A Divergent Synthetic Strategy Based on the Regioselective Reductive Ring-Opening of a Cyclic 1,2-*p*-Methoxybenzylidene Acetal

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Abstract: (1*S*)-*N*,*N*-Dibenzyl-1-[(4*R*)-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl]ethanamine is obtained in five steps from an α-bromo-α′-(*R*)-sulfinyl ketone and is used as a common intermediate for the synthesis of the *p*-methoxybenzyl-protected primary and secondary alcohols, (2*R*,3*S*)-3-(dibenzylamino)-2-[(4-methoxybenzyl)oxy]butan-1-ol and (2*R*,3*S*)-3-(benzylamino)-1-[(4-methoxybenzyl)oxy]butan-2-ol, respectively. These alcohols are further exploited as precursors for the synthesis of a fully protected *syn*-3-amino-2-hydroxybutanoic acid and an *N*-benzyl 2-hydroxymethylaziridine.

Key words: sulfoxides, diols, protecting groups, neighboring-group effects, regioselectivity

α-Hydroxy-β-amino acids (isoserines) constitute an essential moiety in the design and synthesis of a large number of natural products which possess powerful biological activity.[1] Among the isoserine family, protected 3-amino-2-hydroxybutanoic acid derivatives (Figure 1) have proven to be useful intermediates for various types of natural and synthetic compounds.[2] Moreover, the (2*S*,3*R*)-stereoisomer of 3-amino-2-hydroxybutanoic acid (**1**) is the key component of an antibacterial agent, the glycopeptide dideoxykanamycin A. The derivatives of this glycopeptide, having (2*S*,3*S*)- and (2*R*,3*R*)-configurations, have shown potent antibacterial activity similar to that of dideoxykanamycin A.[3]

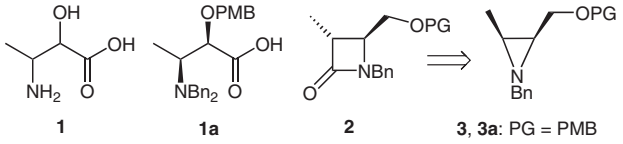
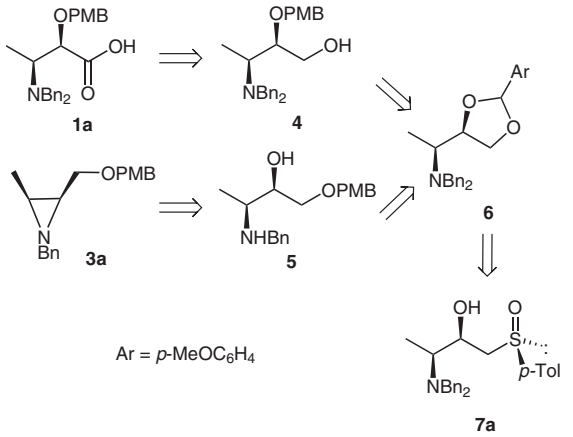


Figure 1 Structures of 3-amino-2-hydroxybutanoic acid derivatives and *N*-benzyl 2-hydroxymethylaziridines

Aziridines have found widespread use as versatile building blocks for the preparation of a variety of important nitrogen-containing compounds.[4] In this context, *N*-benzyl 2-hydroxymethylaziridines **3** (Figure 1) have been used as substrates for carbonylative ring-expansion into β-lactams **2**.[5] In addition, these aziridines have also found application as promoters for the enantioselective addition of dialkylzincs to *N*-(diphenylphosphinoyl) imines.[6] Herein, we report a divergent approach to the synthesis of a fully protected *syn*-3-amino-2-hydroxybutanoic acid **1a** and *N*-benzyl 2-hydroxymethylaziridine (**3a**).

