Microwave-assisted regioselective ring opening of non-activated aziridines by lithium aluminium hydride

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Abstract - A new synthetic protocol for the $LiAlH_4$-promoted reduction of non-activated aziridines under microwave conditions was developed. Thus, ring opening of 2-(acetoxymethyl)aziridines provided the corresponding β-amino alcohols, which were then used as eligible substrates in the synthesis of 5-methylmorpholin-2-ones via condensation with glyoxal in THF. The same procedure was applied for the preparation of novel 5(*R*)- and 5(*S*)-methylmorpholin-2-ones starting from the corresponding enantiopure 2-(hydroxymethyl)aziridines. Additionally, 2-(methoxymethyl)- and 2-(phenoxymethyl)aziridines were treated with $LiAlH_4$ under microwave irradiation, giving rise to either isopropylamines or 1-methoxypropan-2-amines depending on the reaction conditions.

Introduction

The aziridine moiety represents a valuable three-membered ring system in organic chemistry due to its versatility as a building block for the preparation of a large variety of ring opened and ring expanded amines.[1,2] Aziridines bearing an electron-withdrawing substituent at nitrogen (activated aziridines) are known to be reactive towards a large number of nucleophiles with respect to ring opening.[2] On the other hand, electron-donating groups at nitrogen render the aziridine more stable

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and activation towards an aziridinium intermediate is, in most cases, required prior to nucleophilic ring opening.[3-7] The resulting electrophilic species is then attacked by a nucleophile at the more or less substituted position of the aziridine ring depending on the substrate, the type of the nucleophile and the solvent, yielding a functionalized amine.[3-11]

In comparison to the huge number of reports on the ring opening of aziridines by other nucleophiles, their ring opening by hydrides has received very limited interest in the literature despite of the synthetic potential of this approach. The intermediacy of aziridines in direct, non-regioselective ring opening reactions by $LiAlH_4$ has been proposed in an early paper, in which the reduction of *N*-(1,1-dichloro-2-alkylidene)anilines was investigated,[12] and was also deduced indirectly from the experiments of Suzuki.[13] In addition, in one recent report,[14] the reduction of 2-methyl-1-phenylaziridine with $LiAlH_4$ in THF yielded a mixture of ring opened amines (derived from hydride attack at both the more and the less hindered aziridine carbon atom in a 1:2 ratio, respectively) yet showed to be slow and not complete after heating under reflux for 20 hours. Furthermore, the contribution of the electron-withdrawing effect of the phenyl group at nitrogen, facilitating ring opening of the aziridine moiety, should not be neglected.

In addition to the above-mentioned reports, the ring opening of reactive 2-chloroaziridine intermediates by $LiAlH_4$ has been described as well.[15] It should be stressed that several syntheses of aziridines have been reported in the literature based on the reduction of suitable substrates, such as α-halo imines,[15a,16] vinyl azides,[17] oximes[18] and azirines,[19] by nucleophilic complex hydrides. Very recently, the reductive ring opening of highly electrophilic aziridinium salts by hydrides has been reported to afford 2-aminopropanes through regiospecific ring opening at the unsubstituted position.[6c,20] However, up to now, $LiAlH_4$ has been mainly used to reduce functional groups in compounds incorporating an aziridine unit without affecting the three-

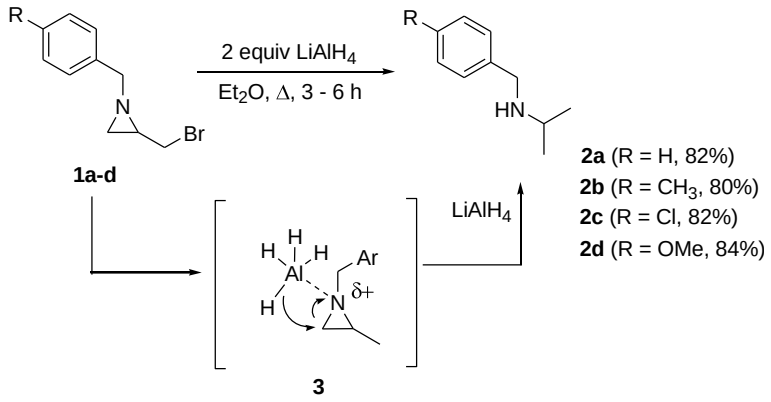
membered ring itself,[21-24] and the hydride-promoted ring opening of non-activated aziridines has not been described in the literature so far.

In the present study, special attention was devoted to the $LiAlH_4$-promoted ring opening of non-activated 2-subtituted aziridines towards biologically and synthetically relevant species. The lack of studies concerning the reduction of aziridines by $LiAlH_4$ is remarkable in view of the large number of papers on the reductive ring opening of their oxygen counterparts, oxiranes. In contrast to previous reports, all of the reactions in the present work proceeded smoothly with high regioselectivity and resulted in full conversion of the substrate, not requiring the presence of Lewis acids. In addition, the regio- and stereoselective reductive ring opening of enantiopure 2-(hydroxymethyl)aziridines by $LiAlH_4$ towards chiral β-amino alcohols was performed, and the resulting β-amino alcohols were applied in the synthesis of novel 5-methylmorpholin-2-ones.

