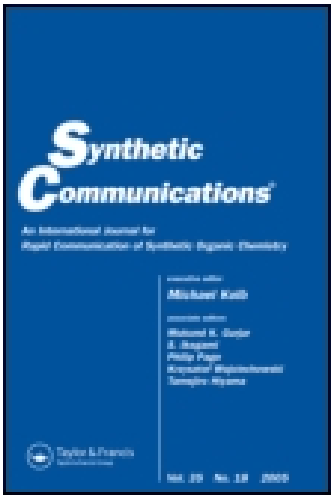

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Stereoselective Synthesis of Hydroxyethylene Dipeptide Isostere from Sugar

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STEREOSELECTIVE SYNTHESIS OF HYDROXYETHYLENE DIPEPTIDE ISOSTERE FROM SUGAR

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ABSTRACT : Regioselective opening of the aziridine ring in the carbohydrate-based precursor led to the stereoselective synthesis of N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid methyl ester, the hydroxyethylene dipeptide isostere moiety of potent HIV-1 protease inhibitor.

INTRODUCTION

The replication cycle of HIV has been a subject of extensive study for possible chemotherapeutic intervention[1]. Among the several specific targets, the enzyme HIV protease, which is required for maturation of the infectious virion, has distinctly emerged as a promising target with over 160 well studied enzyme - inhibitor complex structures[2]. The concept of transition state analogue has been an important underlying principle in the design of these protease inhibitors. The scissile dipeptide of an oligopeptide substrate is replaced by nonhydrolyzable synthetic pseudopeptide insert which mimics the tetrahedral intermediate

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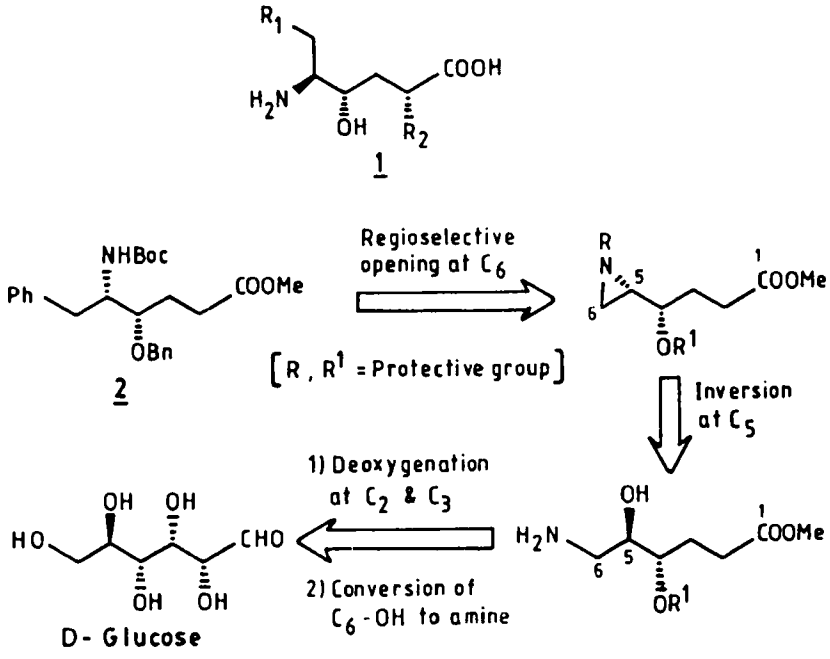
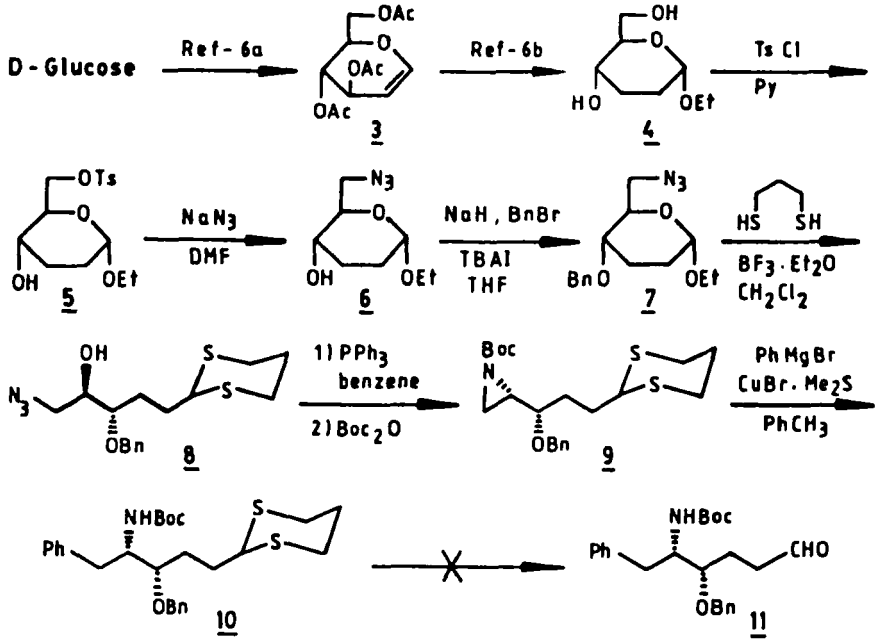


