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A Simple Strategy for the Synthesis of Hydroxyethylene Dipeptide Isostere from D-Glucose

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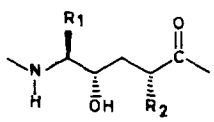
Abstract : A general approach is outlined here for the synthesis of hydroxyethylene dipeptide isostere (**1**) starting from D-glucose which can be employed to introduce any group at P_1 or P_1' positions of such isosteres. A highly stereoselective synthesis of (2R,4S,5S)-N-Boc-O-benzyl-5-amino-4-hydroxy-2-methyl-6-phenylhexanoic acid methyl ester (**2**) is accomplished based on this strategy.

The aspartic protease of the human immunodeficiency virus-1 (HIV-1) is an important enzyme needed for virus replication and thus an ideal target for chemotherapeutic treatment of AIDS[1]. A tremendous amount of work has been carried out in the design and evaluation of a vast array of compounds with diverse structural motifs to find effective inhibitors of HIV-1 protease[2]. The hydroxyethylene 1 (ψ [CH(OH)CH_2]) dipeptide isosteres (-NHCHR_1 ψ CHR_2CO-) which act as transition-state analogues mimicking the tetrahedral intermediate



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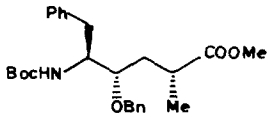

2

formed during the enzyme catalyzed hydrolysis of the scissile peptide bond are used extensively in many such designs[3]. These peptidomimetic analogues have been synthesized from a variety of starting materials including chiral amino acids[4]. The amino acid approach is cumbersome especially when P_1 substitutions are required that are not readily obtained from natural amino acids. Herein, we detail our studies on the development of a general strategy, as depicted in Scheme I, for the synthesis of hydroxyethylene dipeptide isosteres starting from D-glucose[5].

The essence of present approach lies in the regioselective organocuprate opening of a terminal aziridine ring **3**[6], derived easily from vicinal azido alcohol **4**, resulting in the facile incorporation of any requisite group at P_1 position. Based on this simple protocol we have carried out a highly stereoselective synthesis of (2R,4S,5S)-N-Boc-O-benzyl-5-amino-4-hydroxy-

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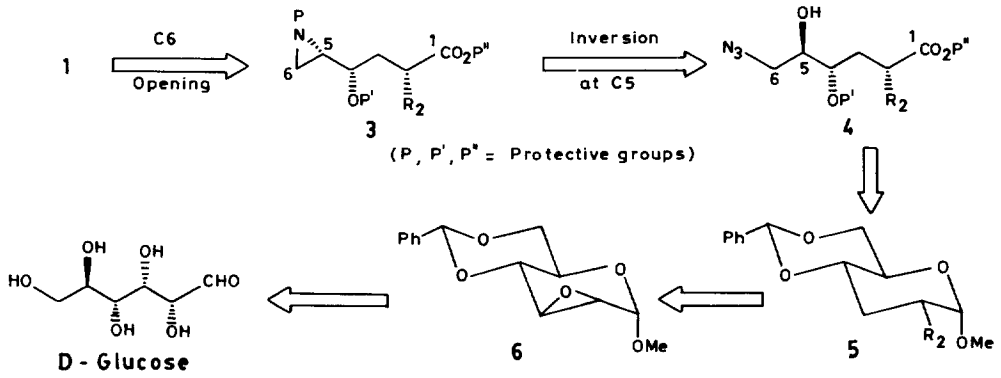
2-methyl-6-phenylhexanoic acid methyl ester, **2** (Boc-Phe[CH((S)-OBn)CH_2]Ala-OMe) (Scheme II), the hydroxyethylene isosteric moiety of potent HIV-1 protease inhibitors[3a].

