Reactivity of *N*-(ω-haloalkyl)-β-lactams with regard to lithium aluminium hydride: novel synthesis of 1-(1-aryl-3-hydroxypropyl)aziridines and 3-aryl-3-(*N*-propylamino)propan-1-ols†

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The reactivity of 4-aryl-1-(2-chloroethyl)azetidin-2-ones and 4-aryl-1-(3-bromopropyl)azetidin-2-ones with regard to lithium aluminium hydride has been evaluated for the first time. 4-Aryl-1-(2-chloroethyl)azetidin-2-ones were transformed into novel 1-(1-aryl-3-hydroxypropyl)aziridines through an unprecedented conversion of β-lactams into 2,3-unsubstituted aziridine derivatives. Unexpectedly, 4-aryl-1-(3-bromopropyl)azetidin-2-ones underwent dehalogenation towards 3-aryl-3-(*N*-propylamino)propan-1-ols upon treatment with $LiAlH_4$. 1-(1-Aryl-3-hydroxypropyl)aziridines were further elaborated by means of ring opening reactions using benzyl bromide in acetonitrile towards 3-aryl-3-[*N*-benzyl-*N*-(2-bromoethyl)amino]propan-1-ols and using aluminium(III) chloride in diethyl ether, affording 3-aryl-3-[*N*-(2-chloroethyl)amino]propan-1-ols.

Introduction

Besides their biological relevance as potential antibiotics, azetidin-2-ones have acquired a prominent place in organic chemistry as synthons for further elaboration, which led to the introduction of the term "β-lactam synthon method" in 1997.[1] Since then, the constrained azetidin-2-one ring has been employed successfully in a large variety of different synthetic methodologies towards all kinds of nitrogen-containing target compounds.[2] One of these useful transformations involves the ring transformation of β-lactams into *C*-substituted aziridine derivatives, which are in their turn interesting synthetic intermediates for further syntheses.[3] Despite the synthetic and biological relevance of 2,3-unsubstituted 1-alkylaziridines,[4] no convenient transformations of β-lactams into this type of aziridine derivatives are available in the literature as an alternative for the use of the parent aziridine *via* *N*-alkylation. The need for alternative methods is justified by the severe acute toxicity, explosion hazard, decomposition during storage and instability towards violent polymerization of aziridine itself.[5] In a recent study, an elegant synthesis of 1-(2-hydroxyethyl)aziridines has been described involving ring opening of epoxides by *in situ* generated aziridine.[6] In the present report, a convenient and straightforward approach towards 1-(3-hydroxypropyl)aziridines is disclosed through conversion of 1-(2-chloroethyl)azetidin-2-ones upon treatment with lithium aluminium hydride. Furthermore, also the reactivity of 1-(3-bromopropyl)-β-lactams towards $LiAlH_4$ was evaluated for the synthesis of the corresponding azetidines, resulting in the unexpected formation of 3-(*N*-propylamino)propan-1-ols instead.

The chemistry of *N*-(ω-haloalkyl)azetidin-2-ones comprises an unexplored field of research, although the combination of the reactive β-lactam ring and the halogenated carbon atom allows the design of a variety of transformations towards relevant target compounds. To date, only two approaches involving the use of *N*-(ω-haloalkyl)-β-lactams are available, the first describing the transformation of 1-(ω-haloalkyl)-4-phenylazetidin-2-ones into 7-phenyl-1,4-diazepan-5-ones[7] and the second dealing with the synthesis of 1-(2- and 3-haloalkyl)azetidin-2-ones as precursors for novel piperazine-, morpholine-, and 1,4-diazepane-annulated β-lactams.[8]

Results and discussion

N-(2-Chloroethyl)imines **2a–e** ($n = 1$), *N*-(3-bromopropyl)imines **2f–j** ($n = 2$) and *N*-(3-chloropropyl)imine **2k** ($n = 2$) were prepared in good yields *via* imination of different benzaldehydes **1** in dichloromethane in the presence of $MgSO_4$ and Et_3N utilizing 1 equivalent of the appropriate amine hydrohalide salt (Scheme 1, Table 1). Subsequently, the obtained imines **2** were used as substrates for a Staudinger reaction upon treatment with 1.1 equivalents of phenoxy-, methoxy- or benzyloxyacetyl chloride in the presence of triethylamine in dichloromethane, affording the corresponding novel 1-(2-chloroethyl)azetidin-2-ones **3a–e** and **3l,m** ($n = 1$), 1-(3-bromopropyl)azetidin-2-ones **3f–j** ($n = 2$) and 1-(3-chloropropyl)azetidin-2-one **3k** ($n = 2$) after 15 hours at room temperature (Scheme 1, Table 1). The relative stereochemistry of β-lactams **3** was assigned as *cis* based on the coupling constants between the protons at C3 and C4 in ^{1}H NMR (4.4–4.7 Hz, $CDCl_3$) in accordance with literature data.[9]

In the next stage, 1-(2-chloroethyl)azetidin-2-ones **3a–e,l–m** were transformed into novel 1-(1-aryl-3-hydroxypropyl)aziridines **4a–g** upon treatment with 2 equivalents of lithium aluminium

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† Electronic supplementary information (ESI) available: Characterisation data of compounds **2c–e,h–j**, **3b–e,g–k**, **4b–e**, **7b,c,e**, **8b–e** and **9b–e**. See DOI: 10.1039/b719686e

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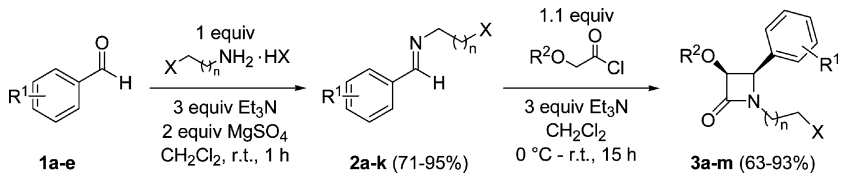