Results and discussion

1-Arylmethyl-2-(bromomethyl)aziridines[25] **1** constitute versatile substrates for further elaboration,[4b,26-28] although their reactivity towards $LiAlH_4$ has not been evaluated up to now. The reaction of aziridines **1** with two molar equivalents of $LiAlH_4$ in dry Et_2O under reflux for 3-6 hours afforded *N*-arylmethyl-*N*-isopropylamines **2** as the sole reaction products quite unexpectedly in high yields (80-84%) (Scheme 1). The suggested mechanistic pathway for this transformation consists of an initial reductive debromination of 2-(bromomethyl)aziridines **1** toward 2-methylaziridines **3** through the action of $LiAlH_4$, either via a nucleophilic or a radical reaction.[29] Subsequently, reductive ring opening takes place via nucleophilic attack of a hydride ion (from $LiAlH_4$) at the less substituted carbon atom of the aziridine moiety in intermediates **3**. Apparently, the reducing agent acts both as the activator of the aziridine ring (through coordination of aluminium with nitrogen[5,14]) and as the provider of the nucleophile (hydride)

which opens up the ring at the less hindered position (Scheme 1). However, the alternative mechanistic pathway comprising an initial hydride attack at the less hindered position of the aziridine moiety of 2-(bromomethyl)aziridines **1** yielding the ring opened intermediates, and their subsequent ring closure towards 2-methylaziridines **3**, should not be neglected. Although attempts to isolate 2-methylaziridines[30] **3** by column chromatography on silica gel failed, their intermediacy was acknowledged upon ^{1}H NMR and ^{13}C NMR analysis of some of the crude reaction mixtures. Furthermore, the presence of aziridines **3** was confirmed by MS analysis of these reaction mixtures.



Scheme 1

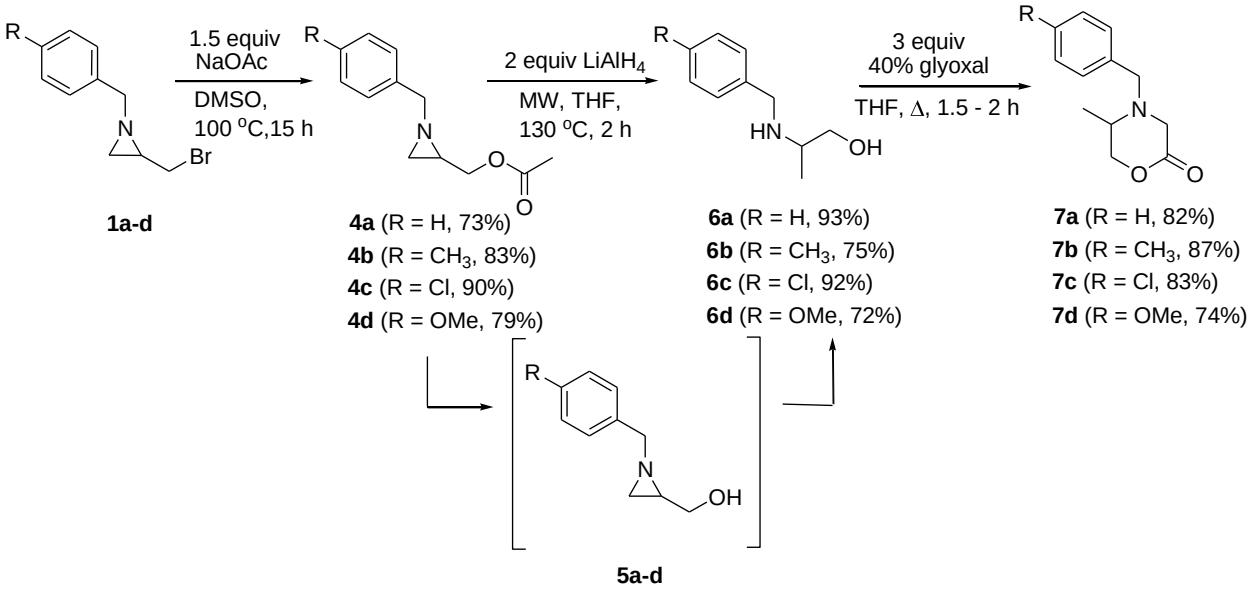
Additionally, in order to confirm the structure of *N*-arylmethyl-*N*-isopropylamines **2**, an independent synthesis of *N*-(4-methoxybenzyl)-*N*-isopropylamine **2d** was performed. Condensation of 4-methoxybenzaldehyde with 1.05 equiv of *i*PrNH$_2$ in CH_2Cl_2 in the presence of $MgSO_4$ afforded the corresponding imine in 75% yield after six hours under reflux, which was then reduced using two molar equiv of $NaBH_4$ in MeOH for two hours under reflux, furnishing *N*-(4-methoxybenzyl)-*N*-isopropylamine **2d** in 96% yield. The spectral data of amine **2d** obtained via both routes were judged to be identical.

Apart from amines **2**, which can of course easily be prepared via other routes, this methodology holds significant synthetic potential for the preparation of a large variety of amines in a convenient way through reductive ring opening of the appropriate aziridine derivatives.

The utility of this $LiAlH_4$-promoted ring opening of non-activated aziridines was demonstrated by the synthesis of versatile β-amino alcohols starting from 2-(acetoxymethyl)aziridines. 1-Arylmethyl-2-(acetoxymethyl)aziridines **4** were smoothly prepared upon treatment of 2-(bromomethyl)aziridines **1** with an excess (1.5 equiv) of sodium acetate in DMSO at 100 °C for 15 hours (Scheme 2). The reaction provided almost pure acetates **4a-d** suitable for further elaboration without prior purification. However, for full characterization, aziridines **4** were purified by column chromatography on silica gel column, affording analytically pure samples.