Scheme I



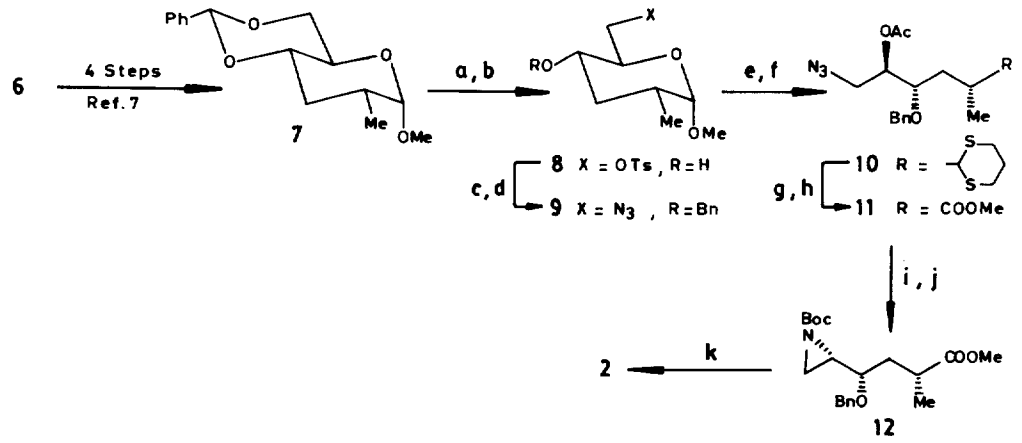
Results and Discussion

Retrosynthetic dissection of **2** revealed that the R-configuration of the 2-methyl group necessitated to begin our synthesis with methyl 2,3-dideoxy-4,6-O-benzylidene-2-methyl-α -D-glucopyranoside **7**[7] having at 2-position the essential equatorial methyl group. Removal of the benzylidene protection by hydrogenation (Scheme II) followed by selective tosylation of the primary hydroxyl group afforded the monotosylated product **8** in 80% yield from **7**. Conversion of the tosylate of **8** to azide, followed by protection of the 4-hydroxyl as benzyl ether furnished the azide **9** in 92% yield from **8**. Opening of the pyranoside ring of **9** with propane-1,3-dithiol in the presence of freshly distilled boron trifluoride etherate and acetylation of the resulting 5-hydroxyl gave **10**[8] (in 75% yield from **9**) which was subsequently converted to the methyl ester **11** in three steps : deprotection of dithiane, oxidation of the aldehyde to carboxylic acid with pyridinium dichromate, followed by esterification with diazomethane with an overall yield of 73% in 3-steps.

Deacetylation of **11** set the stage for carrying out the migration of amino function from C_6 to C_5 with inversion. The azido alcohol on treatment with triphenylphosphine in refluxing toluene[6c] under anhydrous conditions gave directly the aziridine[9] which was treated, in-situ, with Boc_2O to get the Boc-protected intermediate **12** in 85% yield from **11**. The final crucial regioselective aziridine ring opening proceeded smoothly, as expected, using phenyl magnesium bromide in the presence of catalytic amount of cuprous bromide-dimethyl sulfide[6d,10] to give the desired product **2** in 70% yield. It was characterized thoroughly by spectroscopic and analytical methods.

In summary, a highly stereospecific synthesis of a hydroxyethylene isostere **2** was successfully accomplished starting from a carbohydrate precursor and following a simple strategy,

Scheme II[a]



[a]**Reagents and conditions:** (a) 10% Pd/C, H_2, MeOH:DMF (1:1), 25°C, 8 h; (b) TsCl (1 equiv), pyridine, 25°C, 12 h, 80% from **7**; (c) NaN_3 (2 equiv), DMF, 85°C, 4 h; (d) NaH (1 equiv), BnBr (1 equiv), Bu_4NI (0.1 equiv), THF, 25°C, 2 h, 92% from **8**; (e) propane-1,3-dithiol (1.1 equiv), $BF_3.Et_2O$ (1.1 equiv), CH_2Cl_2, 25°C, 45 min.; (f) Ac_2O (1.2 equiv), Et_3N (2 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25°C, 45 min., 75% from **9**; (g) HgO (2.5 equiv), $BF_3.Et_2O$ (2.5 equiv), THF:H_2O (9:1), 25°C, 45 min; (h) PDC (3 equiv), DMF, 25°C, 8 h, then CH_2N_2 (3.5 equiv), diethyl ether, 0-5°C, 15 min., 73% from **10** (i) K_2CO_3 (0.1 equiv), MeOH, 25°C , 45 min.; (j) Ph_3P (2 equiv), toluene, reflux, 20 h, then Boc_2O (2 equiv), 25°C, 3 h, 85% from **11**; (k) PhMgBr (1.2 equiv), CuBr.Me_2S (0.2 equiv), -20°C, 1 h, 70%.