Scheme 1

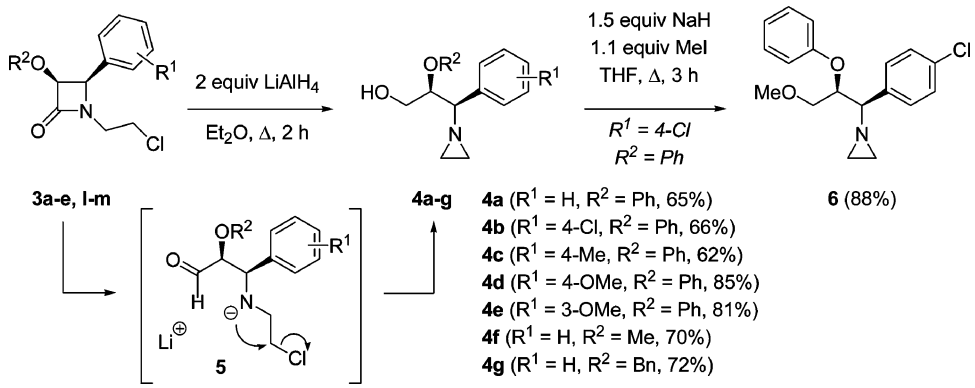
Table 1 Synthesis of *N*-(ω-haloalkyl)imines **2a–k** and Staudinger reaction thereof towards *N*-(ω-haloalkyl)-β-lactams **3a–m**

Entry	R^1	X	*n*	Imines **2** (yield)	R^2	β-Lactams **3** (yield)
1	H	Cl	1	**2a** (90%)	Ph	**3a** (75%)
2	4-Cl	Cl	1	**2b** (89%)	Ph	**3b** (70%)
3	4-Me	Cl	1	**2c** (91%)	Ph	**3c** (63%)
4	4-OMe	Cl	1	**2d** (95%)	Ph	**3d** (67%)
5	3-OMe	Cl	1	**2e** (90%)	Ph	**3e** (82%)
6	H	Br	2	**2f** (78%)	Ph	**3f** (83%)
7	4-Cl	Br	2	**2g** (71%)	Ph	**3g** (89%)
8	4-Me	Br	2	**2h** (73%)	Ph	**3h** (93%)
9	4-OMe	Br	2	**2i** (77%)	Ph	**3i** (81%)
10	3-OMe	Br	2	**2j** (83%)	Ph	**3j** (74%)
11	H	Cl	2	**2k** (83%)	Ph	**3k** (91%)
12	H	Cl	1	**2a** (90%)	Me	**3l** (93%)
13	H	Cl	1	**2a** (90%)	Bn	**3m** (88%)

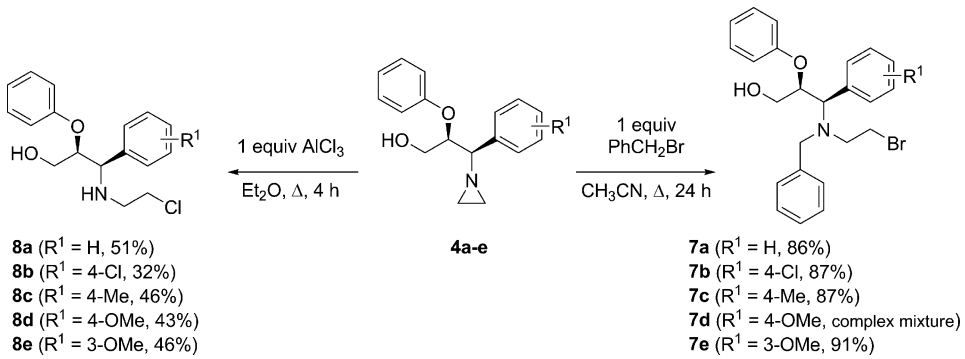
hydride in refluxing diethyl ether for 2 hours (Scheme 2). This reaction proceeds through reduction of the β-lactam moiety by hydride towards an intermediate β-chloro lithio-amide **5**, followed by intramolecular displacement of the chlorine by the nucleophilic nitrogen. In this way, 1-substituted aziridines **4** were obtained in high yields and purity in an elegant and straightforward approach.

Remarkably, all four hydrogen atoms of aziridines **4** were observed as separate signals in ^{1}H NMR and appeared as doublets of doublets with characteristic aziridine chemical shifts (1.08–2.03 ppm, $CDCl_3$). Also in ^{13}C NMR, both aziridine carbon atoms resonated at different δ-values (26.0–26.3 ppm and 30.2–30.4 ppm, $CDCl_3$). It is known in the literature that γ-amino alcohols are characterized by an intramolecular hydrogen bonding between the hydroxyl group and the basic nitrogen atom, resulting in a chair-like conformation.[10] In order to evaluate the effect of this intramolecular hydrogen bonding, a Williamson ether synthesis was performed by treatment of aziridine alcohol **4b** with 1.5 equivalents of sodium hydride followed by the addition of 1.1 equivalents of iodomethane in THF, affording methyl ether **6** in 88% yield after reflux for 3 hours (Scheme 2). NMR analysis of the latter compound **6** revealed that the hydrogen bonding in aziridines **4** cannot be responsible for the observed difference in chemical shift values in NMR for the aziridine carbon and hydrogen atoms, as the same observations were made for this aziridine **6**. These findings are in accordance with analogous results reported for 1-(2-hydroxyethyl)aziridines and the corresponding TMS ethers, as in both cases the four aziridine proton atoms also exhibited separate signals for each proton in ^{1}H NMR.[6] In the literature, non-activated 1-(3-hydroxypropyl)aziridines have been reported only sporadically, *e.g.* for the synthesis of 1,3-disubstituted propanones[11] and 2-amino-4-aryl-3-(1-aziridinylmethyl)quinolines,[12] and thus comprise an interesting class of substrates for further elaboration. Attempts were made to induce intramolecular ring opening of the aziridine ring—activated *in situ* by a Lewis acid ($BF_3{\cdot}Et_2O$, $BF_3{\cdot}$THF, Me_3Al)—by the nucleophilic hydroxyl group. However, all these attempts were unsuccessful, resulting in either recovery of the starting material or the formation of complex reaction mixtures.