Further treatment of 2-(acetoxymethyl)aziridines **4** with two molar equiv of $LiAlH_4$ in Et_2O and heating for six hours under reflux provided crude mixtures containing mainly alcohols **5**, and no traces of ring opened β-amino alcohols **6** were detected. Increasing the reaction time to 24-62 hours led to partial formation of β-amino alcohols **6** (~50%). It was shown that, in order to obtain β-amino alcohols **6** in reasonable yields, a reflux time of several days (4-5) was required. In order to overcome this major drawback, the reaction mixture was subjected to microwave irradiation. Gratifyingly, after heating aziridines **4** in THF at 130 °C for two hours (220 W_{max}) in the presence of two molar equiv of $LiAlH_4$, only the corresponding β-amino alcohols **6** were formed in high purity without traces of 2-(hydroxymethyl)aziridines **5** (Scheme 2). Thus, the nucleophilic attack of hydride at the less substituted carbon atom of aziridines **5** was confirmed and, as a result, β-amino alcohols **6** were obtained in high yields after purification by column chromatography on silica gel. In this way, 2-aminopropan-1-ols **6** were formed selectively through complete regio- and stereoselective conversion of 2-(hydroxymethyl)aziridines **5**. Although several useful routes for the synthesis of β-amino alcohols are available in the

literature,[31-33] some of these approaches suffer from (minor) drawbacks such as low regioselectivity, cumbrous substrate synthesis or low substrate stability. The synthesis of β-amino alcohols **6** through microwave-assisted ring opening of aziridines **4** utilizing $LiAlH_4$ satisfies the requirements for a generally applicable route, i.e. the use of commercially available starting compounds, complete regio- and stereoselectivity and high energy efficiency. Thus, the presented methodology can be regarded as a complementary approach or a worthy alternative for other known routes. β-Amino alcohols are applied extensively in organic chemistry as a building blocks in designing natural and biologically active substances,[33a,34-44] and their chiral versions are also used in catalytic asymmetric synthesis.[31,45]



Scheme 2

In the next part, 2-aminopropan-1-ols **6** were shown to be good substrates for the construction of 5-methylmorpholin-2-ones,[46] which are known as fruitful substrates for the synthesis of

biologically relevant compounds.[47,48] Thus, 2-(arylmethylamino)propan-1-ols **6** were dissolved in THF and treated with three equiv of glyoxal. After heating these mixtures for 2-3 hours, 5-methylmorpholin-2-ones **7a-d** were obtained in good yields (Scheme 2) and column chromatography on silica gel provided analytically pure compounds suitable for full characterization.

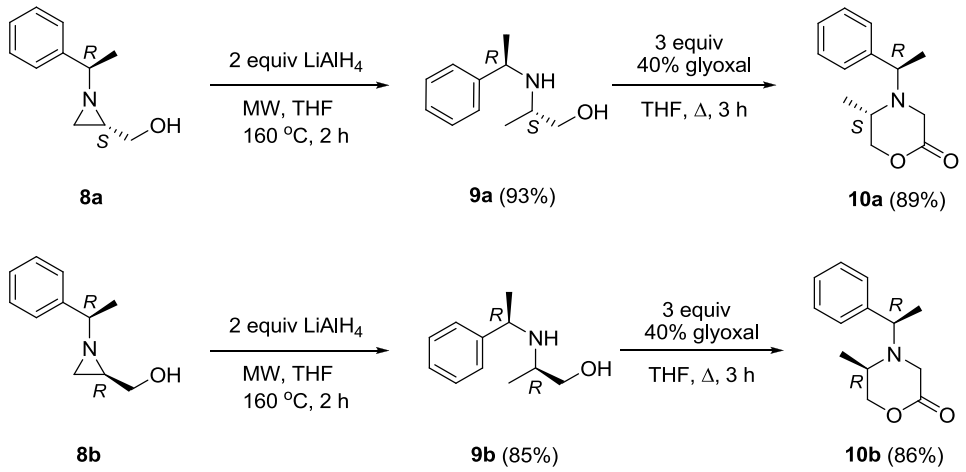
Given the intermediacy of 2-(hydroxymethyl)aziridines **5** in the conversion of acetates **4** into alcohols **6**, efforts were devoted to the evaluation of chiral 2-(hydroxymethyl)aziridines as substrates for a $LiAlH_4$-promoted reductive ring opening. In the literature, only a few studies have been made on ring opening reactions of non-activated enantiomerically pure 2-(hydroxymethyl)aziridines.[32,49-52] For example, the catalytic hydrogenation of aziridine methanols **8a** and **8b** in EtOH using $Pd(OH)_2$ has provided β-amino alcohols **9a** and **9b** in good yields.[49] Recently, the preparation of chiral β-amino alcohols via regio- and stereocontrolled ring opening reactions of chiral aziridines was examined.[53] This approach comprised the reaction of 2-alkyl-substituted aziridines with acetic acid to yield the ring opening products with excellent regioselectivity, which were then treated with $LiAlH_4$ or $Pd(OH)_2$ to provide the corresponding β-amino alcohols. On the other hand, the reaction of the same chiral aziridines with acetyl chloride followed by treatment with water gave isomeric β-amino alcohols through oxazoline intermediates.[53] In addition, the reaction of the latter chiral aziridines with benzyl bromide followed by the treatment with sulfuric acid gave secondary β-amino alcohols via ring opening at the substituted aziridine carbon atom.

In the present work, the synthesis of enantiopure 2-aminopropan-1-ols by means of $LiAlH_4$-promoted reduction of chiral 2-(hydroxymethyl)aziridines **8a** and **8b** was successfully examined. After failing to prepare amines **9a** and **9b** upon treatment with two molar equiv of $LiAlH_4$ under reflux for several days in THF and toluene, the mixture of aziridine **8** and two molar equiv of

$LiAlH_4$ in THF was subjected to microwave conditions (160 °C, 220 W_{max}, two hours). Fortunately, full and selective conversion of aziridines **8a** and **8b** into enantiopure 2-aminopropan-1-ols **9a** and **9b** as single stereoisomers was obtained (Scheme 3).