delineated here, which has immense potential for the synthesis of any hydroxyethylene, as well as dihydroxyethylene dipeptide isostere.

Experimental Section

General procedures. NMR spectra were recorded on Varian Gemini 200 and Varian Unity 400 instruments. IR spectra were recorded on Shimadzu IR-470. MS were recorded on a Finnigan Mat 1210 spectrometer under electron impact (EI) or chemical ionization (CI) conditions. Elemental analyses were performed at University of Hyderabad. Optical rotations were measured on a JASCO DIP-360 instrument.

All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, I_2, and 7% ethanolic phosphomolybdic acid-heat as developing agents. Acme, India, Silica gel (finer than 200 mesh) was used for flash column chromatography.

All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

Methyl 2,3-dideoxy-2-methyl-6-O-tosyl-α-D-glucopyranoside (8). Palladium on activated

charcoal (10%, 0.158 g) was added to a solution of **7** (0.792 g, 3.0 mmol) in methanol and DMF (1:1, 4 mL). The mixture was stirred for 8 h at room temperature under an atmsophere of hydrogen. The reaction mixture was then filtered through Celite and washed with methanol (10 mL). The filtrate was concentrated in vacuo, and the residue was dried thoroughly under vacuum. The crude diol was dissolved in pyridine (8 mL) and treated with TsCl (0.572 g, 3.0 mmol). The reaction mixture was stirred for 12h at room temperature under nitrogen atmosphere. It was then diluted with EtOAc (20 mL) and washed with saturated $CuSO_4$ solution (20 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 20-35% EtOAc in petroleum ether eluant) afforded **8** (0.792 g, 80%) as a syrupy liquid. $[\alpha]_D^{22}$: +89.07° (c 0.97, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.8 (d, J = 8.3 Hz, 2 H, aromatic). 7.36 (d, J = 8.3 Hz, 2 H, aromatic), 4.36 (d, J = 3.2 Hz, 1 H, C1-H), 4.32 (dd, J = 11.1, 4.0 Hz, 1 H, C6-H), 4.14 (dd, J = 11.1, 1.7 Hz, 1 H, C6-H), 3.55 (m, 2 H, C4-H, C5-H), 3.28 (s, 3 H, OCH_3), 2.42 (s, 3 H, $C_6H_4CH_3$), 2.0 (brs, 1 H, OH), 1.8-1.5 (m, 3 H, C3-H, C3-H', C2-H), 0.88 (d, J = 6.6 Hz, 3 H, C2-CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 144.77, 132.92, 129.74, 127.87, 100.67, 70.73, 69.66, 65.58, 54.78, 35.01, 34.06, 21.55, 15.93. IR (neat): ν_{max} 3700-3300, 2920, 1595, 1465, 1360, 1170, 1110, 1080, 1015, 975, 940, 880, 820, 660 cm^{-1}. MS (CI): m/e 330 (M^+).

Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71; Found: C, 54.45; H, 6.68.

