PREPARATION OF BOTH (*D*)- AND (*L*)-SERINOL DERIVATIVES FROM *N*-[(*S*)-α-METHYLBENZYL]-AZIRIDINE-2(*S*)-METHANOL

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Abstract - Both (*D*)- and (*L*)-serinol derivatives were prepared efficiently from enantiomerically pure *N*-[(*S*)-α-methylbenzyl]aziridine-2(*S*)-methanol. Each of those serinols was transformed to the corresponding aldehyde and reacted with an ylide to give a coupling product.

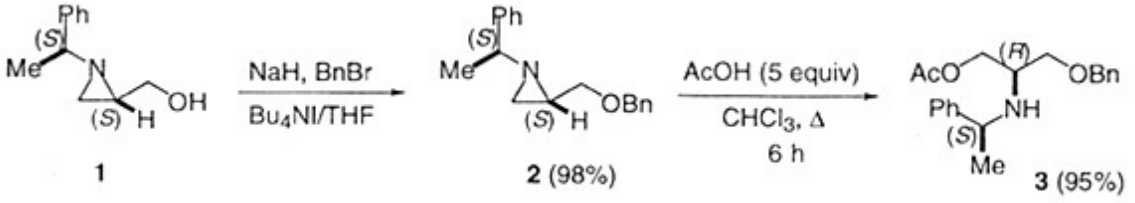
Enantiomerically pure amino alcohols have been widely used as chiral mediators for asymmetric induction in many auxiliary based reactions[1] and also as chiral building blocks for the syntheses of biologically active compounds.[2] The most efficient way to prepare vicinal amino alcohols is the direct reduction of the corresponding amino acids by known reducing reagents.[3]

However, direct reduction of (*D*)- or (*L*)-serine provides an achiral amino diol due to the presence of the hydroxymethyl group in the molecule. Therefore, all three different functional groups in serine should be protected prior to the reduction of the carboxylic acid moiety.[4]

We recently reported the preparation of chiral aziridine-2-methanol derivatives from readily available starting materials.[5] The C(3)-*N* bond of the aziridine ring of the chiral aziridine-2-methanol derivatives can be selectively reduced by catalytic hydrogenation[5] and also cleaved by AcOH to provide a variety of 2-amino-1,3-propanediols which can be precursors for various β-hydroxy-α-amino acids.[6]

We now report an efficient procedure for the preparation of (*D*)- and (*L*)-serinol derivatives from the enantiomerically pure aziridine-2-methanol (**1**). The compound (**1**) and its C-2(*R*) isomer can be easily prepared by reduction of the corresponding carboxylates.[5] The hydroxy group of **1** was protected as the benzyl ether (**2**) using NaH and BnBr. The aziridine C(3)-*N* bond of the benzyl ether (**2**) was then

Scheme 1

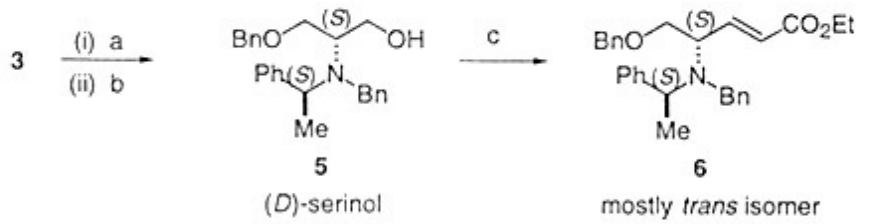


1 **2** (98%) **3** (95%)

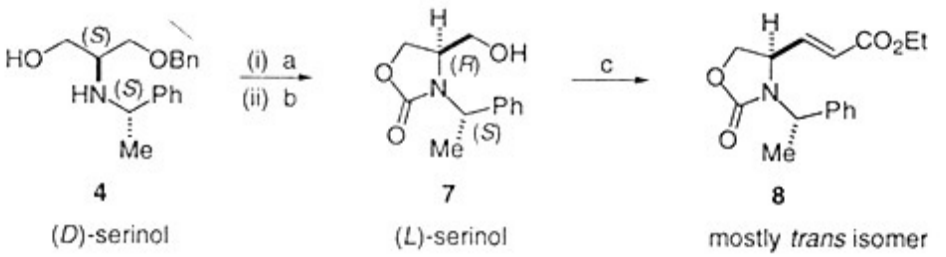
selectively cleaved by treating the compound with 5 equiv of AcOH in refluxing $CHCl_3$ to provide the 2-amino-1,3-propanediol (**3**) in 95% yield.[6] Compound (**3**) is the protected form of serinol and the two hydroxy groups are protected with two different groups, which can be selectively cleaved to provide either (*D*)- or (*L*)-serinol derivative(Scheme 1).