Aziridines are generally recognized as versatile synthetic intermediates in organic chemistry due to their intrinsic reactivity and their usefulness in the synthesis of nitrogen-containing bioactive compounds.[13] A characteristic feature of the aziridine ring comprises its reactivity towards a variety of reagents, as this ring system is susceptible to ring cleavage because of the favourable release of strain energy involved. A very useful application of aziridine ring opening reactions comprises the synthesis of β-halo amines, an extensive class of reactive organic compounds with plentiful applications as synthons in organic chemistry[14] and as anticancer agents (nitrogen mustards) in medicinal chemistry.[15,16]



Scheme 2



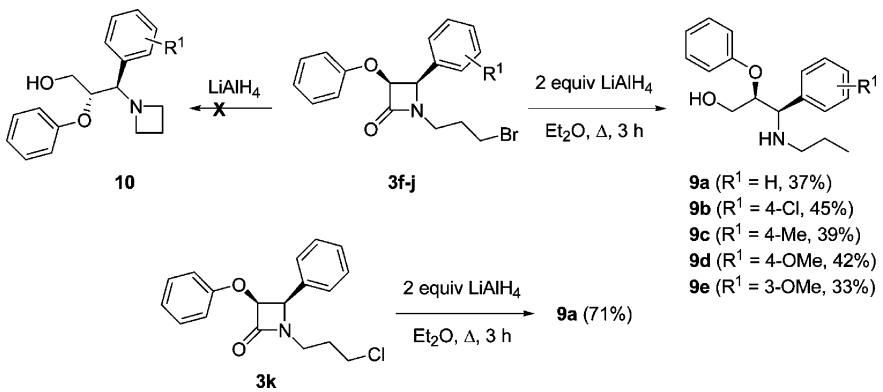
Scheme 3

In order to demonstrate the synthetic potential of non-activated aziridines **4**, and to prove their presence, two different types of ring opening reactions were evaluated towards the synthesis of functionalized β-halo amines. The first approach involved the ring opening of aziridines **4** upon treatment with 1 equivalent of benzyl bromide in acetonitrile, affording β-bromo amines **7** in excellent yields after heating under reflux for 24 hours (Scheme 3). In this transformation, benzyl bromide is responsible for both the activation of the aziridine ring towards an aziridinium intermediate and for the delivery of the nucleophilic bromide anion which induces ring opening of the aziridinium ion. This methodology was applied previously for the ring opening of 1-(arylmethyl)aziridines upon reflux for 5 hours.[17] The presence of an α-branched 1-arylmethyl group in aziridines **4** can account for the longer reaction times (24 hours) due to steric hindrance, as the starting material was recovered when shorter reaction times were used. For aziridine **4d** (R^1 = 4-OMe), only complex reactions mixtures were obtained, even upon shorter reaction times (5 hours).

An alternative approach comprised the reactivity of aziridines **4** with regard to the Lewis acid aluminium(III) chloride. Treatment of aziridines **4** with 1 equivalent of $AlCl_3$ in refluxing diethyl ether for 4 hours afforded the corresponding β-chloro amines **8** in good yields after purification by column chromatography on silica gel (Scheme 3). The use of aluminium(III) chloride offers a new and easy approach towards the synthesis of secondary β-chloro amines through ring opening of non-activated aziridines, as there are no systematic studies available with regard to this methodology.[18]

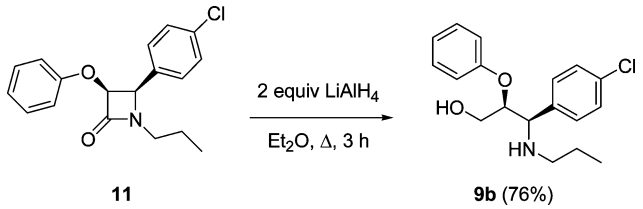
Based on the reactivity of 1-(2-chloroethyl)azetidin-2-ones **3a–e**, the same reductive ring opening and consecutive intramolecular ring closure of 1-(3-bromopropyl)-β-lactams **3f–j** was envisaged towards the corresponding azetidine derivatives. Surprisingly, treatment of 1-(3-bromopropyl)azetidin-2-ones **3f–j** with lithium aluminium hydride in diethyl ether did not afford the anticipated 1-substituted azetidine derivatives **10**, but resulted in the formation of γ-amino alcohols **9a–e** instead (Scheme 4). The presence of an *N*-propyl group in the latter γ-amino alcohols **9** was unexpected, in contrast with the intramolecular substitution by the nitrogen anion in lithium *N*-(2-chloroethyl)amides **5** towards the formation of aziridines **4**, and can be the result of nucleophilic displacement of the bromine by hydride or, more likely, the result of a radical protocol through SET (single electron transfer).[19] In order to exclude a possible influence of the halogen atom (bromine *versus* chlorine), the same method was applied starting from 1-(3-chloropropyl)-3-phenoxy-4-phenylazetidin-2-one **3k**, furnishing *N*-propylamine **9a** in 71% yield. Thus, the higher reactivity of bromoalkanes as compared to chloroalkanes did not correspond to the observed substitution by hydride.

In order to prove the formation of 3-aryl-2-phenoxy-3-(*N*-propylamino)propan-1-ols **9**, an independent synthesis was performed. 1-Propylazetidin-2-one **11** was prepared in 83% overall yield *via* a standard procedure involving imination of 4-chlorobenzaldehyde with propylamine in CH_2Cl_2, followed by Staudinger reaction with phenoxyacetyl chloride in CH_2Cl_2 in the presence of Et_3N. Reductive ring opening of β-lactam **11** by means of 2 equivalents of $LiAlH_4$ in refluxing diethyl



Scheme 4

ether afforded the expected 3-(4-chlorophenyl)-2-phenoxy-3-(*N*-propylamino)propan-1-ol **9b** in 76% yield (Scheme 5), which was identical to the compound obtained from 1-(3-bromopropyl)-β-lactam **3g**.