Methoxybenzylidene acetals of 1,2-glycols are reported to be cleaved by diisobutylaluminum hydride[7] leading to the corresponding mono-*p*-methoxybenzyl ether of the glycol.[8] This method has been used widely for the synthesis of complex natural products.[9] The ring-opening of these acetals to give either primary or secondary protected alcohols occurs, in most cases, selectively at the less hindered side of the substrate.[10] However, Takano[7] observed that, directed by a vicinal basic group, cleavage could take place at the more hindered position. In this context, Riera and co-workers[11a] described the formation of a primary *p*-methoxybenzyl ether by reductive cleavage at the most hindered position[11b–e] of a carbamate-protected amino-acetal, and explained the regioselectivity observed by a directing effect induced by the nitrogen of the vicinal carbamate group. To the best of our knowledge, and despite significant interest in this field, no divergent route from a common starting acetal of a 1,2-glycol toward the two possible protected alcohol regioisomers has been documented.[12]

Inspired by this earlier work, and as an extension of our studies to explore new synthetic applications of vicinal *syn*-*N*,*N*-dibenzylamino alcohol **7a**,[13] we decided to investigate a divergent strategy allowing access to the *p*-methoxybenzyl ethers **4** and **5** from the *p*-methoxyben-



Scheme 1 Divergent strategy for the synthesis of compounds **1a** and **3a**

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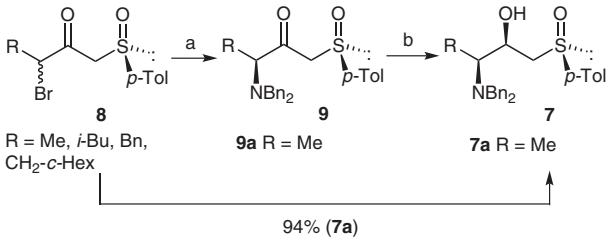
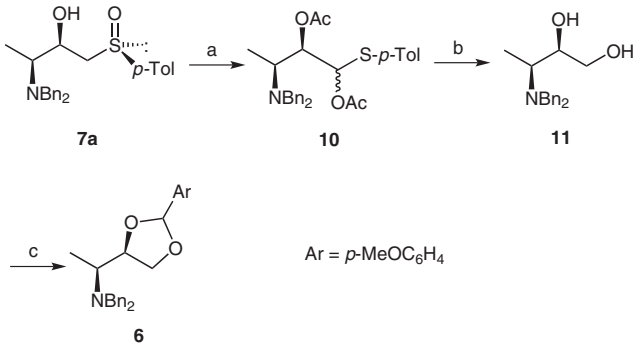
zylidene acetal **6** as a common intermediate (Scheme 1). We projected the transformation of **4** and **5** into fully protected *syn*-3-amino-2-hydroxybutanoic acid **1a** and 2-hydroxymethylaziridine **3a**, respectively.

In a recent paper,[13] we described a novel and efficient method for the synthesis of enantiomerically pure α-*N*,*N*-dibenzylamino-α′-(*R*)-sulfinyl ketones **9**, starting from an epimeric mixture of α-bromo-α′-(*R*)-sulfinyl ketones **8**, via a combined in situ substitution–epimerization process, a so-called dynamic kinetic resolution (Scheme 2). The corresponding *syn*-amino alcohols **7** were obtained by means of a sulfoxide-controlled, highly stereoselective reduction of the carbonyl group using diisobutylaluminum hydride as the reducing agent in the presence of zinc(II) iodide. We improved the yields of this two-step sequence by reacting crude **9** without prior isolation. Starting from **8a** (R = Me), the desired derivative **7a** was obtained in 94% yield in multigram amounts and with excellent stereoselectivity (>95:5).