The acetate group of **3** was easily hydrolyzed by KOH in refluxing ethanol to provide (*D*)-serinol (**4**) as a protected form in 98% yield. Treatment of **4** with BnBr and *i*-Pr_2NEt in refluxing $CHCl_3$ provided the *N,N*-dibenzyl compound (**5**) in 81% yield. Swern oxidation followed by Wittig reaction with a stabilized ylide provided the coupling product (**6**) mostly as the *trans* isomer in 75% yield.

Scheme 2



(a) KOH/EtOH, reflux, 30 min, **4** (98%); (b) BnBr, *i*-$Pr_2NEt/CHCl_3$, reflux (81%); (c) 1) Swern Oxidation, 2) $Ph_3P{=}CHCO_2Et$ (75%)



(a) carbonyldiimidazole (CDI)/$CHCl_3$ (88%); (b) 10% $Pd(OH)_2/C/H_2$, EtOAc/MeOH(1:1) (99%); (c) 1) Swern Oxidation, 2) $Ph_3P{=}CHCO_2Et$ (52%)

To prepare (*L*)-serinol derivative, the amino alcohol (**4**) was reacted with carbonyldiimidazole (CDI) to give a cyclic carbamate in 88% yield. Selective removal of the *O*-benzyl group was accomplished by catalytic hydrogenation in the presence of 10% $Pd(OH)_2$ catalyst to yield the protected (*L*)-serinol (**7**) in 99% yield. Swern oxidation followed by Wittig reaction gave the coupling product (**8**) mostly as the *trans* isomer in 52% yield (Scheme 2). We obtained similar results from the C-2(*R*) isomer of the aziridine-2-methanol (**1**).

The above mentioned preparations of both (*D*)- and (*L*)-serinol derivatives from the enantiomerically pure aziridine-2-methanol derivative solved the problem of racemization which might occur from the direct reduction of the protected serine to serinol. Another advantage of this process is the availability of both enantiomers of serinols from one enantiomer precursor (**1**).

EXPERIMENTAL SECTION

General: NMR spectra were recorded on spectrometers operating at 200 and 300 MHz (^1H) and at 50 and 75 MHz (^{13}C) in deuteriochloroform ($CDCl_3$). Tetrahydrofuran and ether were distilled from sodium-

benzophenone ketyl at atmospheric pressure immediately prior to use. Methylene chloride and DMSO were distilled from calcium hydride prior to use. All other reagents and solvents used were reagent grade.

N-[(S)-α-Methylbenzyl]aziridine-2(S)-methyl benzyl ether (**2**)

To a solution of *N*-[(*S*)-α-Methylbenzyl]aziridine-2(*S*)-methanol (**1**) (1.10 g, 6.19 mmol) in 21 mL of THF was added NaH (60% oil dispersion, 495 mg, 12.4 mmol), Bu_4NI (cat.), and benzyl bromide (0.88 mL, 7.43 mmol). The mixture was stirred for 22 h at rt and then quenched with water. The mixture was extracted with EtOAc (20 mL x 3) and the combined extracts were dried over K_2CO_3 and concentrated. Purification by silica gel flash chromatography (EtOAc/n-hexane=1/9) provided 1.63 g (98%) of **2** as a colorless oil. $[\alpha]^{26}_D$ = -58.4° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.37-7.21 (m, 10H), 4.62 (d, *J* = 7.7 Hz, 2H), 3.56 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.50 (dd, *J* = 10.4, 6.2 Hz, 1H), 2.48 (q, *J* = 6.5 Hz, 1H), 1.87-1.78 (m, 1H), 1.58 (d, *J* = 3.4 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.34 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 144.8, 138.7, 128.6, 128.5, 127.8, 127.7, 127.2, 127.0, 73.0, 72.7, 69.7, 39.0, 31.1, 29.2; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.9; H, 7.9; N, 5.2. Found: C, 80.7; H, 8.0; N, 5.5.

