dichloromethane in the presence of magnesium sulfate afforded the corresponding *N*-allylimines, which were subsequently brominated by bromine in dichloromethane to give *N*-(arylidene)-2,3-dibromopropylamines in a quantitative yield. The latter dibromoimines were used as such because of their instability and hence treated with sodium borohydride in methanol under reflux, furnishing 1-arylmethyl-2-(bromomethyl)aziridines **5a–d** in high overall yields (Scheme 1).[10] These 2-(bromomethyl)aziridines **5** are excellent substrates for the synthesis of 1,2,3-trisubstituted propane derivatives since their structure comprises a three-carbon unit in which the three electrophilic carbon atoms are structurally differentiated from each other, allowing the selective preparation of different substituted amines.



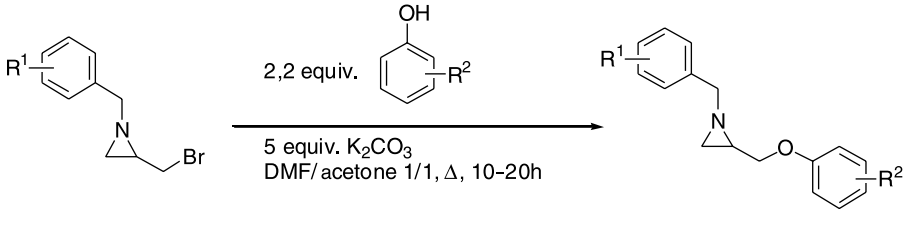
Scheme 1.

The incorporation of an aryloxy moiety into the desired three-carbon units can be very efficiently established by means of a nucleophilic substitution of the bromo atom of the aziridines **5** using a phenolate anion as a nucleophile (Scheme 2). It has already been demonstrated that 1-alkyl-2-(bromomethyl)aziridines can be easily transformed into the corresponding 2-(alkoxymethyl)aziridines upon treatment with alkoxides in alcohol via a direct substitution of the bromo atom (instead of ring opening ring closure, which occurs when *N*-activated aziridines are used).[11] Treatment of aziridines **5** with 2.2 equiv of phenol or, alternatively, a substituted bromo- or chlorophenol, and 5 equiv of K_2CO_3 in a mixture of DMF and acetone (1/1) afforded the corresponding 2-(aryloxymethyl)aziridines **6** in excellent yields and high purity after reflux for 10–20 h (Scheme 2, Table 1). These 2-(aryloxymethyl)aziridines **6** can be considered as synthetic precursors of 2-amino-1-aryloxypropanes at the one hand and 3-amino-1-aryloxypropanes at the other hand, depending on whether ring opening occurs at the less hindered or the more hindered carbon atom of the aziridine ring, respectively.

1-Arylmethyl-2-(bromomethyl)aziridines **5** can be transformed regioselectively into *N*-(2,3-dibromopropyl)amines upon treatment with benzyl bromide in acetonitrile in a straightforward reaction.[12] When this methodology was applied to 1-arylmethyl-2-(aryloxymethyl)aziridines **6**, *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** were isolated in high yields and high purity upon treatment with 1 equiv of a benzyl bromide in acetonitrile and reflux for 5 h (Scheme 3, Table 2). Detailed spectral analysis confirmed the structural identity of these *N*-(2-bromo-3-aryloxypropyl)amines **7**, excluding the formation of the corresponding regioisomers. These results confirm the general regioselectivity with which 2-substituted 1-(arylmethyl)aziridines are transformed into *N*-(2-bromopropyl)-amines upon ring opening with an arylmethyl bromide. *N*-(2-Halo-3-aryloxypropyl)amines such as compounds **7** might be of interest due to their potential biological activities, since some 2-bromo-1-oxypropane-3-amines have already been reported as potential antitumor, antimicrobial and antifungal agents,[13] as well as inhibitors of cytokinine production and secretion.[14]

β-Bromoamines **7** are suitable substrates for the synthesis of different 1,2,3-triheteroatom substituted propane derivatives, since only a nucleophilic substitution of the bromo atom by a heteroatom-centered nucleophile is required.

Consequently, *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** were treated with 2 equiv of sodium methoxide (0.2 N in methanol), yielding a mixture of 2-amino-1-aryloxy-3-methoxypropanes **8** as the major



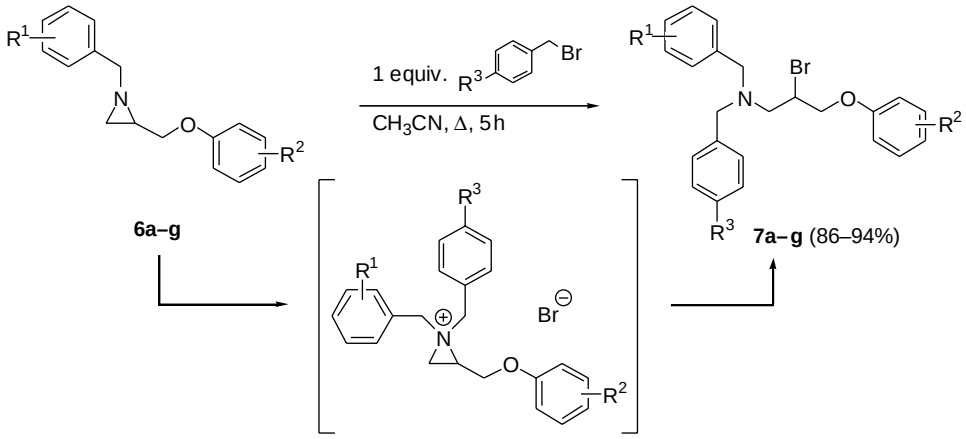
Scheme 2.

Table 1. Synthesis of 2-(aryloxymethyl)aziridines **6**

Entry	R^1	R^2	Compound (% yield)
1	H	3-Cl	**6a** (92)
2	2-Br	H	**6b** (95)
3	2-Cl	H	**6c** (91)
4	2-Br	2-Br	**6d** (90)
5	2-Cl	2-Cl	**6e** (90)
6	2-Cl	2-Br	**6f** (93)
7	4-Me	4-Cl	**6g** (93)

compounds (79–86%) and 3-amino-1-aryloxy-2-methoxypropanes **9** as the minor constituents (14–21%) after reflux for 2 h (Scheme 4, Table 3).