11 **9b** (76%)

Scheme 5

Conclusion

In summary, the reactivity of 1-(2-chloroethyl)- and 1-(3-bromopropyl)azetidin-2-ones with regard to lithium aluminium hydride has been evaluated for the first time. 4-Aryl-1-(2-chloroethyl)azetidin-2-ones were transformed into novel 1-(1-aryl-3-hydroxypropyl)aziridines, whereas 4-aryl-1-(3-bromopropyl)azetidin-2-ones underwent ring opening and dehalogenation towards 3-aryl-3-(*N*-propylamino)propan-1-ols. This is the first report of a conversion of β-lactams into 2,3-unsubstituted aziridine derivatives as an elegant alternative for the use of the parent aziridine. 1-(1-Aryl-3-hydroxypropyl)aziridines were further elaborated by means of ring opening reactions using benzyl bromide or aluminium(III) chloride, affording novel 3-aryl-3-[*N*-benzyl-*N*-(2-bromoethyl)amino]propan-1-ols and 3-aryl-3-[*N*-(2-chloroethyl)amino]propan-1-ols, respectively.

Experimental

^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer AGILENT 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Elemental analyses were performed with a PerkinElmer Series II CHNS/O Analyzer 2400. Dichloromethane was distilled over calcium hydride, while diethyl ether was dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

Synthesis of (*E*)-*N*-arylmethylidene-*N*-(ω-haloalkyl)amines 2

As a representative example, the synthesis of (*E*)-*N*-[(4-methylphenyl)methylidene]-2-chloroethylamine **2c** is described here. To a solution of 2-chloroethylamine hydrochloride (50 mmol, 1 equiv) and magnesium sulfate (100 mmol, 2 equiv) in dichloromethane (125 mL) was added 4-methylbenzaldehyde **1c** (50 mmol, 1 equiv) and triethylamine (150 mmol, 3 equiv). The resulting mixture was stirred for 1 hour at room temperature, followed by filtration of $MgSO_4$ and evaporation of the solvent. Diethyl ether (125 mL) was then added to the residue, and the precipitated hydrochloride salt was removed by filtration and washed with diethyl ether (2 × 30 mL). Evaporation of the solvent afforded (*E*)-*N*-[(4-methylphenyl)methylidene]-2-chloroethylamine **2c** in high purity (> 90% based on ^{1}H NMR), which was used as such in the next step due to its instability.

(*E*)-*N*-(phenylmethylidene)-2-chloroethylamine **2a** and (*E*)-*N*-(phenylmethylidene)-3-halopropylamines **2f**,**k** have been reported previously in the literature.[20]

(*E*)-*N*-[(4-Chlorophenyl)methylidene]-2-chloroethylamine 2b. Light-yellow oil. Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79–3.83 and 3.87–3.92 (2 × 2H, 2 × m, NCH_2CH_2Cl); 7.35–7.39 and 7.64–7.69 (2 × 2H, 2 × m, CH_{arom}); 8.23 (1H, s, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 44.3 (CH_2Cl); 62.6 (NCH_2); 129.0 and 129.6 (4 × HC_{arom}); 134.3 and 137.0 (2 × C_{quat}); 162.2 (C=N). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1651; ν_{max} = 2879, 2825, 1596, 1487, 1436, 1295, 1087, 1047, 843, 828, 656. MS (70 eV): *m*/*z* (%) 202/4/6 (M^+ + 1, 100).

(*E*)-*N*-[(4-Chlorophenyl)methylidene]-3-bromopropylamine 2g. Light-yellow oil. Yield 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26 (2H, quint, J = 6.3 Hz, CH_2CH_2Br); 3.49 (2H, t, J = 6.3 Hz, CH_2Br); 3.75 (2H, t × d, J = 6.3, 1.4 Hz, NCH_2); 7.36–7.41 and 7.64–7.70 (2 × 2H, 2 × m, CH_{arom}); 8.30 (1H, s, HC=N). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 31.7 and 33.3 (CH_2CH_2Br); 58.9 (NCH_2); 129.0 and 129.4 (HC_{arom}); 134.6 and 136.8 (2 × C_{quat}); 160.8 (C=N). IR (NaCl, cm^{-1}): $\nu_{C=N}$ = 1646; ν_{max} = 2844, 1596, 1489, 1276, 1250, 1088, 1014, 822. MS (70 eV): *m*/*z* (%) 260/2/4 (M^+ + 1, 100).

Synthesis of 4-aryl-1-(ω-haloalkyl)azetidin-2-ones 3

As a representative example, the synthesis of *cis*-1-(2-chloroethyl)-3-phenoxy-4-(4-methylphenyl)azetidin-2-one **3c** is described here.

To an ice-cooled solution of (*E*)-*N*-[(4-methylphenyl)methylidene]-2-chloroethylamine **2c** (45.5 mmol, 1 equiv) and triethylamine (136.6 mmol, 3 equiv) in dichloromethane (100 mL) was added dropwise a solution of phenoxyacetyl chloride (50 mmol, 1.1 equiv) in CH_2Cl_2 (30 mL). After stirring for 15 hours at room temperature, the reaction mixture was poured into water (125 mL) and extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent afforded *cis*-1-(2-chloroethyl)-3-phenoxy-4-(4-methylphenyl)azetidin-2-one **3c**, which was purified by recrystallization from absolute ethanol.