Again, the mechanism comprises coordination of aluminium with the aziridine nitrogen atom, enabling C(3)-N cleavage induced by nucleophilic attack of a hydride ion to furnish the corresponding ring opened product. The bond cleavage showed to be highly regioselective, since hydride attack only occured at the less hindered position. Furthermore, the ring opening reaction of chiral aziridines **8** proceeded not only with high regio- but also high stereoselectivity, furnishing the corresponding enantiopure amino alcohols **9a** and **9b** with full retention of configuration.

The preparation of enantiopure six-membered oxazaheterocycles has received significant attention, for example due to their high potential as chiral substrates. In particular, chiral morpholin-2-ones have been used in the asymmetric synthesis of α-amino acids[47] and other natural products.[48] In the present study, enantiopure 5-methylmorpholin-2-ones were prepared by condensation of the corresponding chiral amino alcohols with glyoxal. Thus, chiral β-amino alcohols **8a** and **8b** were treated with three equiv of glyoxal (40%), furnishing enantiopure morpholin-2-ones **10a** and **10b** upon reflux for three hours in THF (Scheme 3). The reaction showed high stereoselectivity since no diastereomers were detected in the crude ^{1}H NMR spectra, which is in accordance with previously reported analogous condensation reactions.[46]



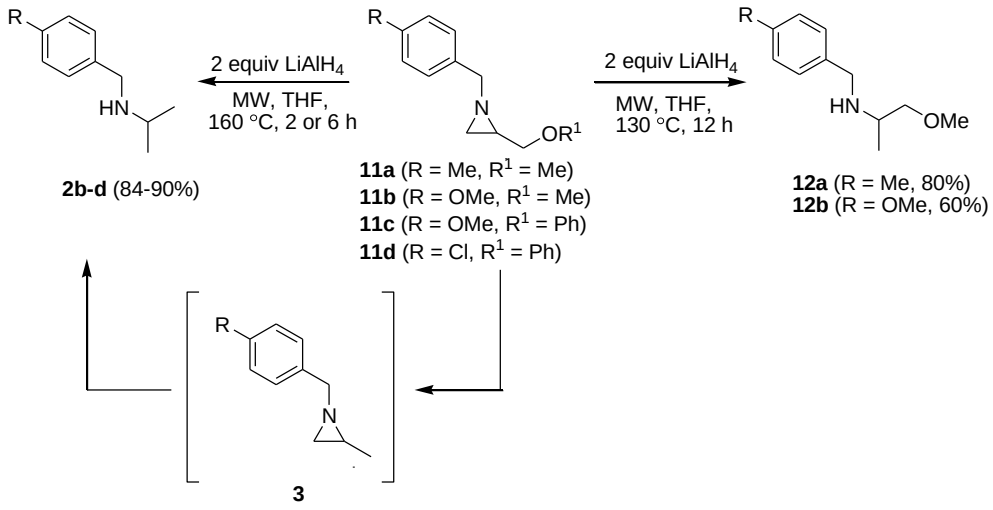
Scheme 3

Attempts to convert enantiopure amino alcohols **9** into chiral 2-methylaziridines were not successful. For this purpose, β-amino alcohols **9a** and **9b** were subjected to Mitsunobu conditions using 1.2 equiv of PPh_3 and 1.2 equiv of diisopropyl azodicarboxylate (or 1.2 equiv of *N*-bromosuccinimide) in THF for 18 hours, or were treated with 1.05 equiv of MsCl and 1.1 equiv of Et_3N (or 1.05 equiv of TsCl and 0.1 equiv of DMAP) in CH_2Cl_2 for 4 hours, although in all cases only complex mixtures were obtained. Furthermore, a number of efforts were made towards the *N*-deprotection of morpholinones **10a** and **10b** through hydrogenolysis (10% $Pd(OH)_2$, EtOAc, r.t, 5 bar H_2). However, ^{1}H NMR and GC-MS analysis of the crude mixtures revealed the presence of deprotected amines only as a minor components (up to 35%) together with the starting compound, even upon prolonged reaction times (more then three days).

In addition to the use of 2-(acetoxymethyl)- and 2-(hydroxymethyl)aziridines, the $LiAlH_4$-promoted ring opening of 2-(methoxymethyl)- and 2-(phenoxymethyl)aziridines **11a-d** was evaluated applying microwave conditions (Scheme 4).