In order to obtain analytically pure samples for detailed spectroscopical analysis, the regioisomers **8** and **9** were separated by means of column chromatography on silica gel (hexane/ethyl acetate 98:2), affording the pure major isomers. The spectral data, thus obtained, confirmed that the major isomers formed in this reaction were 2-amino-1-



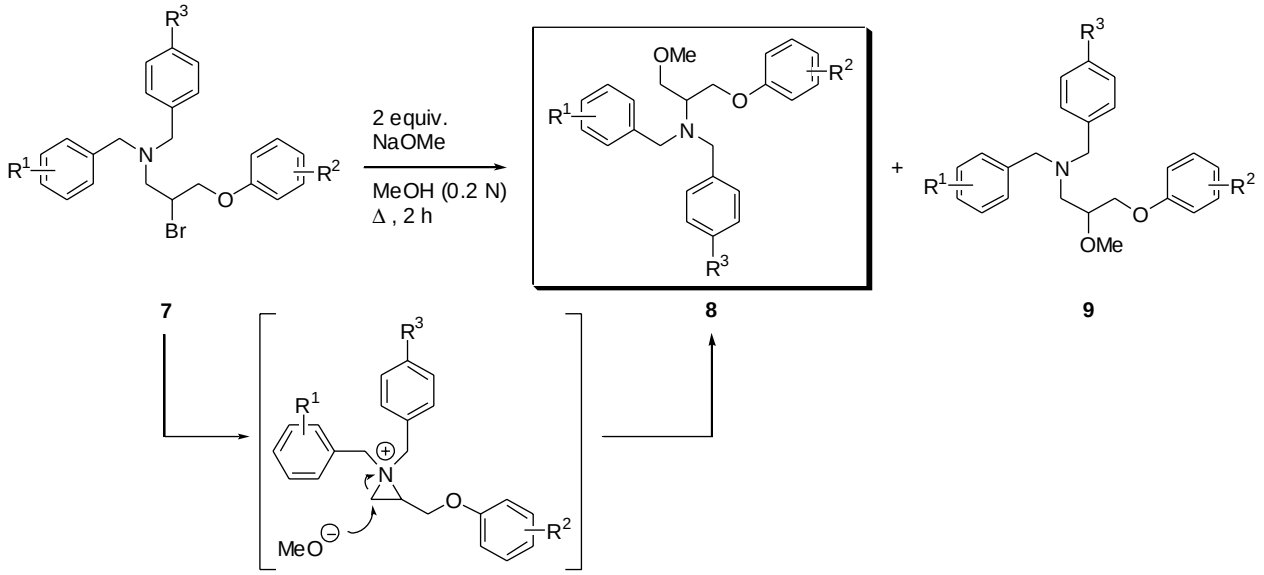
Scheme 3.

Table 2. Synthesis of *N*-(2-bromo-3-aryloxypropyl)amines **7**

Entry	R^1	R^2	R^3	Compound (% yield)
1	H	3-Cl	H	**7a** (89)
2	2-Br	H	H	**7b** (90)
3	2-Cl	H	H	**7c** (89)
4	2-Br	2-Br	H	**7d** (94)
5	2-Cl	2-Cl	H	**7e** (86)
6	2-Cl	2-Br	H	**7f** (91)
7	4-Me	4-Cl	Me	**7g** (89)

aryloxy-3-methoxypropanes **8**, whereas 3-amino-1-aryloxy-2-methoxypropanes **9** were present as the minor isomers. It should be noted that the ratio of major versus minor isomer slightly changes in the benefit of the major regioisomer when the aryloxy moiety is substituted with a halogen atom (Table 3).

The presence of both regioisomers can be rationalized considering the formation of an intermediate aziridinium ion upon heating, which is then attacked by methoxide at the least hindered carbon atom of the aziridine ring furnishing



Scheme 4.

Table 3. Formation of regio-isomers **8** and **9** upon treatment of *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines **7** with sodium methoxide

Entry	R^1	R^2	R^3	Ratio **8/9**[a]	**8** (%)[b]	**9** (%)[b]
1	2-Br	H	H	79/21	**8a** (56)	**9a** (15)
2	2-Cl	H	H	80/20	**8b** (58)	**9b** (15)
3	2-Br	2-Br	H	85/15	**8c** (55)	**9c** (10)
4	2-Cl	2-Br	H	86/14	**8d** (57)	**9d** (9)
5	2-Cl	2-Cl	H	86/14	**8e** (54)	**9e** (9)
6	H	3-Cl	H	86/14	**8f** (49)	**9f** (—)
7	4-Me	4-Cl	Me	87/13	**8g** (55)	**9g** (—)

[a] Based on ^{1}H NMR.
[b] Yield after column chromatography.

the major isomers **8**, in which the amino moiety has moved from the terminus of the propane skeleton towards the central carbon atom. The formation of the minor isomers **9** can be the result of the attack of methoxide at the more hindered carbon atom of the aziridinium ion or, alternatively, the result of a S_N2 substitution reaction of methoxide at CHBr in bromoamines **7**.

In order to study the effect of the concentration of sodium methoxide in this transformation, 2-bromoamine **7g** was treated with a 0.2, 1.0, 1.5 and 2.0 N solution of 2 equiv of sodium methoxide in methanol, respectively. In all cases, the same ratio of isomers **8g** versus **9g** was observed after reaction (87/13). Apparently, the concentration of methoxide has no influence on the reaction outcome. When *N*-(2-bromo-3-aryloxypropyl)amines **7** were heated under reflux in methanol or ethanol, a mixture of the corresponding 2-amino-1-aryloxy-3-alkoxypropanes and 3-amino-1-aryloxy-2-alkoxypropanes was obtained, although in these cases the ratio of both isomers was almost in equilibrium (55/45 and 54/46, respectively). In isopropanol, however, no reaction occurred and the starting material was recovered. Attempts to introduce a hydroxyl group instead of a methoxy group using sodium hydroxide (3 N in H_2O) in CH_2Cl_2–H_2O (1/1) or in DMF–H_2O (3/1) (rt or 80 °C, 30 min–5 h), or using KOH in Et_2O (rt, 6 h) were unsuccessful and the starting material was recovered.

In conclusion, a new and attractive synthetic approach towards 2-amino-1-aryloxy-3-methoxypropanes, valuable compounds with diverse biological activities, has been developed in three efficient steps starting from 1-arylmethyl-2-(bromomethyl)aziridines. The latter aziridines were converted into the corresponding 2-(aryloxymethyl)-aziridines upon treatment with the appropriate phenoxide, followed by regioselective ring opening using benzyl bromide towards *N*,*N*-di(arylmethyl)-*N*-(2-bromo-3-aryloxypropyl)amines. Treatment of the latter amines with sodium methoxide in methanol afforded the desired 2-amino-1-aryloxy-3-methoxypropanes as the major compounds (49–58%) besides the isomeric 3-amino-1-aryloxy-2-methoxypropanes in minor quantities (9–15%).