3-Benzyloxy-2(R)-[(S)-α-methylbenzylamino]propyl acetate (**3**)

To a solution of **2** (337 mg, 1.26 mmol) in 6.50 mL of chloroform was added 0.37 mL (6.55 mmol) of acetic acid. The mixture was refluxed for 6 h and cooled to rt. The mixture was quenched with 1.0 mL of saturated aq. $NaHCO_3$ solution. The aqueous layer was extracted with methylene chloride (10 mL x 4). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by silica gel flash chromatography (EtOAc/n-hexane=3/7) provided 390 mg (95%) of **3** as a colorless oil. $[\alpha]^{25}_D$ = -49.0° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39-7.21 (m, 10H), 4.52 (s, 2H), 4.02 (d, *J* = 5.8 Hz, 2H), 3.88 (q, *J* = 6.6 Hz, 1H), 3.53 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.44 (dd, *J* = 9.5, 4.2 Hz, 1H), 2.84-2.81 (m, 1H), 1.98 (s, 3H), 1.32 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 145.9, 138.4, 128.6, 127.9, 127.8, 127.1, 126.8, 73.1, 68.4, 65.0, 55.5, 53.6, 24.8, 20.6; Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.4; H, 7.7; N, 4.3. Found: C, 73.3; H, 7.8; N, 4.5.

3-Benzyloxy-2(S)-[N-benzyl-N-[(S)-α-methylbenzyl]amino]propan-1-ol (**5**)

To a solution of **3** (887 mg, 2.71 mmol) in 13 mL of EtOH was added 182 mg (3.25 mmol) of KOH. The mixture was refluxed for 30 min, concentrated in *vacuo*, and the residue was dissolved in 2 mL of water. The aqueous layer was extacted with methylene chloride (10 mL x 4). The combined organic extracts were dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave 756 mg of 3-benzyloxy-2(*S*)-[(*S*)-α-methylbenzylamino]propan-1-ol (**4**) as a colorless oil. To the solution of **4** (99 mg, 0.348 mmol) in 1.7 mL of chloroform were added *i*-Pr_2NEt (0.18 mL, 1.04 mmol) and benzyl bromide (62 μL, 0.522 mmol). The mixture was refluxed for 16 h then cooled to rt. Water was added to the mixture and the mixture was extracted with methylene chloride (10 mL x 4). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-hexane=1/5) provided 103 mg (81 %) of **5** as a yellow oil. $[\alpha]^{26}_D$= -89.6° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36-7.19 (m, 15H), 4.24 (s, 2H), 3.94 (q, *J*=7.0 Hz, 1H), 3.88 (d,

J=15.8 Hz, 1H), 3.72 (d, *J*=5.3, 10.4 Hz, 1H), 3.61 (d, *J*=14.9 Hz, 1H), 3.52 (dd, *J*=10.4, 10.9 Hz, 1H), 3.39-3.26 (m, 1H), 3.15-2.89 (m, 2H), 1.39 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.7, 140.9, 138.3, 128.8, 128.6, 128.5, 128.3, 128.1, 127.8, 127.7, 127.5, 127.2, 73.2, 69.2, 61.3, 57.4, 57.0, 50.0, 19.1; Anal. Calcd for $C_{25}H_{29}NO_2$: C, 80.0; H, 7.8; N, 3.7. Found: C, 80.0; H, 7.6; N, 3.9.

trans-5-Benzyloxy-4(S)-{N-benzyl-N-[(S)-α-methylbenzyl]amino}pent-2-enoic acid ethyl ester (**6**)