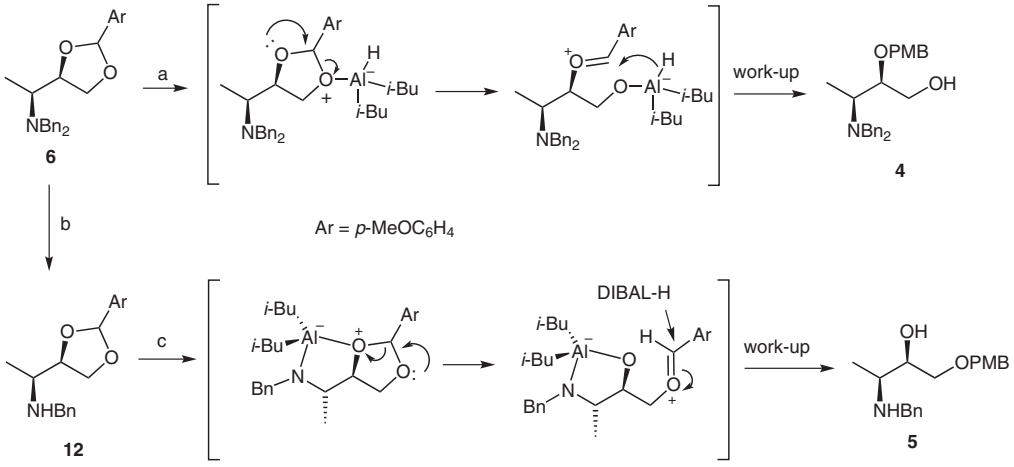
Scheme 2 Synthesis of *syn*-amino alcohol **7a**. *Reagents and conditions*: (a) Bn_2NH, THF, r.t., 84%; (b) (i) ZnI_2, THF, r.t.; (ii) DIBAL-H, THF, –78 °C, 96%.



Scheme 3 Synthesis of *p*-methoxybenzylidene acetal **6**. *Reagents and conditions*: (a) NaOAc, Ac_2O, 130 °C, 82%; (b) LAH, Et_2O, 0 °C, 82%; (c) *p*-anisaldehyde, *p*-TsOH, toluene, 81%.

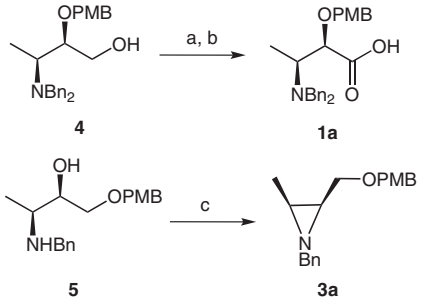
As shown in Scheme 3, the synthesis of key intermediate **6** was readily accomplished from derivative **7a** by taking advantage of the versatility of the chemistry of sulfoxides.[14] In this context, sulfoxide **7a** was subjected to Pummerer rearrangement with sodium acetate in acetic anhydride at 130 °C[15] affording, after concomitant 2-hydroxy group acylation, the corresponding α-acetoxysulfide **10** in 82% yield. Reduction of the ester and the thioacetal functions was accomplished by exposure to lithium aluminum hydride at 0 °C. The resulting 1,2-diol **11** was converted into the *p*-methoxybenzylidene acetal **6** in 81% yield and in a 45:55 diastereoisomeric ratio, by reaction with *p*-anisaldehyde in toluene at reflux temperature, under acidic conditions using a Dean–Stark apparatus.

We next investigated the divergent strategy allowing access to both *p*-methoxybenzyl ethers **4** and **5** starting from *p*-methoxybenzylidene acetal **6** (Scheme 4). Thus, by employing diisobutylaluminum hydride at –78 °C, reductive cleavage of the *N*,*N*-dibenzyl derivative **6** took place at the less hindered side, providing the corresponding secondary *p*-methoxybenzyl protected alcohol **4** as a single regioisomer in 90% yield after silica gel column chromatography. On the other hand, monodebenzylation of **6** following the procedure of Grayson and Davis[16] (*N*-iodosuccinimide in anhydrous dichloromethane) afforded the *N*-monobenzylated *p*-methoxybenzylidene acetal **12** in 83% yield. On reaction with diisobutylaluminum hydride at –78 °C, derivative **12** furnished exclusively the desired primary *p*-methoxybenzyl protected alcohol **5** in 92% yield. The observed regioselectivity in this latter case could be attributed to a chelation directing effect from the nitrogen of the monobenzylated amine as the control element.



Scheme 4 Divergent synthesis of alcohols **4** and **5**. *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, –78 °C, 90%; (b) NIS, CH_2Cl_2, 83%; (c) DIBAL-H, CH_2Cl_2, –78 °C, 92%.