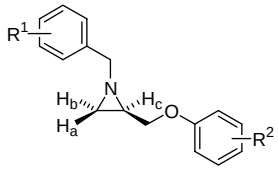
3. Experimental

3.1. General

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer VARIAN MAT 112, 70 eV using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or AGILENT 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Dichloromethane was distilled over calcium hydride, other solvents were used as received from the supplier.

3.2. Synthesis of 1-arylmethyl-2-(aryloxymethyl)aziridines 6

As a representative example, the synthesis of 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** is described here. 1-(2-Chlorophenyl)methyl-2-(bromomethyl)aziridine **5c** (1.30 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46 g, 5 equiv) dissolved in 50 mL of a solvent mixture containing acetone and DMF (1/1 on volumetric basis) and heated under reflux for 10 h. The reaction mixture was poured into brine and extracted with Et_2O (3×50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** (1.24 g, 91%), which was purified by means of column chromatography (hexane/ethyl acetate 4:1) in order to obtain an analytically pure sample.



3.2.1. 1-Phenylmethyl-2-(3-chlorophenoxymethyl)aziridine 6a. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.51 (1H, d, J=6.6 Hz, H_b); 1.79 (1H, d, J=3.6 Hz, H_a); 1.87–1.93 (1H, m, NCH); 3.42 and 3.47 (2H, 2×d, J=13.2 Hz, $C_6H_4CH_2$); 3.82 and 3.93 (2H, 2×d×d, J=10.6, 6.6, 4.6 Hz, CH_2O); 6.70–6.74, 6.86–6.88, 7.07–7.13 and 7.23–7.36 (1H, 2H, 1H and 5H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.72 (NCH_2CH); 37.65 (NCH); 64.22 ($PhCH_2$); 70.40 (CH_2O); 113.12 and 115.13 (2×CH_2OHC_{ortho}); 120.93, 127.17, 128.07, 128.37 and 130.13 (CH_2OHC_{para}, CH_2OHC_{meta}, 2×NCH_2HC_{ortho}, 2×NCH_2HC_{meta} and NCH_2HC_{para}); 134.79 and 138.76 (NCH_2C and CCl); 159.44 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2986; 2925; 2831; 1594; 1579; 1480; 1230; 1028; 733. MS

(70 eV): *m/z* (%): 274/276 ($M^+ + 1$, 100), 91 (10). Light-yellow oil. Anal. Calcd for $C_{16}H_{16}ClNO$: C 70.20, H 5.89, N 5.12. Found: C 70.39, H 6.06, N 4.98.

3.2.2. 1-(2-Bromophenyl)methyl-2-(phenoxymethyl)-aziridine 6b. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.96 (1H, d, J=3.3 Hz, H_a); 2.05–2.10 (1H, m, H_c); 3.58 and 3.66 (2H, 2×d, J=15.2 Hz, $C_6H_4CH_2$); 3.97 and 4.07 (2H, 2×d×d, J=10.4, 6.6, 4.6 Hz, CH_2O); 6.80–6.83, 6.88–6.94, 7.13–7.36, 7.51–7.54 and 7.74–7.77 (2H, 3H, 2H and 2×1H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.52 (NCH_2CH); 38.62 (NCH); 62.60 ($PhCH_2$); 69.06 (CH_2O); 114.43 (2×CH_2OHC_{ortho}); 120.90 (CH_2OHC_{para}); 123.16 (CBr); 127.49; 128.64 and 129.38 (2×$BrHC_{meta}$, $BrHC_{para}$ and 2×CH_2OHC_{meta}); 132.33 ($BrHC_{ortho}$); 137.19 (NCH_2C); 158.27 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3064; 1664; 1594; 1496; 1472; 1242; 1027; 910; 751; 692. MS (70 eV): *m/z* (%): 318/20 ($M^+ + 1$, 100); 277/9 (55), 256/8 (8), 169/71 (15), 121 (16). R_f=0.18; hexane/ethyl acetate 4:1. Light-yellow oil. Anal. Calcd for $C_{16}H_{16}BrNO$: C 60.39, H 5.07, N 4.40. Found: C 60.53, H 5.20, N 4.27.

3.2.3. 1-(2-Chlorophenyl)methyl-2-(phenoxymethyl)-aziridine 6c. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.65 (1H, d, J=6.6 Hz, H_b); 1.94 (1H, d, J=3.3 Hz, H_a); 2.04–2.07 (1H, m, H_c); 3.60 and 3.37 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.96 and 4.06 (2H, 2×d×d, J=10.3, 6.6, 4.8 Hz, CH_2O); 6.80–6.97; 7.17–7.36 and 7.72–7.75 (5H, 3H and 1H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.59 (NCH_2CH); 38.41 (NCH); 60.39 ($PhCH_2$); 69.38 (CH_2O); 114.46 (2×CH_2OHC_{ortho}); 120.84 (CH_2OHC_{para}); 126.84, 128.26, 129.00 and 129.36 ($ClHC_{para}$, 2×$ClHC_{meta}$, $ClHC_{ortho}$ and 2×CH_2OHC_{meta}); 132.84 and 135.99 (CCl and CCH_2N); 158.42 (CH_2OC). IR (NaCl, cm^{-1}): ν_{max}=3063; 2991; 2925; 1599; 1496; 1472; 1242; 1038; 910; 751; 692. MS (70 eV): *m/z* (%): 274/6 ($M^+ + 1$, 100); 231/3 (20). R_f=0.21; hexane/ethyl acetate 4:1. Light-yellow oil. Anal. Calcd for $C_{16}H_{16}ClNO$: C 70.20, H 5.89, N 5.12. Found: C 70.42, H 6.03, N 5.26.

3.2.4. 2-[(2-Bromophenoxy)methyl]-1-(2-bromophenyl)-methylaziridine 6d. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.95 (1H, d, J=3.3 Hz, H_a); 2.10–2.16 (1H, m, H_c); 3.55 and 3.65 (2H, 2×d, J=15.1 Hz, $C_6H_4CH_2$); 3.98 and 4.17 (2H, 2×d×d, J=10.6, 6.9, 4.1 Hz, CH_2O); 6.80–6.86, 6.93–6.96, 7.09–7.37, 7.50–7.55 and 7.73–7.76 (2×1H, 3H, 2H and 1H, 5×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.77 (NCH_2CH); 38.12 (NCH); 63.56 ($PhCH_2$); 71.61 (CH_2O); 112.34 and 113.74 (2×CH_2OHC_{ortho}); 122.18, 123.22, 127.81, 129.56, 132.40 and 133.48 (7×HC_{arom} and NCH_2CCBr); 138.32 (CCH_2N); 155.22 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2892; 1587; 1484; 1461; 1441; 1284; 1249; 1015; 742; 670. MS (70 eV): *m/z* (%): 396/8/400 ($M^+ + 1$, 100). R_f=0.20; hexane/ethyl acetate 4:1. White crystals; mp=82.4–82.6 °C. Anal. Calcd for $C_{16}H_{15}Br_2NO$: C 48.39, H 3.81, N 3.53. Found: C 48.21, H 4.11, N 3.37.