Methyl 2,3,6-trideoxy-6-azido-4-O-benzyl-2-methyl-α-D-glucopyranoside (9). To a solution of **8** (0.561 g, 1.7 mmol) in dry DMF (5 mL) was added NaN_3 (0.221 g, 3.4 mmol). The reaction mixture was heated for 4h at 85-90°C under nitrogen atmosphere. It was then brought to room temperature, diluted with EtOAc (30 mL), washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. To a solution of the resulting crude product in dry THF (4 mL) was added NaH (60% suspension in oil, 0.068 g, 1.7 mmol) under nitrogen atmosphere, and stirred for 0.5 h at room temperature. To the mixture was then added BnBr (0.291 g, 1.7 mmol) followed by Bu_4NI (0.062 g, 0.17 mmol) and stirring continued for another 2h. It was then diluted with EtOAc (20 mL), washed with saturated NH_4Cl solution (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 2-5% EtOAc in petroleum ether eluant) to give the desired product **9** (0.455 g, 92%) as a syrupy liquid. $[\alpha]_D^{22}$: +167.95° (c 1.71, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.28 (m, 5 H, Ph), 4.62 (d, J = 11.6 Hz, 1 H, CHHPh), 4.38 (d, J = 11.6 Hz, 1 H, CHHPh), 4.44 (d, J = 3.4 Hz, 1 H, C1-H), 3.7 (m, 1 H, C4-H), 3.52-3.27 (m, 3 H, C6-H, C6-H', C5-H), 3.33 (s, 3 H, OCH_3), 2.0-1.7 (m, 2 H, C3-H, C2-H), 1.50 (ddd, J = 11.2 Hz, 1 H, C3-H), 0.96 (d, J = 6.7 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.13, 128.40, 127.72, 127.69, 100.66, 73.74, 70.43, 70.30, 54.84, 51.85, 33.92, 31.46, 16.20. IR (neat): ν_{max} 3440, 2930, 2100, 1450, 1390, 1345, 1310, 1295, 1285, 1210, 1185, 1100, 1060, 1010, 960, 940, 720, 695 cm^{-1}. MS (CI): m/e 292 (M^++H).

Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.65; H, 7.23; N, 14.38.

(2R,4S,5R)-5-Acetoxy-6-azido-4-benzyloxy-2-(1,3-dithian-2-yl)hexane (10). To a solution of **9** (0.349 g, 1.2 mmol) in methylene chloride (4 mL) was added propane-1,3-dithiol (0.133 g, 1.32 mmol) under nitrogen atmosphere followed by addition of freshly distilled boron trifluoride etherate (0.186 g, 1.32 mmol) at 0°C and the reaction mixture was stirred at room temperature for 45 minutes. It was then poured into saturated $NaHCO_3$ solution (10 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was taken in dry methylene chloride (3 mL) and treated sequentially with Et_3N (0.242 g, 2.4 mmol), Ac_2O (0.148 g, 1.44 mmol) and DMAP (0.014 g, 0.12 mmol). The reaction mixture was stirred for 1h at room temperature. It was then diluted with EtOAc (10 mL), washed with saturated NH_4Cl solution (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 2-5% EtOAc in petroleum ether eluant) afforded **10** (0.368 g, 75%) as a syrupy liquid. $[\alpha]_D^{22}$: -13.78° (c 1.19, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.35 (brs, 5 H, Ph), 5.18 (m, 1 H, C<u>H</u>-OAc), 4.63 and 4.53 (ABq, J = 11.4 Hz, 2 H, C<u>H</u>$_2$Ph), 3.95 (d, J = 3.5 Hz, 1 H, S-C<u>H</u>-S), 3.65 (m, 1 H, C<u>H</u>OBn), 3.56 (dd, J = 13.2, 7.4 Hz, 1 H, C6-<u>H</u>), 3.42 (dd, J = 13.2, 3.8 Hz, 1 H, C6-<u>H'</u>), 2.90-2.66 (m, 4 H, S-C<u>H</u>$_2$), 2.1 (s, 3 H, COC<u>H</u>$_3$), 2.2-1.5 (m, 5 H, C<u>H</u>, C<u>H</u>$_2$), 1.52 (d, J = 6.7 Hz, 3 H, C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.11, 137.81, 128.44, 128.11, 127.82, 76.11, 75.85, 73.59, 72.01, 54.41, 50.32, 34.95, 30.98, 30.67, 26.28, 20.95, 17.97. IR (neat): ν_{max} 3400, 2950, 2150, 1740, 1665, 1600, 1495, 1450, 1420, 1350, 1270, 1095, 1070, 1020, 740, 690 cm^{-1}. MS (CI): m/e 409 (M^+).