2-(Methoxymethyl)aziridines **11a** and **11b** were prepared through conversion of 2-(bromomethyl)aziridines **1** upon treatment with two equiv of sodium methoxide in methanol (2M) under reflux for 15 hours.[54] Remarkably, treatment of these aziridines **11a** and **11b** with two equiv of $LiAlH_4$ under microwave conditions resulted in different reaction products depending on the temperature used. Indeed, treatment of aziridine **11a** and **11b** for 2 hours at 160 °C yielded isopropylamines **2**, whereas mainly β-methoxyamines **12a** and **12b** were obtained after 12 hours at 130 °C. The formation of isopropylamines **2** can be explained considering the initial replacement of the methoxy group by means of $LiAlH_4$ (via a nucleophilic or radical pathway) furnishing 2-methylaziridines **3**, which subsequently underwent reductive ring opening via nucleophilic attack of a hydride ion (from $LiAlH_4$) at the less substituted carbon atom of the aziridine moiety. Again, spectroscopic evidence for the intermediacy of 2-methylaziridines **3** was obtained through careful analysis of the reaction mixtures. Apparently, at 130 °C nucleophilic aziridine ring opening by hydride took place prior to replacement of the methoxy group, and β-methoxyamines **12a** and **12b** were obtained as the major components in the reaction mixtures. The reaction of 2-(phenoxymethyl)aziridines **11c** and **11d**, obtained by treatment of 2-(bromomethyl)aziridines **1** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 under reflux for 10 hours in a mixture of DMF and acetone (1/1),[4b] with two equiv of $LiAlH_4$ furnished surprisingly isopropylamines **2** after 6 hours at 160 °C under microwave irradiation. However, when these aziridines **11c** and **11d** were heated at 130 °C (or 140 °C) for 10-15 hours, 2-methylaziridines **3** were obtained in a mixture together with starting compounds **11c** and **11d**. Increasing the temperature to 160 °C led to the full conversion of aziridines **11c** and **11d** into isopropylamines **2**. These observations can be explained considering the better leaving group capacities of the phenoxy substituent as compared to the methoxy group, resulting in a more rapid formation of intermediate 2-methylaziridines **3**. The unexpected behaviour of the phenoxy group as a leaving

group is remarkable, as no other reports on the conversion of phenoxyalkanes into the corresponding alkanes using hydride reagents have been reported in the literature. Thus, attempts were made to convert *n*-decylphenylether into n-decane using $LiAlH_4$ under microwave conditions. However, the reaction showed to be potentially dangerous under microwave irradiation at 160 °C, leading to an explosive reaction outcome. Therefore, this method can not to be regarded as a general synthetic approach for alkane formation as such.



Scheme 4

In conclusion, the microwave-assisted reductive ring opening of 2-substituted non-activated aziridines utilizing $LiAlH_4$ has been reported for the first time in a highly regio- and stereoselective way. 2-(Acetoxymethyl)aziridines provided β-amino alcohols upon treatment with $LiAlH_4$ under microwave irradiation, which were then used to produce synthetically relevant 5-methylmorpholin-2-ones in a straightforward way. Besides, the microwave-assisted conversion of chiral aziridine substrates by means of $LiAlH_4$ furnished the corresponding enantiopure β-amino alcohols, which were then exposed to glyoxal to give chiral 5(*R*)- and 5(*S*)-morpholin-2-

ones. In addition, 2-(methoxymethyl)aziridines provided isopropylamines or β-methoxyamines upon treatment with $LiAlH_4$ under microwave irradiation, depending on the temperature applied. Thus, $LiAlH_4$ can be regarded as a useful reagent for a new type of reductive aziridine ring opening in a selective way under microwave conditions, paving the way for a variety of novel applications in organic chemistry.

Experimental section

General

^1H 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 recorded on an Agilent 1100 series mass spectrometer using either a direct inlet system (electron spray, 4000 V) or LC-MS coupling (UV detector). IR spectra were recorded on a Perkin-Elemer Spectrum BX FT-IR spectrometer. All compounds were analysed in neat form with an ATR (Attenuated Total Reflectance) accessory. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use. Microwave reactions were performed in a CEM Discover Microwave Reactor in a 80 ml sealed vessel using a fiber-optic temperature sensor.

Synthesis of 1-arylmethyl-2-(acetoxymethyl)aziridines 4

As a representative example, the synthesis of 1-(4-chlorophenyl)methyl-2-(acetoxymethyl)aziridine **4c** is described here. 1-(4-Chlorophenyl)methyl-2-

(bromomethyl)aziridine (2.60 g, 10 mmol)[25] was added to a stirred solution of NaOAc (1.23 g, 1.5 equiv) in DMSO (20 ml) at room temperature, and the mixture was heated at 100 °C for 15 h. The reaction mixture was poured into water (20 ml) and extracted with Et_2O (3 x 20 ml). The combined organic extracts were washed with H_2O (2 x 15 ml) and brine (20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-chlorophenyl)methyl-2-(acetoxymethyl)aziridine **4c** (2.16 g, 90%), which was purified by filtration through silica gel (hexane/ethyl acetate 2:1) in order to obtain an analytically pure sample.

1-(4-Methylphenyl)methyl-2-(acetoxymethyl)aziridine 4b. Yield 83%, light-yellow oil, R_f = 0.15 (hexane/ethyl acetate 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (1H, d, J = 6.0 Hz); 1.77 (1H, d, J = 3.3 Hz); 1.81–1.89 (1H, m); 1.97 (3H, s); 2.34 (3H, s); 3.30 and 3.54 (2H, 2 x d, J = 13.2 Hz); 3.82 and 4.17 (2H, 2 x d x d, J = 11.5, 7.2, 4.4 Hz); 7.13-7.25 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 21.1, 31.8, 36.9, 64.0, 66.6, 128.0, 129.0, 135.7, 136.6, 170.9. IR (neat, cm^{-1}): ν_{CO} = 1737; ν_{max} = 2924; 1370; 1230; 1032; 802. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.35, H 8.03, N 6.44.

1-(4-Chlorophenyl)methyl-2-(acetoxymethyl)aziridine 4c. Yield 90%, light-yellow oil, R_f = 0.12 (hexane/ethyl acetate 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (1H, d, J = 6.6 Hz); 1.79 (1H, d, J = 3.9 Hz); 1.80–1.90 (1H, m); 1.98 (3H, s); 3.26 and 3.56 (2H, 2 x d, J = 13.8 Hz); 3.79 and 4.20 (2H, 2 x d x d, J = 11.6, 7.4, 4.4 Hz); 7.24-7.32 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.9, 32.0, 37.2, 63.5, 66.6, 128.5, 129.5, 132.9, 137.4, 171.0. IR (neat, cm^{-1}): ν_{CO} = 1737; ν_{max} = 2986; 2832; 1491; 1370; 1231; 1087; 1033; 806. 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 60.28, H 6.12, N 5.79.