3.2.5. 2-[(2-Chlorophenoxy)methyl]-1-(2-chlorophenyl)-methylaziridine 6e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (1H, d, J=6.3 Hz, H_b); 1.95 (1H, d, J=3.6 Hz, H_a); 2.04–2.18 (1H, m, H_c); 3.54 and 3.72 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.96 and 4.17 (2H, 2×d×d, J=10.5, 7.2, 4.3 Hz, CH_2O); 6.80–6.98, 7.10–7.36 and 7.73–7.76 (3H; 4H and 1H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 31.57 (NCH_2CH); 38.20 (NCH); 60.70 ($PhCH_2$); 71.07 (CH_2O); 113.62 (CH_2OHC_{ortho}); 120.82 and 122.86 (CH_2OCCC and CH_2OHC_{para}); 127.06, 127.65, 128.23, 129.29, 129.49, 130.22 (4×NCH_2HC_{arom} and 2×CH_2OHC_{meta}); 132.84 and 135.99 ($CClCCH_2N$ and CCH_2N); 158.42 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2896; 1591; 1489; 1446; 1250; 1061; 742; 698. MS (70 eV): *m/z* (%): 308/10/12 ($M^+ + 1$, 100). R_f=0.20; hexane/ethyl acetate 4:1. Light-yellow crystals; mp=57.5–58.6 °C. Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C 62.35, H 4.91, N 4.54. Found: C 62.51, H 5.12, N 4.35.

3.2.6. 2-[(2-Bromophenoxy)methyl]-1-(2-chlorophenyl)-methylaziridine 6f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (1H, d, J=6.6 Hz, H_b); 1.95 (1H, d, J=3.3 Hz, H_a); 2.05–2.16 (1H, m, H_c); 3.57 and 3.67 (2H, 2×d, J=15.0 Hz, $C_6H_4CH_2$); 3.98 and 4.16 (2H, 2×d×d, J=10.5, 6.9, 4.1 Hz, CH_2O); 6.80–6.85, 6.93–6.96, 7.17–7.35, 7.51–7.54 and 7.71–7.74 (2×1H, 4H and 2×1H, 5×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.82 (NCH_2CH); 38.12 (NCH); 61.09 ($PhCH_2$); 71.60 (CH_2O); 112.33 and 113.73 (2×CH_2OHC_{ortho}); 122.16, 127.18, 128.24, 128.54, 129.14, 133.00 and 133.47 (7×HC_{arom} and CCl); 136.68 (CCH_2N); 155.22 (CH_2OC). IR (KBr, cm^{-1}): ν_{max}=2894; 1586; 1484; 1442; 1249; 1033; 743. MS (70 eV): *m/z* (%): 352/4/6 ($M^+ + 1$, 100). R_f=0.17; hexane/ethyl acetate 4:1. White crystals; mp=78.8–79.7 °C. Anal. Calcd for $C_{16}H_{15}BrClNO$: C 54.49, H 4.29, N 3.97. Found: C 54.66, H 4.52, N 3.81.

3.2.7. 1-(4-Methylphenyl)methyl-2-(4-chlorophenoxymethyl)aziridine 6g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (1H, d, J=6.6 Hz, H_b); 1.81 (1H, d, J=3.6 Hz, H_a); 1.91–1.98 (1H, m, NCH); 2.33 (3H, s, $PhCH_3$); 3.47 and 3.42 (2H, d×d, J=13.2, 3.9 Hz, $ArCH_2$); 3.86 and 3.93 (2H, 2×d×d, J=10.4, 6.3, 4.8 Hz, $HCHO$); 6.76–6.81 and 7.11–7.25 (2H and 6H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.09 ($PhCH_3$); 31.70 (NCH_2CH); 37.67 (NCH); 64.00 ($ArCH_2$); 70.46 (CH_2O); 115.88 ($OCCH_{ortho}$); 125.56 (CCl); 128.04, 129.03 and 129.20 (CH_{arom}); 135.67 and 136.71 (CCH_3 and CCH_2N); 157.28 (CH_2OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=2922; 1757; 1675; 1595; 1581; 1491; 1347; 1286; 1243; 1171; 1094; 1064; 1022; 824; 666. MS (70 eV): *m/z* (%): 288/90 ($M^+ + 1$, 100). R_f=0.24; hexane/ethyl acetate 7:3. Light-yellow oil. Anal. Calcd for $C_{17}H_{18}ClNO$: C 70.95, H 6.30, N 4.87. Found: C 71.18, H 6.51, N 4.72.

3.3. Synthesis of *N*-(2-bromo-3-aryloxypropyl)amines 7

As a representative example, the synthesis of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** is described here. To a solution of 1-(2-chlorophenyl)methyl-2-(phenoxymethyl)aziridine **6c** (2.73 g, 10 mmol) in 50 mL acetonitrile was added benzyl bromide (1.71 g, 1 equiv) under stirring and the resulting mixture was heated for 5 h under reflux. Evaporation of the solvent afforded *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** (3.95 g, 89%), which was purified by means of column chromatography (hexane/ethyl acetate 1:1) in order to obtain an analytically pure sample.

3.3.1. *N*,*N*-Di(phenylmethyl)-*N*-(2-bromo-3-(3-chlorophenoxy)propyl)amine 7a. ^{1}H NMR (270 MHz, $CDCl_3$):

δ 2.91 and 3.08 (2H, 2×d×d, J=13.5, 8.7, 5.1 Hz, N(*HCH*)CH); 3.56 and 3.72 (4H, 2×d, J=13.2 Hz, 2×PhCH_2N); 3.93–3.99 and 4.07–4.19 (1H and 2H, 2×m, BrCH and (HCH)O); 6.64–6.68, 6.73–6.74, 6.88–6.96 and 7.13–7.43 (1H, 1H, 2H and 10H, 4×m, CH_{arom}). ^{13}C NMR (68 MHz): δ 48.57 (CHBr); 57.50 (NCH_2CH); 59.37 (2×NCH_2Ar); 70.06 (CH_2O); 113.08 and 114.98 (2×OHC_{ortho}), 121.18, 127.28, 128.34, 128.96, 130.10 (OHC_{meta}, OHC_{para}, 4×NCH_2HC_{ortho}, 4×NCH_2HC_{meta} and 2×NCH_2HC_{para}); 134.71 (CCl); 138.63 (2×NCH_2C); 158.85 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=3064; 3029; 2928; 2805; 1595; 1480; 1454; 1247; 1229; 749; 697. MS (70 eV): *m/z* (%): 444/46/48 (M^++1, 12), 396/8 (90), 364/6 (100). Colorless oil. Anal. Calcd for $C_{23}H_{23}BrClNO$: C 62.11, H 5.21, N 3.15. Found: C 62.26, H 5.42, N 3.02.