***cis*-1-(2-Chloroethyl)-3-phenoxy-4-phenylazetidin-2-one 3a.** Yellow crystals. Recrystallization from EtOH. Yield 75%. Mp. 137.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28 (1H, d × d × d, J = 14.6, 7.1, 5.1 Hz, (*H*CH)N); 3.54 (1H, d × d × d, J = 11.6, 6.4, 5.1 Hz, (*H*CH)Cl); 3.66 (1H, d × d × d, J = 11.6, 7.1, 5.0 Hz, (HC*H*)Cl); 3.91 (1H, d × d × d, J = 14.6, 6.4, 5.0 Hz, (HC*H*)N); 5.11 (1H, d, J = 4.4 Hz, NCH); 5.51 (1H, d, J = 4.4 Hz, OCH); 6.71–6.75, 6.85–6.91, 7.09–7.16 and 7.26–7.37 (2H, 1H, 2H and 5H, 4 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.5 (CH_2Cl); 42.2 (NCH_2); 63.3 (NCH); 82.3 (OCH); 115.6 (2 × $O(HC)_{ortho}$); 122.2 ($O(HC)_{para}$); 128.5, 128.7, 129.0 and 129.3 (2 × $O(HC)_{meta}$ and 5 × $(HC)_{arom}$); 132.8 (NCHC_{quat}); 156.9 (OC_{quat}); 166.3 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1758; ν_{max} = 3012, 1597, 1494, 1412, 1242, 752. MS (70 eV): *m*/*z* (%) 302/4 (M^+ + 1, 100). Anal. Calcd for $C_{17}H_{16}ClNO_2$: C 67.66, H 5.34, N 4.64. Found: C 67.78, H 5.51, N 4.77.

***cis*-1-(3-Bromopropyl)-3-phenoxy-4-phenylazetidin-2-one 3f.** Yellow crystals. Recrystallization from EtOH. Yield 83%. Mp. 89.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97–2.19 (2H, m, CH_2CH_2Br); 3.09–3.23 (1H, m, (*H*CH)N); 3.40 (2H, t, J = 6.6 Hz, CH_2Br); 3.53–3.67 (1H, m, (HC*H*)N); 4.95 (1H, d, J = 4.4 Hz, NCH); 5.45 (1H, d, J = 4.4 Hz, OCH); 6.70–6.74, 6.85–6.99, 7.09–7.16 and 7.24–7.43 (2H, 1H, 2H and 5H, 4 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.3 and 30.5 (CH_2CH_2Br); 39.7 (NCH_2); 62.9 (NCH); 82.0 (OCH); 115.6 (2 × O(HC)$_{ortho}$); 122.1 (O(HC)$_{para}$); 128.4, 128.7, 129.0 and 129.3 (2 × O(HC)$_{meta}$ and 5 × HC$_{arom}$); 133.0 (NCHC_{quat}); 156.9 (OC_{quat}); 166.3 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1749; ν_{max} = 2944, 1598, 1495, 1457, 1417, 1244, 749. MS (70 eV): m/z (%) 360/2 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{18}BrNO_2$: C 60.01, H 5.04, N 3.89. Found: C 60.17, H 5.21, N 4.02.

***cis*-1-(2-Chloroethyl)-3-methoxy-4-phenylazetidin-2-one 3l.** Yellow crystals. Recrystallization from EtOH. Yield 93%. Mp. 61.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.12 (3H, s, OMe); 3.23 (1H, d × d × d, J = 14.6, 7.2, 5.2 Hz, (*H*CH)N); 3.50 (1H, d × d × d, J = 11.3, 6.3, 5.2 Hz, (*H*CH)Cl); 3.62 (1H, d × d × d, J = 11.3, 7.2, 5.3 Hz, (HC*H*)Cl); 3.83 (1H, d × d × d, J = 14.6, 6.3, 5.3 Hz, (HC*H*)N); 4.77 (1H, d, J = 4.5 Hz, OCH); 4.91 (1H, d, J = 4.5 Hz, NCH); 7.34–7.44 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.4 and 41.9 (NCH_2CH_2Cl); 58.3 (OMe); 62.9 (NCH); 85.9 (OCH); 128.5, 128.6 and 129.0 (5 × HC$_{arom}$); 133.5 (NCHC_{quat}); 167.5 (C=O). IR (KBR, cm^{-1}): $\nu_{C=O}$ = 1744; ν_{max} = 2948, 1399, 1364, 1202, 1100, 998, 881, 702. MS (70 eV): m/z (%) 240/2 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C 60.13, H 5.89 N 5.84. Found C 60.31, H 6.08 N 5.70.

***cis*-3-Benzyloxy-1-(2-chloroethyl)-4-phenylazetidin-2-one 3m.** Yellow crystals. Recrystallization from EtOH. Yield 88%. Mp. 106.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (1H, d × d × d, J = 14.6, 7.1, 5.2 Hz, (*H*CH)N); 3.49 (1H, d × d × d, J = 11.4, 6.4, 5.2 Hz, (*H*CH)Cl); 3.61 (1H, d × d × d, J = 11.4, 7.1, 5.3 Hz, (HC*H*)Cl); 3.83 (1H, d × d × d, J = 14.6, 6.4, 5.3 Hz, (HC*H*)N); 4.16 (1H, d, J = 11.2 Hz, (*H*CH)O); 4.30 (1H, d, J = 11.2 Hz, (HCH)O); 4.90 (1H, d, J = 4.4 Hz, NCH); 4.95 (1H, d, J = 4.4 Hz, OCH); 6.91–6.94, 7.19–7.22 and 7.35–7.41 (2H, 3H and 5H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 41.4 and 42.0 (NCH_2CH_2Cl); 63.1 (NCH); 72.4 (OCH_2Ar); 83.9 (OCH); 128.1, 128.3, 128.4, 128.7 and 129.0 (10 × HC$_{arom}$); 133.7 (NCHC_{quat}); 136.4 (OCH_2C_{quat}); 167.4 (C=O). IR (KBR, cm^{-1}): $\nu_{C=O}$ = 1761; ν_{max} = 2905, 1400, 1365, 1171, 1099, 1008, 880, 752, 700. MS (70 eV): m/z (%) 316/8 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{18}ClNO_2$: C 68.46, H 5.75 N 4.44. Found C 68.26, H 5.94 N 4.29.