1-(4-Methoxyphenyl)methyl-2-(acetoxymethyl)aziridine 4d. Yield 79%, light-yellow oil, R_f = 0.08 (hexane/ethyl acetate 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (1H, d, J = 6.6 Hz); 1.77

(1H, d, *J* = 3.3 Hz); 1.79–1.89 (1H, m); 1.97 (3H, s); 3.26 and 3.52 (2H, 2 x d, *J* = 13.0 Hz); 3.80 (3H, s); 3.86 and 4.17 (2H, 2 x d x d, *J* = 11.6, 7.7, 4.7 Hz); 6.85-6.88 and 7.25-7.28 (4H, 2 x m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 31.8, 36.9, 55.3, 63.6, 66.6, 113.7, 129.3, 131.0, 158.8, 170.9. IR (neat, cm^{-1}): ν_{CO} = 1736; ν_{max} = 2952; 2835; 1511; 1234; 1031; 818. MS (70 eV): *m/z* (%): 236 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: C 66.45, H 7.57, N 5.81.

Synthesis of 2-(arylmethylamino)propan-1-ols 6 from 1-arylmethyl-2-(acetoxymethyl)aziridines 4

As a representative example, the synthesis of 2-{[(4-chlorophenyl)methyl]amino}propan-1-ol **6c** is described here. 1-(4-Chlorophenyl)methyl-2-(acetoxymethyl)aziridine **4c** (1.20 g, 5 mmol) was dissolved in dry THF (50 ml), after which $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 ml sealed glass vessel, provided with appropriate stirrer bar and subjected to microwave conditions (130 °C, 220 W_{max}, two hours). Afterwards, the reaction mixture was poured into water (20 ml) and extracted with Et_2O (3 x 20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{[(4-chlorophenyl)methyl]amino}propan-1-ol **6c** (0.92 g, 92%), which was purified by filtration through silica gel column (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample. CAUTION: strict safety measurements have to be applied for $LiAlH_4$-promoted reactions under microwave irradiation in order to cover the risk of explosion.

2-{[(4-Methylphenyl)methyl]amino}propan-1-ol 6b. Yield 75%, light-yellow crystals, R_f = 0.17 (dichloromethane/methanol 9:1), Mp = 71.7-72.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* = 6.6 Hz); 2.33 (3H, s); 2.74 (2H, br s); 2.77–2.88 (1H, m); 3.27 and 3.57 (2H, 2 x d x d, *J* = 11.0, 6.9, 3.9 Hz); 3.68 and 3.83 (2H, 2 x d, *J* = 12.9 Hz); 7.07-7.25 (4H, m). ^{13}C NMR (75

MHz, $CDCl_3$): δ 16.7, 21.2, 50.5, 53.9, 65.2, 128.4, 129.3, 136.0, 137.1. IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3277; ν_{max} = 2846; 1460; 1063; 886; 812. MS (70 eV): *m/z* (%): 180 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.92, H 9.48, N 9.47.

2-{[(4-Chlorophenyl)methyl]amino}propan-1-ol 6c. Yield 92%, light-yellow crystals, R_f = 0.19 (dichloromethane/methanol 9:1), Mp = 64.6-65.6 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 6.6 Hz); 2.31 (2H, br s); 2.75-2.85 (1H, m); 3.27 and 3.56 (2H, 2 x d x d, *J* = 10.8, 7.2, 3.8 Hz); 3.68 and 3.83 (2H, 2 x d, *J* = 13.2 Hz); 7.23-7.33 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 17.2, 50.4, 53.9, 65.6, 128.7, 129.5, 132.9, 138.8. IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3312; ν_{max} = 2927; 1491; 1256; 1043; 730. MS (70 eV): *m/z* (%): 200/2 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_{14}ClNO$: C 60.15, H 7.07, N 7.01. Found: C 60.05, H 7.18, N 7.10.

2-{[(4-Methoxyphenyl)methyl]amino}propan-1-ol 6d. Yield 72%, light-yellow crystals, R_f = 0.08 (dichloromethane/methanol 9:1), Mp = 59.4-60.4 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 7.2 Hz); 1.95 (2H, br s); 2.72–2.81 (1H, m); 3.20 and 3.52 (2H, 2 x d x d, *J* = 10.5, 6.6, 3.9 Hz); 3.61 and 3.74 (2H, 2 x d, *J* = 12.9 Hz); 3.72 (3H, s); 6.78-6.81 and 7.15-7.19 (4H, 2 x m). ^{13}C NMR (75 MHz, ref= $CDCl_3$): δ 17.1, 50.6, 53.7, 55.4, 65.6, 113.9, 129.4, 132.4, 158.8. IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3294; ν_{max} = 2834; 1511; 1245; 1034; 819. MS (70 eV): *m/z* (%): 196 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO_2$: C 67.66, H 8.78, N 7.17. Found: C 67.76, H 8.91, N 7.14.

Synthesis of optically active 2-aminopropan-1-ols 9 from chiral aziridine alcohols 8

As a representative example, the synthesis of (*S*)-[1(*R*)-phenylethylamino]propan-1-ol **9a** is described here. Aziridine alcohol **8a** (0.88 g, 5 mmol) was diluted in dry THF (50 ml), and $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 ml sealed vessel, provided with appropriate stirrer bar and subjected to

microwave conditions (160 °C, 220 W_{max}, two hours). The resulting reaction mixture was subsequently poured into water (15 ml) and extracted with Et_2O (3 x 20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2(*S*)-[1(*R*)-phenylethylamino]propan-1-ol **9a** (0.83 g, 93%), which was purified by filtration through silica gel (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample.