3.3.2. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-bromo-3-phenoxypropylamine 7b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97 and 3.14 (2H, 2×d×d, J=13.8, 8.3, 5.9 Hz, N(*HCH*)CH); 3.75 (2H, d, J=13.8 Hz, PhCH_2N); 3.64 and 3.83 (2H, 2×d, J=13.6 Hz, PhCH_2N); 3.99–4.06 and 4.13–4.27 (1H and 2H, 2×m, BrCH and (HCH)O); 6.76–6.79, 6.93–6.98, 7.06–7.12, 7.17–7.45 and 7.49–7.68 (2H, 1H, 1H, 8H and 2H; 5×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.10 (CHBr); 57.99, 59.10 and 59.63 (3×NCH_2); 70.09 (CH_2O); 114.78, 121.22, 124.66, 127.48, 128.48, 128.86, 129.26, 129.52, 131.27 and 132.99 (14×CH_{arom} and CBr); 138.03 and 138.52 (2×NCH_2C); 158.29 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3062; 3029; 2926; 2832; 1599; 1496; 1243; 1027; 753; 692. MS (70 eV): *m/z* (%): 488/90/92 (M^++1, 10); 409/11 (25); 408/10 (100); 365/7/9 (65). R_f=0.60; hexane/ethyl acetate 4:1. Anal. Calcd for $C_{23}H_{23}Br_2NO$: C 56.46, H 4.74, N 2.86. Colorless oil. Found: C 56.62, H 4.95, N 2.97.

3.3.3. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine 7c. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.96 and 3.13 (2H, 2×d×d, J=13.9, 8.3, 5.6 Hz, N(*HCH*)CH); 3.74 (2H, d, J=14.8 Hz, PhCH_2N); 3.62 and 3.84 (2H, 2×d, J=13.5 Hz, PhCH_2N); 3.99–4.06 and 4.13–4.23 (1H and 2H, 2×m, BrCH and (HCH)O); 6.76–6.98, 7.12–7.41 and 7.51–7.55 (5H, 8H and 1H; 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 48.97 (CHBr); 56.06, 57.52 and 59.14 (3×NCH_2); 69.61 (CH_2O); 114.46, 120.95, 126.56, 128.14, 128.53, 128.82, 128.89, 129.23, 129.38, 130.85, 133.92 (14×CH_{arom} and CCl); 136.04 and 138.22 (2×NCH_2C); 157.91 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3030; 2832; 1598; 1497; 1243; 909; 754; 735; 692. MS (70 eV): *m/z* (%): 444/6 (M^++1, 10); 364/6 (100); 321 (23); 323 (21). R_f=0.85; hexane/ethyl acetate 1:1. Colorless oil. Anal. Calcd for $C_{23}H_{23}BrClNO$: C 62.11, H 5.21, N 3.15. Found: C 62.32, H 5.38, N 2.96.

3.3.4. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-bromo-3-(2-bromophenoxy)propyl)amine 7d. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.01 and 3.24 (2H, 2×d×d, J=13.8, 7.6, 5.8 Hz, N(*HCH*)CH); 3.69 and 3.73 (2H, 2×d, J=13.6 Hz, PhCH_2N); 3.78 and 3.83 (2H, 2×d, J=14.2 Hz, PhCH_2N); 4.10–4.21 (3H, m, BrCH and (HCH)O); 6.71 (1H, d×d, J=8.0, 1.4 Hz, CH_{arom}); 6.83 (1H, d×t, J=7.4, 1.4 Hz, CH_{arom}); 7.06 (1H, d×t, J=7.7, 1.7 Hz, CH_{arom}); 7.19–7.34 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.62 (CHBr); 58.00, 59.22 and 59.71 (3×NCH_2); 70.81 (CH_2O); 112.58, 113.43, 122.34, 127.44, 128.43, 128.80, 128.89, 129.14, 129.27, 131.31, 132.97 and 133.50 (13×CH_{arom} and 2×CBr); 138.06 and 138.54 (2×NCH_2C); 154.68 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3062; 3028; 2930; 2833; 1586; 1481; 1442; 1278; 1248; 1030; 749; 698. MS (70 eV): *m/z* (%): 566/68/70/72 (M^++1, 5); 486/88/90 (100). R_f=0.88; hexane/ethyl acetate 1:1. Colorless oil. Anal. Calcd for $C_{23}H_{22}Br_3NO$: C 48.62, H 3.90, N 2.47. Found: C 48.79, H 4.03, N 2.30.

3.3.5. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-(2-chlorophenoxy)propyl)amine 7e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 and 3.21 (2H, 2×d×d, J=13.8, 7.6, 5.4 Hz, N(*HCH*)CH); 3.62-3.92 (4H, m, 2×PhCH_2N); 4.19-4.23 (3H, m, BrCH and (HCH)O); 6.74 (1H, d×d, J=8.1, 1.0 Hz, CH_{arom}); 6.86-6.91 and 7.10-7.34 (1H and 10H, 2×m, CH_{arom}); 7.52 (1H, d, J=7.2 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.91 (CHBr); 56.39, 58.07 and 59.78 (3×NCH_2); 70.88 (CH_2O); 113.81, 122.05, 123.44, 127.00, 127.56, 127.84, 128.59, 128.70, 129.38, 129.81, 130.57, 131.38, 134.48 (13×CH_{arom} and 2×CCl); 136.55 and 138.72 (2×NCH_2C); 154.00 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3064; 3028; 2931; 2833; 1590; 1486; 1445; 1278; 1249; 748; 699. MS (70 eV): m/z (%): 478/80/82/84 (M^++1; 5); 399/401/403 (65); 398/400/402 (100). R_f = 0.62; hexane/ethyl acetate 4/1. Colorless oil. Anal. Calcd for $C_{23}H_{22}BrCl_2NO$: C 57.64, H 4.63, N 2.92. Found: C 57.84, H 4.75, N 2.76.