***cis*-4-(4-Chlorophenyl)-3-phenoxy-1-propylazetidin-2-one 11.** Yellow crystals. Recrystallization from EtOH. Yield 89%. Mp. 102.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.4 Hz, CH_3); 1.43–1.59 (2H, m, CH_2CH_3); 2.89–2.98 and 3.40–3.50 (2 × 1H, 2 × m, (HCH)N); 4.91 (1H, d, J = 4.4 Hz, NCH); 5.43 (1H, d, J = 4.4 Hz, OCH); 6.71–6.75, 6.87–6.98, 7.10–7.17 and 7.23–7.28 (2H, 1H, 2H and 4H, 4 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 11.7 (CH_3); 20.9 (*C*H_2CH_3); 42.4 (NCH_2); 61.7 (NCH); 81.8 (OCH); 115.5 (2 × O(HC)$_{ortho}$); 122.2 (O(HC)$_{para}$); 128.6, 129.4 and 130.0 (2 × O(HC)$_{meta}$ and 2 × Cl(HC)$_{ortho}$(HC)$_{meta}$); 132.0 and 134.7 (NCHC_{quat} and ClC$_{quat}$); 156.8 (OC$_{quat}$); 165.9 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$ = 1748; ν_{max} = 2959, 1599, 1495, 1408, 1241, 1090, 825, 749, 688. MS (70 eV): m/z (%) 316/8 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{18}ClNO_2$: C 68.46, H 5.75, N 4.44. Found: C 68.52, H 5.84, N 4.57.

Synthesis of 1-(1-aryl-3-hydroxypropyl)aziridines 4

As a representative example, the synthesis of 1-[3-hydroxy-1-(4-methoxyphenyl)-2-phenoxypropyl]aziridine **4d** is described here. To an ice-cooled solution of *cis*-1-(2-chloroethyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one **3d** (20 mmol) in dry diethyl ether (125 mL) was added lithium aluminium hydride (40 mmol, 2 equiv) in small portions. After reflux for 2 hours, the reaction mixture was cooled to 0 °C and water was added in order to quench the excess of $LiAlH_4$. The resulting suspension was filtered over Celite® and washed with diethyl ether (40 mL), and the filtrate was poured into water (100 mL) and extracted with Et_2O (3 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent *in vacuo* afforded 1-[3-hydroxy-1-(4-methoxyphenyl)-2-phenoxypropyl]aziridine **4d**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 4/1).

1-(3-Hydroxy-2-phenoxy-1-phenylpropyl)aziridine 4a. Colorless crystals. R_f = 0.07 (hexane/EtOAc 4/1). Yield 65%. Mp. 106.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (1H, d × d, J = 7.2, 4.4 Hz, (*H*CH)N(HCH)); 1.62 (1H, d × d, J = 7.2, 4.2 Hz, (HCH)N(*H*CH)); 1.75 (1H, d × d, J = 5.7, 4.2 Hz, (HC*H*)N(HCH)); 2.02 (1H, d × d, J = 5.7, 4.4 Hz, (HCH)N(HC*H*)); 2.87 (1H, d, J = 5.8 Hz, NCH); 3.15 (1H, broad s, OH); 3.52 and 3.71 (2H, 2 × d × d, J = 11.6, 5.8, 4.7 Hz, (*H*C*H*)OH); 4.73–4.79 (1H, m, OCH); 6.96–7.06 and 7.26–7.45 (3H and 7H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.2 and 30.2 (2 × NCH_2); 61.9 (CH_2OH); 75.0 (NCH); 80.0 (OCH); 116.1 (2 × O(HC)$_{ortho}$); 121.5 (O(HC)$_{para}$); 127.9, 128.3, 128.4 and 129.8 (2 × O(HC)$_{meta}$ and 5 × HC$_{arom}$); 138.6 (NCHC_{quat}); 158.2 (OC$_{quat}$). IR (KBr, cm^{-1}): ν_{OH} = 3206; ν_{max} = 2931, 2844, 1596, 1585, 1492, 1242, 1012, 763, 695. MS (70 eV): m/z (%) 270 (M^+ + 1, 100). Anal. Calcd for $C_{17}H_{19}NO_2$: C 75.81, H 7.11, N 5.20. Found: C 75.39, H 7.19, N 5.35.

1-(3-Hydroxy-2-methoxy-1-phenylpropyl)aziridine 4f. Colourless oil. R_f = 0.03 (hexane/EtOAc 3/1). Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (1H, d × d, J = 7.0, 4.3 Hz, (*H*CH)N(HCH)); 1.59 (1H, d × d, J = 7.0, 4.3 Hz, (HCH)N(*H*CH)); 1.73 (1H, d × d, J = 5.9, 4.3 Hz, (HC*H*)N(HCH)); 2.07 (1H, d × d, J = 5.9, 4.3 Hz, (HCH)N(HC*H*)); 2.66 (1H, d, J = 5.7 Hz, NCH); 3.06 (1H, broad s, OH); 3.33–3.39 (1H, m, (*H*CH)OH); 3.53 (1H, d × d, J = 11.5, 5.7 Hz, (HC*H*)OH); 3.60–3.66 (1H, m, OCH); 7.27–7.40 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): 26.0 and 30.2 (2 × NCH_2); 58.9 (OMe); 61.6 (CH_2OH); 75.5 (NCH); 84.1 (OCH); 127.7, 128.2 and 128.3 (5 × HC$_{arom}$); 139.2 (C$_{quat}$). IR (NaCl, cm^{-1}): ν_{OH} = 3301; ν_{max} = 2928, 1452, 1362, 1261, 1116, 1066, 752, 700. MS (70 eV): m/z (%) 208 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{17}NO_2$: C 69.54, H 8.27, N 6.76. Found C 69.75, H 8.42, N 6.52.