Next, we focused our efforts on exploring the synthetic potential of this methodology (Scheme 5). Swern oxidation of the primary hydroxy group of compound **4** provided the corresponding unstable aldehyde, which without further purification was submitted to a sodium chlorite ($NaClO_2$) mediated Pinnick[17] oxidation reaction. The fully protected *syn*-3-amino-2-hydroxybutanoic acid **1a** was obtained in 44% yield (over the two steps) as a single diastereomer according to ^{1}H NMR analysis (de >95:5). Furthermore, ring-closure of the vicinal amino alcohol moiety in derivative **5**, under Mitsunobu conditions, provided a straightforward route to aziridine **3a**.[18] To this end, alcohol **5** was transformed into the fully protected 2-hydroxymethylaziridine **3a** in 77% yield (de >95:5) by reaction with triphenylphosphine and diisopropyl azodicarboxylate. The *syn* configuration was confirmed unambiguously by analysis of the coupling constants in the ^{1}H NMR spectrum ($^3J_{2,3}$ = 5.8 Hz).[5a]



Scheme 5 Synthesis of fully protected *syn*-3-amino-2-hydroxybutanoic acid **1a** and 2-hydroxymethylaziridine **3a**. *Reagents and conditions*: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78 °C; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, 2-methyl-2-butene, 44% (two steps); (c) DIAD, Ph_3P, THF, 77%.

In conclusion, employing *syn*-*N*,*N*-dibenzylamino alcohol **7a** as a model substrate, we have demonstrated a divergent and efficient approach to synthetically useful 1- and 2-*p*-methoxybenzyl ether protected 3-amino-1,2-diols **4** and **5** via 3-(*N*,*N*-dibenzyl)-1,2-*p*-methoxybenzylidene acetal **6** as a common precursor. The synthetic potential of this procedure was further exemplified by the synthesis of enantiopure fully protected *syn*-3-amino-2-hydroxybutanoic acid **1a** and *N*-benzyl 2-hydroxymethylaziridine **3a** from the primary and secondary alcohols **4** and **5**. Extension of this method to the synthesis of other biologically important molecules is currently under investigation.

All reagents and solvents were purchased from commercial sources. THF was dried by distillation over sodium–benzophenone. Reactions were conducted in flame- or oven-dried glassware under an Ar atmosphere. Analytical TLC was performed on Merck Kieselgel silica gel 60F_{254} plates. Column chromatography was carried out on Merck Kieselgel silica gel 60 (63–200 μm). Melting points were obtained with a Büchi apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer polarimeter at 25 °C, 589 nm (Na wavelength), and concentrations are given in g/100 mL. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz (or 400 MHz and 100 MHz), respectively, in $CDCl_3$ using a Bruker Avance spectrometer. Chemical shifts (ppm) are reported relative to the residual solvent peak [$CHCl_3$, 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)]. Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br s = broad singlet), coupling constant(s) (*J*, Hz), integration. High-resolution mass spectra (HRMS) were measured on a Micromass spectrometer using electrospray ionization (ESI) and Q-Tof detection.

(2*R*,3*S*)-3-(Dibenzylamino)-1-(*p*-tolylthio)butane-1,2-diyl Diacetate (10)

A soln of aminohydroxysulfoxide **7a** (1.4 g, 3.44 mmol) and NaOAc (2.81 g, 34.3 mmol) in Ac_2O (60 mL) was heated at 130 °C for 6 h and then allowed to cool to r.t. The mixture was filtered through Celite, the filter cake washed with EtOAc, and the filtrate concentrated under reduced pressure. AcOH was co-evaporated with toluene to give the crude product, which was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 99:1 to 90:10) to afford a 1:1 diastereomeric mixture of **10**.