3.3.6. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-(2-bromophenoxy)propyl)amine 7f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 and 3.23 (2H, 2×d×d, J=11.1, 7.7, 5.5 Hz, N(*HCH*)CH); 3.63–3.86 (4H, m, 2×PhCH_2N); 4.11–4.20 (3H, m, BrCH and (HCH)O); 6.70 (1H, d×d, J=8.3, 1.4 Hz, CH_{arom}); 6.82 (1H, d×t, J=7.43, 1.38 Hz, CH_{arom}); 7.19–7.33 and 7.47–7.53 (10H and 1H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 48.65 (CHBr); 56.65, 58.04 and 59.72 (3×NCH_2); 70.74 (CH_2O); 112.57, 113.38, 122.34, 126.84, 127.41, 128.44, 129.23, 129.68, 131.22, 133.51 and 134.37 (13×CH_{arom}, CCl and CBr); 136.45 and 138.63 (2×NCH_2C); 154.68 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3028; 2929; 2833; 1586; 1481; 1443; 1278; 1247; 1052; 1031; 749; 698. MS (70 eV): *m/z* (%): 522/4/6/8 (M^++1, 5); 443/5/7(20); 442/4/6(100). R_f=0.59; hexane/ethyl acetate 4:1. Colorless oil. Anal. Calcd for $C_{23}H_{22}Br_2ClNO$: C 52.75, H 4.23, N 2.67. Found: C 52.88, H 4.47, N 2.74.

3.3.7. *N*,*N*-Di[(4-methylbenzyl)methyl]-*N*-[2-bromo-3-(4-chlorophenoxy)propyl]amine 7g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (6H, s, 2×CH_3); 2.88 and 3.06 (2H, 2×d×d, J=13.6, 8.7, 5.4 Hz, N(*HCH*)CH); 3.50 and 3.66 (4H, 2×2×d, J=13.4 Hz, 2×Ar(*HCH*)N); 3.95–4.00 and 4.10–4.17 (1H and 2H, 2×m, CHBr and (HCH)O); 6.65–6.70 and 7.07–7.29 (2H and 10H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.10 (2×CH_3); 48.92 (CHBr); 57.52 and 59.12 (2×NCH_2Ar); 70.22 (CH_2O); 115.93, 128.96, 129.02 and 129.22 (CH_{arom}); 129.47 (CCl); 135.69 and 136.79 (2×CH_3C and 2×NCH_2C_{quat}); 156.88 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=3021; 2922; 2823; 1596; 1582; 1514; 1491; 1454; 1370; 1286; 1244; 1171; 1092; 1021; 823; 808. MS (70 eV): *m/z* (%): 392/4 (M^+−Br, 100). R_f=0.53; hexane/ethyl acetate 4:1.

White crystals; mp = 54.4 °C. Anal. Calcd for $C_{25}H_{27}BrClNO$: C 63.50, H 5.76, N 2.96. Found: C 63.66, H 5.88, N 2.78.

3.4. Synthesis of 2-amino-1-aryloxy-3-methoxypropanes 8

As a representative example, the synthesis of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)]amino-1-phenoxy-3-methoxypropane **8b** is described here. To *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **7c** (1.19 g, 3 mmol) was added slowly under stirring a solution of sodium methoxide in methanol (60 mL, 0.2 N, 12 mmol), and the resulting solution was heated under reflux for 2 h. The resulting reaction mixture was poured into brine (50 mL) and extracted with CH_2Cl_2 (3×50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)]-amino-1-phenoxy-3-methoxypropane **8b** and *N*-benzyl-*N*-(2-chloorbenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine **9b** (4/1). Isolation of the major isomer was realized by means of column chromatography (SiO_2) (hexane/EtOAc 49:1).

3.4.1. 2-[*N*-Benzyl-*N*-(2-bromoarylmethyl)]amino-1-phenoxy-3-methoxypropane 8a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28–3.34 (1H, m, NCH); 3.32 (3H, s, CH_3O); 3.63–3.73 (2H, m, CH_2OMe); 3.88 (2H, s, NCH_2); 3.97 (2H, d, J=3.3 Hz, NCH_2); 4.11–4.21 (2H, m, CH_2OPh); 6.89–6.95 (3H, m, CH_{arom}); 7.03 (1H, d×t, J=7.7, 1.7 Hz, CH_{arom}); 7.16–7.29 and 7.37–7.40 (6H and 2H, 2×m, CH_{arom}); 7.46 (1H, d×d, J=8.0, 1.1 Hz, CH_{arom}); 7.68 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 55.03 and 55.70 (2×NCH_2); 57.09 (NCH); 59.20 (OCH_3); 66.76 (*C*H_2OPh); 71.69 (*C*H_2OCH_3); 114.70, 120.83, 124.31, 127.03, 127.44, 128.36, 128.86, 129.59, 130.79, 132.68 (14×CH_{arom} and CBr); 139.41 and 140.28 (2×*C*CH_2N); 159.00 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2926; 2876; 1600; 1496; 1244; 909; 753; 734; 693. MS (70 eV): *m*/*z* (%): 440/2 (M^++1; 100). R_f=0.11; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{26}BrNO_2$: C 65.46, H 5.95, N 3.18. Found: C 65.62, H 6.14, N 3.08.

3.4.2. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-phenoxy-3-methoxypropane 8b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28–3.39 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.64–3.72 (2H, m, CH_2OMe); 3.88 (2H, s, NCH_2); 3.98 and 4.04 (2×1H, 2×d, J=15.4 Hz, NCH_2); 4.14–4.22 (2H, m, CH_2OPh); 6.89–6.96, 7.11–7.39 and 7.67–7.69 (3H, 10H and 1H, 3×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.26 and 55.62 (2×NCH_2); 56.90 (NCH); 59.15 (OCH_3); 66.65 (*C*H_2OPh); 71.60 (*C*H_2OCH_3); 114.58, 120.73, 126.73, 126.94, 127.91, 128.28, 128.76, 129.33, 129.52, 130.57 and 133.96 (14×CH_{arom} and CCl); 137.75 and 140.25 (2×*C*CH_2N); 158.90 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2925; 2876; 1600; 1496; 1244; 1037; 753; 692. MS (70 eV): *m*/*z* (%): 396/98 (M^++1, 100). R_f=0.10; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C 72.81, H 6.62, N 3.54. Found: C 72.96, H 6.80, N 3.39.