To a solution of oxalyl chloride (17 μL, 0.193 mmol) in 0.5 mL of methylene chloride under a nitrogen at -78 °C was added DMSO (18 μL, 0.258 mmol). The mixture was stirred for 5 min at -78 °C and 3-benzyloxy-2(*S*)-{*N*-benzyl-*N*-[(*S*)-α-methylbenzyl]amino}propan-1-ol (**5**) (47 mg, 0.129 mmol) in 0.2 mL of methylene chloride was added dropwise. After stirring for 15 min at -78 °C, triethylamine (54 μL, 0.387 mmol) was added and the mixture was stirred for 15 min. The reaction mixture was diluted with methylene chloride (5 mL) and washed with water. The organic layer was dried over $MgSO_4$ and evaporated. To the crude aldehyde dissolved in THF (0.7 mL) was added (carbethoxymethyl)triphenylphosphorane (54 mg, 0.155 mmol) at 0 °C. The mixture was stirred at rt for 19 h, diluted with EtOAc (5 mL) and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by silica gel flash chromatography (EtOAc/n-hexane=1/19) provided 43 mg (75 %) of **6** as oil. $[\alpha]^{28}_D$= +40.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40-7.18 (m, 15H), 7.12 (dd, *J*=15.9, 6.9 Hz, 1H), 5.97 (d, *J*=15.8 Hz, 1H), 4.31 (s, 2H), 4.21 (q, *J*=7.1 Hz, 2H), 4.06 (q, *J*=6.9 Hz, 1H), 3.79 (s, 2H), 3.71-3.61 (m, 1H), 3.51-3.43 (m, 2H), 1.38 (d, *J*=6.8 Hz, 3H), 1.31 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.8, 148.2, 144.3, 141.0, 138.3, 128.5, 128.4, 128.3, 127.9, 127.7, 127.0, 122.9, 72.9, 71.1, 60.3, 57.3, 56.9, 51.1, 16.8, 14.1; Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.5; H, 7.5;N, 3.2. Found: C, 78.5; H, 7.5; N, 3.2.

4(R)-Hydroxymethyl-3-[(S)-α-methylbenzyl]oxazolidin-2-one (**7**)

To a solution of **4** (110 mg, 0.387 mmol) in 2 mL of $CHCl_3$ was added 75 mg (0.464 mmol) of carbonyldiimidazole at 0 °C. The mixture was heated to 50 °C, stirred for 17 h , and concentrated in *vacuo*. Purification by silica gel flash chromatography (EtOAc/n-hexane=3/7) provided 106 mg (88%) of the *O*-benzyl ether as a colorless oil. To a solution of the *O*-benzyl ether (185 mg, 0.596 mmol) in 2 mL of EtOAc:MeOH (1:1) was added 20 mg of 10% $Pd(OH)_2$. The mixture was stirred under a balloon pressure of hydrogen for 2 h at rt. The reaction mixture was filtrered and concentrated to give 130 mg (99%) of **7** as a white solid. mp 91-95 °C; $[\alpha]^{27}_D$ = -93.0° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.48-7.27 (m, 5H), 5.25 (q, *J* = 7.3 Hz, 1H), 4.36-4.17 (m, 2H), 4.00-3.89 (m, 1H), 3.26-3.10 (m, 2H), 1.69 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 159.2, 141.5, 128.9, 128.2, 126.9, 65.0, 61.3, 54.9, 51.2, 15.7; Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.2; H, 7.0; N, 6.2.

trans-3-[2-Oxo-3-[(S)-α-methylbenzyl]oxazolidin-4(R)-yl]acrylic acid ethyl ester (**8**)

To a solution of oxalyl chloride (69 μL, 0.793 mmol) in 2 mL of methylene chloride under a nitrogen at -78 °C was added DMSO (75 μL, 1.06 mmol). The mixture was stirred for 5 min at -78 °C and **7** (117 mg, 0.529 mmol) in 0.6 mL of methylene chloride was added dropwise. After 15 min of stirring at -78

°C, triethylamine (0.22 mL, 1.59 mmol) was added and the mixture was stirred for another 15 min. The reaction mixture was diluted with methylene chloride (10 mL) and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. To the residue dissolved in THF (2.6 mL) was added (carbethoxymethyl)triphenylphosphorane (221 mg, 0.635 mmol) at 0°C. The mixture was stirred at rt for 15 h, diluted with EtOAc (10 mL) and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by silica gel flash chromatography (EtOAc/n-hexane=3/7) provided 80 mg (52 %) of **8** as a white solid. mp 52-53 °C $[\alpha]^{28}_D$= -66.7° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.36-7.23 (m, 5H), 6.28 (dd, *J*=15.6, 8.6 Hz, 1H), 5.71 (d, *J*=15.7 Hz, 1H), 4.97 (q, *J*=7.1 Hz, 1H), 4.42 (dd, *J*=8.6, 5.9 Hz, 1H), 4.40-4.32 (m, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 3.97-3.89 (m, 1H), 1.70 (d, *J*=7.2 Hz, 3H), 1.24 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.0, 157.7, 143.5, 140.3, 128.8, 128.5, 128.1, 127.7, 124.8, 66.0, 60.5, 55.7, 52.4, 16.2, 13.8; Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6;N, 4.8. Found: C, 66.4; H, 6.5; N, 4.8.

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