Yield: 1.38 g (82%); colorless oil; R_f = 0.22 (cyclohexane–EtOAc, 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ (diastereomeric mixture) = 7.26–6.97 (m, 14 H, CH_{arom}), 6.30 [d, *J* = 6.1 Hz, 0.5 H, C*H*(OAc)S, (B)], 6.06 [d, *J* = 4.6 Hz, 0.5 H, C*H*(OAc)S, (A)], 5.28 [dd, *J* = 4.6, 7.7 Hz, 0.5 H, C*H*(OAc), (A)], 5.07 [dd, *J* = 6.2, 6.2 Hz, 0.5 H, C*H*(OAc), (B)], 3.82–3.70 [m, 2 H, N(CH_aH$_b$Ph)$_2$], 3.30–3.23 [m, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.19–3.12 [m, 1 H, C*H*(NBn$_2$)], 2.24 (s, 3 H, CH_{3arom}), 2.02 [m, 3 H, C(O)CH_3], 1.87–1.80 [m, 3 H, C(O)CH_3], 1.07 [d, *J* = 6.9 Hz, 1.5 H, CH_3CH(NBn$_2$), (B)], 0.91 [d, *J* = 6.9 Hz, 1.5 H, CH_3CH(NBn$_2$), (A)].

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomeric mixture) = 170.3, 170.2, 169.6, 169.4, 139.8, 139.7, 138.9, 138.5, 134.3, 133.7, 129.94, 129.91, 129.3, 129.1, 128.8, 128.3, 127,5, 127.1, 127.0, 82.1, 79.2, 75.5, 75.2, 54.6, 54.2, 53.7, 52.7, 21.34, 21.26, 21.2, 21.1, 21.0, 9.74, 9.71.

ESI-MS: *m*/*z* = 492.3 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{34}NO_4S$: 492.2209; found: 492.2207.

(2*R*,3*S*)-3-(Dibenzylamino)butane-1,2-diol (11)

LAH (170 mg, 4.35 mmol) was added portionwise to a soln of thioacetal **10** (440 mg, 0.90 mmol) in Et_2O (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Excess LAH was decomposed with EtOAc (5 mL, dropwise), and then brine (20 mL) was added. The phases were separated and the aq fraction was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 4:1 to 1:1) to give diol **11**.

Yield: 210 mg (82%); colorless oil; R_f = 0.23 (cyclohexane–EtOAc, 2:1); $[\alpha]_D^{25}$ +53.9 (*c* 1.52, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 10 H, CH_{arom}), 3.81 [d, *J* = 13.2 Hz, 2 H, N(CH_aH$_b$Ph)$_2$], 3.72 (dd, *J* = 2.7, 11.6 Hz, 1 H, CH_aH$_b$OH), 3.53–3.48 (m, 1 H, C*H*OH), 3.38–3.28 (m, 1 H, CH$_a$$H_b$OH), 3.29 [d, *J* = 13.2 Hz, 2 H, N(CH$_a$$H_b$Ph)$_2$], 2.85 [qd, *J* = 6.7, 9.5 Hz, 1 H, C*H*(NBn$_2$)], 1.04 (d, *J* = 6.7 Hz, 3 H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8, 129.1, 128.6, 127.4, 71.5, 63.3, 54.2, 53.4, 8.2.

ESI-MS: *m*/*z* = 286.2 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}NO_2$: 286.1807; found: 286.1801.

(1*S*)-*N*,*N*-Dibenzyl-1-[(4*R*)-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl]ethanamine (6)

p-Anisaldehyde (0.32 mL, 2.80 mmol) and *p*-TsOH (10 mg) were added to a soln of diol **11** (540 mg, 1.89 mmol) in anhyd toluene (20 mL). The soln was heated at reflux temperature for 20 h, and H_2O was removed using a Dean–Stark trap. The mixture was then allowed to cool to r.t., filtered and the filtrate concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 10:1) to afford a 45:55 diastereomeric mixture of acetal **6**.