3.4.3. 2-[*N*-Benzyl-*N*-(2-bromobenzyl)]amino-1-(2-bromophenoxy)-3-methoxypropane 8c. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30–3.39 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.75 (2H, d, J=6.1 Hz, CH_2OMe); 3.90 and 3.97 (2H, 2×d, J=14.2 Hz, N(HCH)); 4.01–4.09 (2H, m, NCH_2); 4.18–4.27 (2H, m, CH_2OPh); 6.78–6.90 (2H, m, CH_{arom}); 7.06 (1H, d×t, J=7.6, 1.7 Hz, CH_{arom}); 7.16–7.33 (5H, m, CH_{arom}); 7.40–7.60 (4H, m, CH_{arom}); 7.72 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.90 and 55.64 (2×NCH_2); 56.75 (NCH); 59.22 (OCH_3); 67.43 (*C*H_2OPh); 71.25 (*C*H_2OCH_3); 112.15, 112.80, 121.84, 124.24, 126.96, 127.44, 128.31, 128.52, 128.80, 130.83, 132.62, 133.44 (13×CH_{arom} and 2×CBr); 139.29 and 140.25 (2×*C*CH_2N); 155.35 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3062; 2925; 2875; 1587; 1481; 1442; 1277; 1248; 1121; 1030; 961. MS (70 eV): *m*/*z* (%): 518/20/22 (M^++1, 100). R_f=0.04; hexane/ethyl acetate 98:2. Colorless oil. Anal. Calcd for $C_{24}H_{25}Br_2NO_2$: C 55.51, H 4.85, N 2.70. Found: C 55.39, H 5.05, N 2.59.

3.4.4. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-(2-bromophenoxy)-3-methoxypropane 8d. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.32-3.36 (1H, m, NCH); 3.33 (3H, s, CH3O); 3.75 (2H, d, J=5.9 Hz, CH_2OMe); 3.89 and 3.97 (2×1H, 2×d, J=14.2 Hz, NCH_2); 4.01 and 4.07 (2×1H, 2×d, J=15.0 Hz, NCH_2); 4.20-4.24 (2H, m, CH_2OPh); 6.79-6.88 and 7.09-7.30 (2H and 7H, 2×m, CH_{arom}); 7.40 (1H, d, J=7.3 Hz, CH_{arom}); 7.54 (1H, d×d, J=7.7, 1.5 Hz, CH_{arom}); 7.70 (1H, d, J=7.6 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.19 and 55.56 (2×NCH_2); 56.68 (NCH); 58.94 (OCH_3); 67.37 (*C*H_2OPh); 71.14 (*C*H_2OCH_3); 112.02, 112.69, 121.67, 126.60, 126.77, 127.76, 128.12, 128.32, 128.61, 129.16, 130.55, 133.24 and 133.82 (13×HC_{arom}, CBr and CCl); 137.59 and 140.09 (2×*C*CH_2N); 155.20 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3063; 3027; 2926; 2926; 2877; 1587; 1481; 1442; 1248; 1031; 749; 699. MS (70 eV): m/z (%): 472/4/6 (M^+-1; 100). R_f=0.04; hexane/ethyl acetate 98/2. Colorless oil. Anal. Calcd for $C_{24}H_{25}BrClNO_2$: C 60.71, H 5.31, N 2.95. Found: C 60.93, H 5.43, N 3.05.

3.4.5. 2-[*N*-Benzyl-*N*-(2-chlorobenzyl)]amino-1-(2-chlorophenoxy)-3-methoxypropane 8e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31–3.90 (1H, m, NCH); 3.33 (3H, s, CH_3O); 3.73 (2H, d, J=6.1 Hz, CH_2OMe); 3.88 and 3.96 (2×1H, 2×d, J=14.0 Hz, NCH_2); 4.01 and 4.05 (2×1H, 2×d, J=15.1 Hz, NCH_2); 4.22 (2H, d, J=5.5 Hz, CH_2OPh); 6.84–6.90 and 7.10–7.42 (2H and 10H, 2×m, CH_{arom}); 7.72 (1H, d×d, J=7.7, 1.7 Hz, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 52.24 and 55.62 (2×NCH_2); 56.71 (NCH); 59.20 (OCH_3); 67.46 (*C*H_2OPh); 71.33 (*C*H_2OCH_3); 112.96, 121.33, 122.91, 126.81, 126.96, 127.77, 127.95, 128.32, 128.32, 128.79, 129.35, 130.35, 130.68 and 133.99 (13×HC_{arom} and 2×CCl); 137.75 and 140.28 (2×CCH_2N); 154.53 (*C*OCH_2). IR (NaCl, cm^{-1}): ν_{max}=3064; 3027; 2926; 2877; 1590; 1486; 1446; 1249; 1062; 748; 698. MS (70 eV): *m*/*z* (%): 428/30/32 (M^+−1, 100). R_f=0.08; hexane/ethyl acetate 49:1. Colorless oil. Anal. Calcd for $C_{24}H_{25}Cl_2NO_2$: C 66.98, H 5.86, N 3.25. Found: C 67.13, H 6.02, N 3.11.

3.4.6. 2-(*N*,*N*-Dibenzyl)amino-1-(3-chlorophenoxy)-3-methoxypropane 8f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.27–3.32 (1H, m, CHN); 3.31 (3H, s, OCH_3); 3.62 and 3.65 (2H, 2×d×d, J=9.9, 6.1, 5.8 Hz, (HCH)OCH_3); 3.78–3.87 (4H, m, 2×NCH_2); 4.10 and 4.13 (2H, 2×d×d, J=9.6, 6.3, 5.5 Hz, (*HCH*)OAr); 6.74–6.78, 6.89–6.93 and

7.13–7.39 (1H, 2H and 11H, 3×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.42 (2×NCH_2); 55.96 (NCH); 58.92 (OCH_3); 67.21 (CH_2OAr); 71.64 (CH_2OCH_3); 112.97, 115.05, 120.88, 126.94, 128.25, 128.74, 129.21, 130.15 and 130.77 (HC_{arom}); 134.96 (CCl); 140.36 (2×NCH_2C_{quat}) 159.72 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}= 3063; 3028; 2925; 1595; 1454; 1099; 1072; 745; 698. MS (70 eV): *m/z* (%): 396/8 (M^++1, 100). R_f=0.14; hexane/ethyl acetate 97:3. Colorless oil. Anal. Calcd for $C_{24}H_{26}ClNO_2$: C 72.81, H 6.62, N 3.54. Found: C 73.01, H 6.84, N 3.41.