2(*S*)-[1(*R*)-phenylethylamino]propan-1-ol 9a. Yield 93%, colorless liquid, R_f = 0.18 (dichloromethane/methanol 9:1), $[\alpha]_D^{28}$ = + 115.6 (c = 0.41, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d x d, *J* = 6.9, 1.4 Hz); 1.36 (3H, d, *J* = 6.6 Hz); 2.51–2.61 (1H, m); 2.55 (2H, br s); 3.16-3.23 (1H, m); 3.40 (1H, d x d, *J* = 10.8, 4.2 Hz); 3.93 (1H, q, *J* = 6.6 Hz); 7.19-7.34 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 25.2, 51.4, 54.9, 66.5, 126.6, 127.1, 128.6, 145.1. IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3292; ν_{max} = 2965; 1452; 1044; 762; 731; 699. MS (70 eV): *m/z* (%): 180 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.94, H 9.84, N 7.69.

2(*R*)-[1(*R*)-phenylethylethylamino]propan-1-ol 9b. Yield 85%, white crystals. R_f = 0.08 (dichloromethane/methanol 9:1), Mp = 49.5-51.1 °C, $[\alpha]_D^{28}$ = - 2.3 (c = 0.36, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, d, *J* = 6.6 Hz); 1.35 (3H, d, *J* = 6.4 Hz); 2.30 (2H, br s); 2.68–2.80 (1H, m); 3.20 and 3.59 (2H, 2 x d x d, *J* = 10.5, 6.1, 3.8 Hz); 3.87 (1H, q, *J* = 6.4 Hz); 7.22-7.36 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2, 24.1, 51.6, 55.4, 64.9, 126.4, 127.1, 128.6, 145.9. IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3292; ν_{max} = 2965; 1452; 1045; 761; 700. MS (70 eV): *m/z* (%): 180 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.78, H 9.72, N 7.82.

Synthesis of 5-methylmorpholin-2-ones 7 from 2-(arylmethylamino)propan-1-ols 6

As a representative example, the synthesis of 4-(4-methylphenyl)methyl-5-methylmorpholin-2-one **7b** is described here. To a solution of 2-{[(4-methylphenyl)methyl]amino}propan-1-ol **6b** (0.72 g, 4 mmol) in THF (30 ml) an aqueous solution of glyoxal (40%, 1.74 g, 3 equiv) was added, and the resulting mixture was heated for 2.5 h under reflux. The reaction mixture was then poured into water (20 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 7:1) in order to obtain an analytically pure sample (0.76 g, 87%).

4-(4-Methylphenyl)methyl-5-methylmorpholin-2-one 7b. Yield 87%, yellow liquid, R_f = 0.07 (petroleum ether/ethyl acetate 7:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, d, J = 6.1 Hz); 2.34 (3H, s); 2.82–2.92 (1H, m); 3.11 and 3.43 (2H, 2 x d, J = 18.2 Hz); 3.27 and 3.88 (2H, 2 x d, 12.9 Hz); 4.09 and 4.34 (2H, 2 x d x d, J = 11.0, 7.7, 3.6 Hz); 7.09-7.19 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 21.1, 51.1, 52.5, 57.3, 73.7, 128.8, 129.3, 133.6, 137.3, 168.2. IR (neat, cm^{-1}): ν_{CO} = 1742; ν_{max} = 2923; 1227; 1055; 807. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.47, H 8.06, N 6.27.

4-(4-Chlorophenyl)methyl-5-methylmorpholin-2-one 7c. Yield 83%, yellow solid, R_f = 0.05 (petroleum ether/ethyl acetate 7:1), Mp = 55.5-58.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, J = 6.0 Hz); 2.84–2.93 (1H, m); 3.11 and 3.41 (2H, 2 x d, J = 17.6 Hz); 3.29 and 3.88 (2H, 2 x d, 13.2 Hz); 4.09 and 4.35 (2H, 2 x d x d, J = 11.0, 7.7, 3.6 Hz); 7.23-7.35 (4H, m). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 12.5, 51.4, 52.6, 57.1, 73.7, 128.8, 130.2, 133.4, 135.6, 168.0. IR (neat, cm^{-1}): ν_{CO} = 1741; ν_{max} = 2969; 1490; 1227; 1056; 810. 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 60.27, H 6.11, N 5.98.

4-(4-Methoxyphenyl)methyl-5-methylmorpholin-2-one 7d. Yield 74%, yellow solid, R_f = 0.05 (petroleum ether/ethyl acetate 7:1), Mp = 48.3–51.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H,

d, *J* = 6.6 Hz); 2.82–2.92 (1H, m); 3.11 and 3.43 (2H, 2 x d, *J* = 17.6 Hz); 3.26 and 3.86 (2H, 2 x d, *J* = 12.6 Hz); 3.81 (3H, s); 4.09 and 4.34 (2H, 2 x d x d, *J* = 11.0, 7.7, 3.3 Hz); 6.84-6.89 and 7.18-7.25 (4H, 2 x m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 51.1, 52.4, 55.3, 57.0, 73.7, 114.0, 130.1, 128.6, 161.3, 167.9. IR (neat, cm^{-1}): ν_{CO} = 1739; ν_{max} = 2965; 1511; 1243; 1031; 822. MS (70 eV): *m/z* (%): 236 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: C 66.31, H 7.24, N 5.88.