Yield: 620 mg (81%); yellowish oil; R_f = 0.35 (cyclohexane–EtOAc, 6:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ (diastereomeric mixture) = 7.46–7.20 (m, 12 H, CH_{arom}), 6.90 [d, J = 8.8 Hz, 0.9 H, CH_{arom}, (A)], 6.85 [d, J = 8.8 Hz, 1.1 H, CH_{arom}, (B)], 5.79 [s, C*H*-Ar, 0.45 H, (A)], 5.76 [s, C*H*-Ar, 0.55 H, (B)], 4.33–4.26 (m, 1 H, C*H*O), 4.14–4.07 [m, 0.45 H, CH_aH_bO, (A)], 3.98–3.87 [m, 2.55 H, CH_aH_bO, (B) and N(CH_aH_bPh)$_2$], 3.85–3.73 (m, 4 H, OCH_3 and CH$_a$$H_b$O), 3.64–3.58 [m, 2 H, N(CH$_a$$H_b$Ph)$_2$], 3.05–2.88 (m, 1 H, C*H*N), 1.14–1.08 (m, 3 H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomeric mixture) = 160.4, 160.3, 140.6, 140.5, 130.6, 129.9, 128.8, 128.7, 128.3, 128.22, 128.18, 127.8, 126.79, 126.75, 113.8, 113.7, 104.0, 103.3, 80.0, 79.1, 68.5, 67.6, 55.34, 55.32, 54.42, 54.38, 54.2, 53.9, 11.9, 11.8.

ESI-MS: m/z = 404.3 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{30}NO_3$: 404.2226; found: 404.2225.

(2*R*,3*S*)-3-(Dibenzylamino)-2-[(4-methoxybenzyl)oxy]butan-1-ol (4)

To a soln of acetal **6** (120 mg, 0.297 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added DIBAL-H (1.5 M in toluene, 0.9 mL, 1.35 mmol). The soln was stirred at –78 °C for 1 h and then treated with MeOH (5 mL). The mixture was allowed to warm to r.t. and the solvents were evaporated under reduced pressure. The resulting crude solid was treated with EtOAc (5 mL) and a sat. soln of potassium sodium tartrate (5 mL). The mixture was then stirred overnight. The phases were separated and the aq layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 4:1) to afford the alcohol **4**.

Yield: 108 mg (90%); colorless oil; R_f = 0.25 (cyclohexane–EtOAc, 4:1); [α]$_D^{25}$ +1.7 (*c* 1.2, Me_2CO).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.13 (m, 12 H, CH_{arom}), 6.79–6.74 (m, 2 H, CH_{arom}), 4.59 (d, J = 11.4 Hz, 1 H, OCH_aH$_b$Ar), 4.37 (br s, 1 H, O*H*), 4.30 (d, J = 11.4 Hz, 1 H, OCH$_a$$H_b$Ar), 4.08 [d, J = 13.2 Hz, 2 H, N(CH_aH_bPh)$_2$], 3.87–3.82 (m, 1 H, C*H*O), 3.70 (s, 3 H, OCH_3), 3.37 (dd, J = 3.2, 11.8 Hz, 1 H, CH_aH_bOH), 3.24–3.15 [m, 3 H, N(CH$_a$$H_b$Ph)$_2$ and CH$_a$$H_b$OH], 2.93 (qd, J = 3.4, 6.8 Hz, 1 H, C*H*N), 1.09 (d, J = 6.9 Hz, 3 H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 139.6, 130.8, 129.2, 128.5, 127.1, 113.7, 81.4, 71.6, 62.9, 55.6, 55.4, 55.3, 8.7.

ESI-MS: m/z = 406.2 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{32}NO_3$: 406.2382; found: 406.2375.

(1*S*)-*N*-Benzyl-1-[(4*R*)-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl]ethanamine (12)

Powdered 4 Å MS (250 mg) were flame-dried and cooled under Ar after which NIS (277 mg, 1.23 mmol) was added. To this solid mixture was added a soln of **6** (170 mg, 0.421 mmol) in anhyd CH_2Cl_2 (6 mL). The resulting suspension was stirred at r.t. for 1.5 h, filtered and rinsed with CH_2Cl_2 (5 mL). The organic layer was washed with aq sat. $Na_2S_2O_3$ soln (2 × 5 mL), H_2O (5 mL), and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 6:1 + 2% Et_3N) to afford a 45:55 diastereomeric mixture of **12**.