Anal. Calcd for $C_{19}H_{27}N_3O_3S_2$: C, 55.72; H, 6.64; N, 10.26. Found: C, 55.61; H, 6.67; N, 10.21.

Methyl (2R,4S,5R)-5-acetoxy-6-azido-4-benzyloxy-2-methylhexanoate (11). To a solution of **10** (0.347 g, 0.85 mmol) in 10% aqueous THF (3.5 mL) were added boron trifluoride etherate (0.299 g, 2.12 mmol) and HgO (0.453 g, 2.12 mmol). Stirring continued for 45 minutes at room temperature. The reaction mixture was then poured into brine (20 mL) and extracted with EtOAc (2x10 mL). The combined organic extracts were again washed with brine (2x10 mL) till the aqueous layer showed neutral pH, dried (Na_2SO_4) and concentrated in vacuo. The residue was taken in dry DMF (3.5 mL), PDC (0.958 g, 2.55 mmol) was added and the reaction mixture was stirred for 8h at room temperature under nitrogen atmosphere. It was then poured into a mixture of EtOAc (10 mL), brine (10 mL) and shaken. The solids were filtered through sintered funnel and the residue was washed with EtOAc (10 mL). From the combined filtrate organic layer was separated and washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in diethyl ether (4 mL) and treated with diazomethane in diethyl ether (0.2 M, 15.0 mL, 3 mmol). After 15 minutes excess of diazomethane was removed by bubbling nitrogen into the reaction mixture. The solution was then concentrated in vacuo and purification by column chromatography (SiO_2, 2-5% EtOAc in petroleum ether eluant) afforded **11** (0.216 g, 73%) as a syrupy liquid. $[\alpha]_D^{22}$: -34.78° (c 1.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.35 (brs, 5 H, Ph), 5.18 (m, 1 H, C<u>H</u>OAC), 4.56 and 4.42 (ABq, J = 11.0 Hz, 2 H, C<u>H</u>$_2$Ph), 3.65 (s, 3 H, OC<u>H</u>$_3$), 3.7-3.4 (m, 3 H, C6-<u>H</u>,

C6-H', C4-H), 2.72 (m, 1 H, CHCO$_2$Me), 2.18 (s, 3 H, COCH$_3$), 2.05-1.52 (m, 2 H, C3-H, C3-H'), 1.24 (d, J = 7.0 Hz, 3 H, CH$_3$). ^{13}C NMR (CDCl$_3$, 50 MHz): δ 175.83, 169.19, 137.43, 128.0, 127.87, 127.46, 75.92, 72.63, 72.31, 51.08, 50.16, 35.11, 34.37, 20.46, 18.01. IR (CHCl$_3$): ν_{max} 3400, 2950, 2100, 1745, 1450, 1370, 1350, 1215, 1090, 1060, 1030, 940, 840, 740, 690 cm^{-1}. MS (CI): m/e 350 (M$^+$+H).

Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.63; N, 12.03. Found: C, 58.51; H, 6.60; N, 12.08.