3.4.7. 2-*N*,*N*-Di[(4-methylbenzyl)methyl]amino-1-(4-chlorophenoxy)-3-methoxypropane 8g. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (6H, s, 2×CH_3); 3.25–3.30 (1H, m, CHN); 3.30 (3H, s, CH_3O); 3.59–3.66 (2H, m, CH_2OMe); 3.75 and 3.77 (4H, 2×2×d, *J*=14.3 Hz, 2×N(HCH)); 4.06 and 4.08 (2H, 2×d×d, *J*=9.9, 6.1, 5.5 Hz, (*HCH*)OAr); 6.74–6.81 and 6.97–7.28 (2H and 10H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.08 (2×CH_3); 54.87 (2×NCH_2); 55.64 (NCH); 59.00 (OCH_3); 67.33 (CH_2OAr); 71.53 (CH_2OCH_3); 115.79 (2×HC_{ortho}); 125.38 (CCl); 128.59, 128.86 and 129.21 (CH_{arom}); 136.28 and 137.29 (2×CH_3C and 2×NCH_2C); 157.48 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max}=2923; 1596; 1513; 1491; 1242; 1207; 1094; 1019; 910; 823; 734. MS (70 eV): *m/z* (%): 424/6 (M^++1; 100); 307 (62). R_f=0.15; hexane/ethyl acetate 97:3. Colorless oil. Anal. Calcd for $C_{26}H_{30}ClNO_2$: C 73.65, H 7.13, N 3.30. Found: C 73.84, H 7.30, N 3.16.

3.5. Detectable signals derived from the minor constituents 9

3.5.1. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine 9a. ^1H NMR (300 MHz, $CDCl_3$): δ 2.70 and 2.77 (2H, 2×d×d, *J*=13.5, 6.6, 5.2 Hz, CH(*HCH*)N); 3.44 (3H, s, CH_3O); 3.56–3.79 (5H, m, OCH and 2×NCH_2Ph); 3.85 and 4.01 (2H, 2×d×d, *J*=10.0, 5.6, 3.7 Hz, (HCH)OPh); 6.79–7.57 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.37 (CH_2N); 58.50 (OCH_3); 59.17 and 59.95 (2×NCH_2Ph); 68.64 (CH_2O); 78.55 (OCH); 114.67, 120.77, 120.88, 124.60, 127.23, 127.40, 128.38, 128.57, 129.19, 129.42, 129.51, 131.07 and 132.87 (14×CH_{arom} and CBr); 138.64 and 139.15 (2×CCH_2N); 158.90 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=3063; 3029; 2928; 2827; 1600; 1496; 1244; 1027; 752; 734; 692. MS (70 eV): *m/z* (%): 440/2 (M^++1, 100). R_f=0.10; hexane/ethyl acetate 49:1. Colorless oil.

3.5.2. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-methoxy-3-phenoxypropyl)amine 9b. ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 and 2.77 (1H, 2×d×d, *J*=13.5, 6.6, 5.2 Hz, CH(*HCH*)N); 3.45 (3H, s, CH_3O); 3.58–3.68 and 3.73–3.85 (3H and 2H, 2×m, OCH and 2×NCH_2Ph); 3.86 and 4.02 (H, 2×d×d, *J*=11.6, 5.6, 3.6 Hz, CH_2OPh); 6.81–7.59 (14H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 54.34 (CH_2N); 56.57 (OCH_3); 58.04 and 59.97 (2×NCH_2Ph); 68.58 (CH_2O); 78.53 (OCH); 114.63, 120.75, 126.77, 127.20, 128.26, 128.37, 129.13, 129.41, 129.56, 129.56, 130.94 and 134.28 (14×CH_{arom} and CCl); 137.00 and 139.19 (2×CCH_2N); 158.87 ($COCH_2$). IR (NaCl, cm^{-1}): ν_{max}=2928; 1600; 1496; 1245; 752; 692. MS (70 eV): *m/z* (%): 396/8 (M^++1, 100). R_f=0.07; hexane/ethyl acetate 49:1. Colorless oil.

3.5.3. *N*-Benzyl-*N*-(2-bromobenzyl)-*N*-[2-methoxy-3-(2-bromophenoxy)propyl]amine 9c. ^1H NMR (300 MHz, $CDCl_3$): δ 2.72 and 2.79 (2H, 2×d×d, *J*=13.6, 6.5, 5.5 Hz, CH(*HCH*)N); 3.50 (3H, s, CH_3O); 3.65–4.10 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.74–7.75 (14H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.64 (CH_2N); 58.51 (OCH_3); 59.03 and 59.82 (2×NCH_2Ph); 70.33 (CH_2O); 78.47 (OCH); aromatic signals could not be seen separately. R_f=0.03; hexane/ethyl acetate 49:1. Colorless oil.

3.5.4. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-[2-methoxy-3-(2-bromophenoxy)propyl]amine 9d. ^1H NMR (270 MHz, $CDCl_3$): δ 2.70 and 2.78 (2H, 2×d×d, *J*=13.6, 6.4, 5.3 Hz, CH(*HCH*)N); 3.50 (3H, s, CH_3O); 3.62–4.06 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.73–3.83, 7.10–7.35 and 7.47–7.55 (14H, 3×m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.75 (CH_2N); 56.60 (OCH_3); 58.51 and 59.91 (2×NCH_2Ph); 70.37 (CH_2O); 78.54 (OCH); aromatic signals could not be seen separately. R_f=0.03; hexane/ethyl acetate 49:1. Colorless oil.

3.5.5. *N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-[2-methoxy-3-(2-chlorophenoxy)propyl]amine 9e. ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 and 2.75 (2H, 2×d×d, *J*=13.7, 6.5, 5.5 Hz, CH(*HCH*)N); 3.47 (3H, s, CH_3O); 3.53–4.12 (7H, m, OCH, 2×NCH_2Ph and CH_2OPh); 6.58–7.52 (14H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.63 (CH_2N); 56.59 (OCH_3); 58.45 and 59.89 (2×NCH_2Ph); 70.37 (CH_2O); 78.54 (OCH); aromatic signals could not be observed separately. R_f=0.06; hexane/ethyl acetate 49:1. Colorless oil.

3.5.6. *N*,*N*-Dibenzyl-*N*-[2-methoxy-3-(3-chlorophenoxy)-propyl]amine 9f. MS (70 eV): *m/z* (%): no M^+; 350 (10); 254 (10); 210 (100); 181 (7); 91 (90).

3.5.7. *N*,*N*-Di[(4-methylbenzyl)methyl]-*N*-[2-methoxy-3-(4-chlorophenoxy)propyl]amine 9g. ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (6H, s, 2×CH_3); 2.58 and 2.70 (2H, 2×d×d, *J*=13.5, 7.4, 4.7 Hz, N(*HCH*)CH); 3.36 (3H, s, OCH_3); 3.57–4.05 (7H, m, C*H*OMe, 2×NCH_2Ar and 2×CH_2OAr); 6.69–6.72 and 6.97–7.28 (2H and 10H, 2×m, CH_{arom}). MS (70 eV): *m/z* (%): no M^+; 378/80 (34); 282 (34); 238 (19); 105 (100). Colorless oil.

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