Yield: 110 mg (83%); colorless oil; R_f = 0.20 and 0.23 (cyclohexane–EtOAc, 5:1 + 2% Et_3N).

^{1}H NMR (300 MHz, $CDCl_3$): δ (diastereomeric mixture) = 7.35–7.18 (m, 7 H, CH_{arom}), 6.87–6.82 (m, 2 H, CH_{arom}), 5.74 [s, 0.45 H, C*H*Ar, (A)], 5.71 [s, 0.55 H, C*H*Ar, (B)], 4.19–4.15 [m, 0.45 H, CH_aH_bO, (A)], 4.09–3.79 [m, 3.1 H, CH_aH_bO, (B), C*H*O and NCH_aH_bPh], 3.76–3.74 (m, 3 H, OCH_3), 3.73–3.66 [m, 1.45 H, CH$_a$$H_b$O, (A) and NCH$_a$$H_b$Ph], 2.86–2.74 (m, 1 H, C*H*N), 2.20 (br s, 1 H, N*H*), 1.06–1.01 (m, 3 H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (diastereomeric mixture) = 159.4, 159.3, 139.33, 139.26, 129.0, 128.6, 127.4, 127.13, 127.11, 127.07, 126.9, 125.91, 125.90, 112.73, 112.70, 103.2, 102.4, 79.6, 79.3, 67.1, 66.6, 54.3, 53.7, 53.5, 49.9, 49.8, 15.0, 14.6.

ESI-MS: m/z = 314.3 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{24}NO_3$: 314.1756; found: 314.1748.

(2*R*,3*S*)-3-(Benzylamino)-1-[(4-methoxybenzyl)oxy]butan-2-ol (5)

To a soln of acetal **12** (110 mg, 0.351 mmol) in CH_2Cl_2 (10 mL) at –78 °C was added DIBAL-H (1.5 M in toluene, 1.2 mL, 1.8 mmol). The mixture was allowed to warm to –40 °C over 3 h and then treated with MeOH (10 mL). After warming to r.t., the solvents were evaporated under reduced pressure. The resulting solid was treated with EtOAc (10 mL) and a sat. aq soln of potassium sodium tartrate (10 mL). The mixture was then stirred vigorously for 2 h. The phases were separated and the aq fraction extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was precipitated from pentane, and washed with pentane to afford the alcohol **5**.

Yield: 102 mg (92%); white solid; mp 34 °C; R_f = 0.23 (cyclohexane–EtOAc, 2:1 + 2% Et_3N); [α]$_D^{25}$ +24.3 (*c* 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 7 H, CH_{arom}), 6.87 (d, J = 8.6 Hz, 2 H, CH_{arom}), 4.52 (d, J = 11.6 Hz, 1 H, OCH_aH$_b$Ar), 4.46 (d, J = 11.6 Hz, 1 H, OCH$_a$$H_b$Ar), 3.91 (d, J = 12.9 Hz, 1 H, NCH_aH$_b$Ph), 3.80 (s, 3 H, OCH_3), 3.69 (d, J = 12.9 Hz, 1 H, NCH$_a$$H_b$Ph), 3.61–3.54 (m, 1 H, CH_aH$_b$CHOH), 3.51–3.43 (m, 2 H, CH$_a$$H_b$CHOH and C*H*OH), 2.82–2.75 (m, 1 H, C*H*N), 1.09 (d, J = 6.4 Hz, 3 H, CH_3CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 130.4, 129.6, 128.6, 128.3, 127.2, 113.9, 74.0, 73.3, 71.6, 55.4, 54.6, 51.4, 16.8.

ESI-MS: m/z = 316.3 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{26}NO_3$: 316.1913; found: 316.1912.