(2S)-N-Boc-2-[(1S,3R)-1-benzyloxy-3-(methoxycarbonyl)but-1-yl]aziridine (12). To a solution of **11** (0.209 g, 0.6 mmol) in dry MeOH (3 mL) was added anhydrous potassium carbonate (0.08 g, 0.06 mmol), and stirred for 45 minutes at room temperature under nitrogen atmosphere. The reaction mixture was diluted with EtOAc (20 mL), washed with saturated NH_4Cl solution (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was taken in dry toluene (2.5 mL) and triphenylphosphine (0.314 g, 1.2 mmol) was added at room temperature. The reaction mixture was then refluxed for 20h under nitrogen atmosphere. It was then brought to room temperature and di-tert-butyldicarbonate (0.261 g, 1.2 mmol) was added. Stirring was continued for 3h at room temperature. The reaction mixture was then diluted with EtOAc (10 mL), washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 5-15% EtOAc in petroleum ether eluant) afforded **12** (0.185 g, 85%) as a syrupy liquid $[\alpha]_D^{22}$: -109.82° (c 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45 (m, 5 H, Ph), 5.0 and 4.57 (ABq, J = 11.4 Hz, 2 H, CH$_2$Ph), 3.57 (s, 3 H, OCH$_3$), 3.0 (ddd, J = 10.18, 7.0, 2.93 Hz, 1 H, CHOBn), 2.78 (m, 1 H, CHCO$_2$Me), 2.46 (dt, J = 7.0, 3.7 Hz, 1 H, C5-H), 2.30 (d, J = 7.0 Hz, 1 H, C6-H), 1.90 (d, J = 3.7 Hz, 1 H, C6-H'), 1.92-1.6 (m, 2 H, C3-H, C3-H'), 1.49 (s, 9 H, Boc), 1.20 (d, J = 7.2 Hz, 3 H, CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.74, 161.94, 138.41, 128.22, 128.16, 128.04, 81.41, 77.92, 71.51, 41.05, 37.04, 35.64, 27.92, 27.39, 18.18. IR ($CHCl_3$): ν_{max} 3450, 2980, 1720, 1600, 1450, 1365, 1310, 1155, 840, 785 cm^{-1}. MS (CI): m/e 364 (M$^+$+H).

Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.98; H, 8.01; N, 3.87.

Methyl (2R,4S,5S)-N-Boc-O-benzyl-5-amino-4-hydroxy-2-methyl-6-phenylhexanoate (2). To a solution of PhMgBr (2.0M in diethyl ether, 0.27 ml, 0.54 mmol) and CuBr.Me$_2$S (0.092 g, 0.09 mmol) in toluene (1.8 mL) at -20°C was added a solution of **12** (0.163 g, 0.45 mmol) in toluene (0.5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 1h at the same temperature. It was then diluted with EtOAc (20 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 5-8% EtOAc in petroleum ether eluant) afforded **2** (0.138 g, 70%) as a syrupy liquid. $[\alpha]_D^{22}$: -12.83° (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.07 (m, 10 H, Ph), 4.78 (d, J = 9.4 Hz, 1 H, NHBoc), 4.58 and 4.43 (ABq, J = 11.0 Hz, 2 H, OCH$_2$Ph), 3.87 (m, 1 H, C4-H), 3.57 (s, 3 H, OCH$_3$), 3.39 (dt, J = 7.2, 1.7 Hz, 1 H, C5-H), 2.80 (d, J = 7.2 Hz, 2 H, CH$_2$Ph), 2.55 (m, 1 H, CHCO$_2$Me), 1.87 (m, 1 H, C3-H), 1.64 (m, 1 H, C3-H), 1.40 (s, 9 H, Boc), 1.08 (d, J = 7.0 Hz, 3 H, CH$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.34, 155.40, 138.45, 138.27,

129.21, 128.49, 128.47, 128.09, 127.87, 126.35, 79.02, 76.35, 72.42, 54.07, 51.48, 38.51, 35.93, 34.85, 28.51, 17.33. IR ($CHCl_3$) : ν_{max} 2900, 1710, 1495, 1450, 1360, 1135, 845, 700 cm^{-1}. MS (CI): m/e 441 (M^+).

Anal. Calcd for $C_{26}H_{35}NO_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.5; H, 7.97; N, 3.15.

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8. Acetylation was necessary to prevent the formation of hemiacetal during the deprotection of dithiane moiety.

9. Presence of even trace amount of moisture in the reaction mixture gave amino alcohol as the by-product, which could be easily converted back to aziridine on treatment with DEAD and Ph_3P.

10. Use of an excess of CuBr-Me_2S led to the formation of 6-bromo compound as a by-product.

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