Synthesis of chiral 5-methylmorpholin-2-ones 10 from chiral 2-aminopropan-1-ols 9

As a representative example, the synthesis of 5(*S*)-methyl-4-[1(*R*)-phenylethyl]morpholin-2-one **10a** is described here. To a solution of 2(*S*)-[1(*R*)-phenylethylamino]propan-1-ol **9a** (0.72 g, 4 mmol) in THF (30 ml) an aqueous solution of glyoxal (40%, 1.74 g, 3 equiv) was added, and the resulting mixture was heated for 3 h under reflux. The reaction mixture was then poured into water (20 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 3:1) in order to obtain an analytically pure sample (0.78 g, 89%).

5(*S*)-Methyl-4-[1(*R*)-phenylethyl]morpholin-2-one 10a. Yield 89%, light yellow solid, R_f = 0.25 (hexane/ethyl acetate 3:1), Mp = 37.1–40.2 °C, $[\alpha]_D^{28}$ = + 25.0 (c = 0.44, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, d, *J* = 6.6 Hz); 1.35 (3H, d, *J* = 6.8 Hz); 2.82–2.91 (1H, m); 3.38 and 3.74 (2H, 2 x d, *J* = 17.9 Hz); 3.66 (1H, q, *J* = 6.8 Hz); 4.00 and 4.37 (2H, 2 x d x d, *J* = 11.0, 3.3, 3.3 Hz); 7.24-7.34 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.0, 21.0, 47.2, 48.3, 60.2, 74.1, 127.3, 127.6, 128.7, 142.7, 168.6. IR (neat, cm^{-1}): ν_{CO} = 1737; ν_{max} = 2973; 1224; 1004; 701. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.27, H 7.93, N 6.33.

5(*R*)-Methyl-4-[1(*R*)-phenylethyl]morpholin-2-one 10b. Yield 86%, light yellow liquid, R_f = 0.18 (hexane/ethyl acetate 3:1), $[\alpha]_D^{28}$ = + 9.6 (c = 0.37, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, *J* = 6.6 Hz); 1.34 (3H, d, *J* = 6.6 Hz); 3.11 and 3.28 (2H, 2 x d, *J* = 18.2 Hz); 3.26–3.36 (1H, m); 3.74 (1H, q, *J* = 6.6 Hz); 4.14 and 4.47 (2H, 2 x d x d, *J* = 10.8, 5.2, 3.6 Hz); 7.22-7.39 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6, 16.6, 47.6, 48.3, 59.1, 73.9, 127.38, 127.44, 128.6, 142.8, 168.8. IR (neat, cm^{-1}): ν_{CO} = 1740; ν_{max} = 2972; 1206; 1050; 700. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.01, H 8.00, N 6.52.

Synthesis of 1-methoxypropan-2-amines 12 from 1-arylmethyl-2-(methoxymethyl)aziridines 11a and 11b

As a representative example, the synthesis of *N*-(4-methylphenyl)methyl-*N*-(2-methoxy-1-methylethyl)amine **12a** is described here. 1-(4-Methylphenyl)methyl-2-(methoxymethyl)aziridine **11a** (0.96 g, 5 mmol) was dissolved in dry THF (25 ml), after which $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 ml sealed vessel, provided with appropriate stirrer bar and subjected to microwave conditions (130 °C, 250 W_{max}, 12 h). Afterwards, the reaction mixture was poured into water (20 ml) and extracted with Et_2O (3 x 20 ml). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-(4-methylphenyl)methyl-*N*-(2-methoxy-1-methylethyl)amine **12a** (0.27 g, 80%), which was purified by filtration through silica gel column (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample.

***N*-(4-methylphenyl)methyl-*N*-(2-methoxy-1-methylethyl)amine 12a.** Yield 80%, light-yellow oil, R_f = 0.23 (dichloromethane/methanol 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 6.1 Hz); 2.33 (3H, s); 2.08 (1H, br s); 2.89–2.99 (1H, m); 3.27 and 3.34 (2H, 2 x d x d, *J* = 9.4,

7.7, 4.4 Hz); 3.32 (3H, s); 3.69 and 3.86 (2H, 2 x d, J = 12.9 Hz); 7.12-7.26 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 21.1, 50.9, 51.8, 58.9, 77.1, 128.2, 129.1, 136.5, 137.2. IR (neat, cm^{-1}): ν_{NH} = 3325; ν_{max} = 2923; 2875; 2826; 1514; 1450; 1373; 1197; 1162; 1106; 805. MS (70 eV): *m/z* (%): 194 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{19}NO$: C 74.57, H 9.91, N 7.25. Found: C 74.68, H 9.48, N 7.47.

***N*-(4-methoxyphenyl)methyl-*N*-(2-methoxy-1-methylethyl)amine 12b.** Yield 60%, dark-yellow oil, R_f = 0.21 (dichloromethane/methanol 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (3H, d, J = 6.1 Hz); 2.24 (1H, br s); 2.89–2.99 (1H, m); 3.25-3.36 (2H, m); 3.67 and 3.83 (2H, 2 x d, J = 12.7 Hz); 3.80 (3H, s); 6.85-6.88 (4H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 50.7, 51.8, 55.3, 58.8, 77.0, 113.8, 129.4, 132.4, 158.6. IR (neat, cm^{-1}): ν_{NH} = 3324; ν_{max} = 2928; 2877; 2832; 1612; 1511; 1462; 1244; 1105; 1035; 822. MS (70 eV): *m/z* (%): 210 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69. Found: C 68.61, H 9.48, N 6.47.

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