(2*R*,3*S*)-3-(Dibenzylamino)-2-[(4-methoxybenzyl)oxy]butanoic Acid (1a)

To a soln of DMSO (0.05 mL, 0.705 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C was added oxalyl chloride (0.03 mL, 0.350 mmol). The mixture was stirred for 25 min at –78 °C, and then a soln of alcohol **4** (103 mg, 0.254 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred at –78 °C for 45 min, after which Et_3N (0.14 mL, 1.00 mmol) was added, the system warmed to 0 °C over 4 h and then quenched with sat. aq NH_4Cl soln (5 mL). The phases were separated, and the aq layer extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde was used without further purification in the next step. To a soln of this aldehyde in *t*-BuOH (2

mL) were added successively a soln of NaH_2PO_4 (62 mg, 0.397 mmol) in H_2O (0.5 mL), 2-methyl-2-butene (0.15 mL, 1.42 mmol), and $NaClO_2$ (80%, 94 mg, 0.831 mmol). The mixture was stirred at r.t. for 3 h, and then concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel (cyclohexane–EtOAc, 1:2) to give the carboxylic acid **1a**.

Yield: 47 mg (44%); colorless oil; R_f = 0.15 (cyclohexane–EtOAc, 1:2); $[\alpha]_D^{25}$ +38.9 (*c* 2.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 12 H, CH_{arom}), 6.78–6.76 (m, 2 H, CH_{arom}), 4.78 (d, *J* = 11.4 Hz, 1 H, CH_aH_bAr), 4.44 (d, *J* = 11.4 Hz, 1 H, CH$_a$$H_b$Ar), 4.36 [d, *J* = 13.1 Hz, 2 H, N(CH_aH_bPh)$_2$], 3.70 (s, 3 H, OCH_3), 3.62 (d, *J* = 3.2 Hz, 1 H, C*H*O), 3.36 [d, *J* = 13.2 Hz, 2 H, (NCH$_a$$H_b$Ph)$_2$], 3.17 (qd, *J* = 3.2, 6.9 Hz, 1 H, C*H*N), 1.15 (d, *J* = 6.9 Hz, 3 H, CH_3CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 159.4, 134.2, 130.1, 129.8, 129.5, 129.0, 128.6, 113.7, 78.6, 72.7, 55.2, 54.9, 54.6, 8.5.

ESI-MS: *m*/*z* = 420.2 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{30}NO_4$: 420.2175; found: 420.2169.

(2*S*,3*S*)-1-Benzyl-2-{[(4-methoxybenzyl)oxy]methyl}-3-methylaziridine (3a)

DIAD (95%, 0.035 mL, 0.170 mmol) was added to a soln of Ph_3P (48 mg, 0.183 mmol) in THF at 0 °C. The mixture was stirred for 25 min at 0 °C, then alcohol **5** (48 mg, 0.152 mmol) was added. The soln was allowed to warm to r.t., stirred overnight, and then the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (cyclohexane–EtOAc, 8:1) to give the aziridine **3a**.

Yield: 35 mg (77%); colorless oil; R_f = 0.24 (cyclohexane–EtOAc, 5:1); $[\alpha]_D^{25}$ –21.4 (*c* 0.70, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 7 H, CH_{arom}), 6.86 (d, *J* = 8.7 Hz, 2 H, CH_{arom}), 4.47 (d, *J* = 11.5 Hz, 1 H, CH_aH_bAr), 4.39 (d, *J* = 11.5 Hz, 1 H, CH$_a$$H_b$Ar), 3.80 (s, 3 H, OC$H_3$), 3.60–3.55 (m, 2 H, C$H_aH_b$O and C$H_aH_b$Ph), 3.49–3.45 (m, 2 H, CH$_a$$H_b$O and CH$_a$$H_b$Ph), 1.80 (q, *J* = 5.8 Hz, 1 H, CH$_2$C*H*N), 1.68 (quin, *J* = 5.8 Hz, 1 H, CH$_3$C*H*N), 1.17 (d, *J* = 5.8 Hz, 3 H, CH_3CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 139.5, 130.6, 129.5, 128.5, 128.0, 127.0, 113.9, 72.8, 68.9, 64.5, 55.4, 42.7, 38.6, 13.6.

ESI-MS: *m*/*z* = 298.1 $[M + H].^+$

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_2$: 298.1807; found: 298.1796.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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