1-(2-Benzyloxy-3-hydroxy-1-phenylpropyl)aziridine 4g. Colourless oil. R_f = 0.05 (hexane/EtOAc 3/1). Yield 72%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (1H, d × d,

J = 7.1, 4.3 Hz, (*H*CH)N(HCH)); 1.55 (1H, d × d, J = 7.1, 4.3 Hz, (HCH)N(*H*CH)); 1.72 (1H, d × d, J = 5.9, 4.3 Hz, (HC*H*)N(HCH)); 2.05 (1H, d × d, J = 5.9, 4.3 Hz, (HCH)N(HC*H*)); 2.67 (1H, d, J = 5.8 Hz, NCH); 3.00 (1H, broad s, OH); 3.35–3.41 (1H, m, (*H*CH)OH); 3.53 (1H, d × d, J = 11.4, 5.8 Hz, (HC*H*)OH); 3.88 (1H, q, J = 5.8 Hz, OCH); 4.67 (1H, d, J = 11.6 Hz, O(*H*CH)Ar); 4.82 (1H, d, J = 11.6 Hz, O(HC*H*)Ar); 7.27–7.42 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 26.0 and 30.4 (2 × NCH_2); 62.0 (CH_2OH); 73.1 (OCH_2Ar); 75.9 (NCH); 82.0 (OCH); 127.7, 127.9, 127.9, 128.3 and 128.6 (10 × HC_{arom}); 138.5 and 139.3 (2 × C_{quat}). IR (NaCl, cm^{-1}): ν_{OH} = 3306; ν_{max} = 2868, 1453, 1355, 1260, 1110, 1055, 735, 697. MS (70 eV): m/z (%) 284 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{21}NO_2$: C 76.29, H 7.47, N 4.94. Found C 76.48, H 7.67, N 4.79.

Synthesis of 1-[1-(4-chlorophenyl)-3-methoxy-2- phenoxypropyl]-aziridine 6

To an ice-cooled solution of 1-[1-(4-chlorophenyl)-3-hydroxy-2-phenoxypropyl]aziridine **4b** (0.25 g, 0.8 mmol) in THF (5 mL) was added NaH (0.05 g, 1.5 equiv, 60% dispersion in mineral oil) and the mixture was stirred for 30 minutes at room temperature. Subsequently MeI (0.13 g, 1.1 equiv) was added dropwise to the ice-cooled reaction mixture, which was then refluxed for 3 hours. Extraction with Et_2O (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent and removal of the solvent *in vacuo* afforded 1-[1-(4-chlorophenyl)-3-methoxy-2-phenoxypropyl]aziridine **6** (0.23 g, 88%), which was purified by means of column chromatography on silica gel (hexane/EtOAc 6/1).

1-[1-(4-Chlorophenyl)-3-methoxy-2-phenoxypropyl]aziridine 6. Colorless oil. R_f = 0.14 (hexane/EtOAc 6/1). Yield 88%. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (1H, d × d, J = 7.0, 4.3 Hz, (*H*CH)N(HCH)); 1.64 (1H, d × d, J = 5.6, 4.3 Hz, (HC*H*)N(HCH)); 1.70 (1H, d × d, J = 7.0, 4.3 Hz, (HCH)N(*H*CH)); 1.97 (1H, d × d, J = 5.6, 4.3 Hz, (HCH)N(HC*H*)); 2.79 (1H, d, J = 6.5 Hz, NCH); 3.12 (1H, d × d, J = 10.4, 5.0 Hz, (*H*CH)OMe); 3.26 (3H, s, OMe); 3.65 (1H, d × d, J = 10.4, 3.2 Hz, (HC*H*)OMe); 4.64 (1H, d × d × d, J = 6.5, 5.0, 3.2 Hz, OCH); 6.94–7.05 and 7.26–7.40 (3H and 6H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 25.3 and 30.5 (2 × NCH_2); 59.3 (OMe); 71.6 and 73.7 (*C*H_2OMe and NCH); 81.9 (OCH); 116.5 (2 × $O(HC)_{ortho}$); 121.5 ($O(HC)_{para}$); 128.6 and 129.7 (2 × $O(HC)_{meta}$ and 2 × $Cl(HC)_{ortho}(HC)_{meta}$); 133.5 and 138.4 ($ClC_{quat}$ and $NCHC_{quat}$); 158.6 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{max} = 2923, 1597, 1489, 1234, 1088, 1013, 752, 691. MS (70 eV): m/z (%) 318/20 (M^+ + 1, 100). Anal. Calcd for $C_{18}H_{20}ClNO_2$: C 68.03, H 6.34, N 4.41. Found: C 68.21, H 6.55, N 4.58.

Synthesis of 3-aryl-3-[*N*-benzyl-*N*-(2-bromoethyl)amino]-2-phenoxypropan-1-ols 7

As a representative example, the synthesis of 3-[*N*-benzyl-*N*-(2-bromoethyl)amino]-2-phenoxy-3-phenylpropan-1-ol **7a** is described here. To a solution of 1-(3-hydroxy-2-phenoxy-1-phenylpropyl)aziridine **4a** (1 mmol) in acetonitrile (10 mL) was added benzyl bromide (1 mmol, 1 equiv), and the resulting mixture was heated under reflux for 24 hours. Evaporation of the solvent afforded 3-[*N*-benzyl-*N*-(2-bromoethyl)amino]-2-phenoxy-3-phenylpropan-1-ol **7a**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1).

3-[*N*-Benzyl-*N*-(2-bromoethyl)amino]-2-phenoxy-3-phenylpropan-1-ol 7a. Yellow oil. R_f = 0.07 (hexane/EtOAc 9/1). Yield 86%. ^1H NMR (300 MHz, $CDCl_3$): δ 2.67–2.76 (1H, m, N(*H*CH)CH_2Br); 3.07–3.24 (2H, m, CH_2Br); 3.28–3.38 (1H, m, N(HC*H*)CH_2Br); 3.43 (1H, d, J = 13.7 Hz, N(*H*CH)Ar); 3.56 and 3.86 (2H, 2 × d × d, J = 11.9, 4.6, 4.4 Hz, (HCH)O); 3.93 (1H, d, J = 13.7 Hz, N(HC*H*)Ar); 4.09 (1H, d, J = 6.3 Hz, NCH); 4.78–4.83 (1H, m, OCH); 6.89–7.10 and 7.19–7.59 (3H and 12H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 30.7 (CH_2Br); 53.7 (N*C*H_2CH_2Br); 56.6 (NCH_2Ar); 62.6 (CH_2OH); 65.2 (NCH); 79.1 (OCH); 116.2 (2 × $O(HC)_{ortho}$); 121.6 ($O(HC)_{para}$); 127.5, 128.1, 128.6, 128.7, 129.0, 129.5 and 129.9 (2 × $O(HC)_{meta}$ and 10 × HC_{arom}); 136.3 and 139.4 ($NCHC_{quat}$ and NCH_2C_{quat}); 158.2 (OC_{quat}). IR (NaCl, cm^{-1}): ν_{OH} = 3271; ν_{max} = 3029, 2959, 2874, 1597, 1494, 1454, 1233, 1048, 756, 696. MS (70 eV): m/z (%) 360 (M^+ − Br, 100). Anal. Calcd for $C_{24}H_{26}BrNO_2$: C 65.46, H 5.95, N 3.18. Found: C 65.69, H 6.14, N 2.99.

Synthesis of 3-aryl-3-[*N*-(2-chloroethyl)amino]-2-phenoxypropan-1-ols 8

As a representative example, the synthesis of 3-[(2-chloroethyl)amino]-3-(4-methoxyphenyl)-2-phenoxypropan-1-ol **8d** is described here. To a suspension of $AlCl_3$ (15 mmol, 1 equiv) in dry diethyl ether (120 mL) was added 1-[3-hydroxy-1-(4-methoxyphenyl)-2-phenoxypropyl]aziridine **4d** (15 mmol, 1 equiv), and the resulting mixture was heated under reflux for 4 hours. Afterwards, the reaction mixture was poured into water (100 mL), extracted with Et_2O (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$). Filtration of the drying agent and removal of the solvent afforded 3-[(2-chloroethyl)amino]-3-(4-methoxyphenyl)-2-phenoxypropan-1-ol **8d**, which was purified by column chromatography on silica gel (hexane/EtOAc 6/1).

3-[(2-Chloroethyl)amino]-2-phenoxy-3-phenylpropan-1-ol 8a. Light-yellow oil. R_f = 0.13 (hexane/EtOAc 4/1). Yield 51%. ^1H NMR (300 MHz, $CDCl_3$): δ 2.77 (2H, t, J = 5.7 Hz, NCH_2); 3.26 (2H, broad s, NH and OH); 3.42–3.62 (3H, m, CH_2Cl and (*H*CH)OH); 3.80 (1H, d × d, J = 11.8, 3.4 Hz, (HC*H*)OH); 4.13 (1H, d, J = 6.0 Hz, NCH); 4.35 (1H, d × t, J = 6.0, 3.4 Hz, OCH); 6.92–7.08 and 7.20–7.42 (4H and 6H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 44.8 (CH_2Cl); 48.4 (NCH_2); 62.2 (CH_2OH); 64.0 (NCH); 82.3 (OCH); 116.9 (2 × $O(HC)_{ortho}$); 122.0 ($O(HC)_{para}$); 128.2, 128.9, 129.8 and 129.9 (5 × HC_{arom} and 2 × $O(HC)_{meta}$); 139.4 ($NCHC_{quat}$); 158.2 (OC_{quat}). IR (NaCl, cm^{-1}): $\nu_{OH, NH}$ = 3338; ν_{max} = 3063, 2929, 1597, 1587, 1493, 1455, 1235, 1040, 754, 693. MS (70 eV): m/z (%) 306/8 (M^+ + 1, 100). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.67, H 6.59, N 4.58. Found: C 66.89, H 6.82, N 4.62.

Synthesis of 3-aryl-2-phenoxy-3-(*N*-propylamino)propan-1-ols 9

3-Aryl-2-phenoxy-3-(*N*-propylamino)propan-1-ols **9** were prepared starting from 4-aryl-3-phenoxy-1-(3-bromopropyl)azetidin-2-ones **3f–j** applying the same procedure as described above for the synthesis of 1-(1-aryl-3-hydroxy-2-phenoxypropyl)aziridines **4**.

2-Phenoxy-3-phenyl-3-(*N*-propylamino)propan-1-ol 9a. Light-yellow oil. $R_f = 0.12$ (hexane/EtOAc 4/1). Yield 37%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (3H, t, $J = 7.4$ Hz, CH_3); 1.34–1.49 (2H, m, CH_2CH_3); 2.31–2.41 (2H, m, NCH_2); 3.65 and 3.82 (2 × 1H, 2 × d × d, $J = 12.0$, 3.6, 2.8 Hz, (HCH)O); 4.02 (1H, d, $J =$ 4.4 Hz, NCH); 4.22–4.28 (1H, m, OCH); 6.70–6.92 and 7.04–7.32 (3H and 7H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 11.9 (CH_3); 23.2 (CH_2CH_3); 49.2 (NCH_2); 63.1 (CH_2OH); 65.2 (NCH); 81.1 (OCH); 117.0 (2 × $O(HC)_{ortho}$); 121.9 ($O(HC)_{para}$); 127.9, 128.0, 128.7 and 129.7 (2 × $O(HC)_{meta}$ and 5 × HC_{arom}); 139.9 ($NCHC_{quat}$); 158.0 (OC_{quat}). IR (NaCl, cm^{-1}): $\nu_{OH,\,NH} = 3351$; $\nu_{max} = 2958$, 2930, 2873, 1598, 1588, 1494, 1455, 1239, 1041, 753, 701, 692. MS (70 eV): *m*/*z* (%) 286 ($M^+ + 1$, 100). Anal. Calcd for $C_{18}H_{23}NO_2$: C 75.76, H 8.12, N 4.91. Found: C 75.92, H 8.29, N 5.14.

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