Scheme - 1

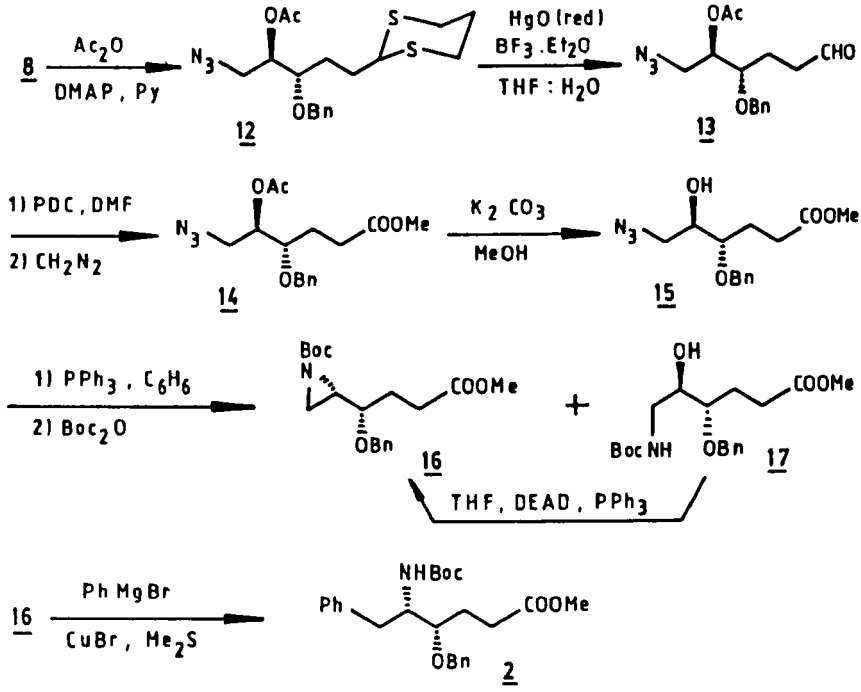
formed during the enzyme catalysed hydrolysis of the peptide bond. Several effective inhibitors have been designed and developed.[3] The hydroxyethylene dipeptide isosteres (1) have formed an important class of inhibitors mainly due to their high affinity for the HIV-1 protease[1a]. Various strategies have been employed in the syntheses of these peptidomimetics. However, the bulk of these approaches have been from chiral amino acids[3]. Only a few have come through carbohydrates[4]. We report here in detail the highly stereoselective synthesis of N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid methyl ester[5] (2), the hydroxyethylene dipeptide isostere moiety of potent inhibitor of HIV-1 protease starting from a carbohydrate precursor.



Scheme - 2

RESULTS AND DISCUSSION

D-Glucose emerged as the potential starting material from the retrosynthetic dissection of the target isosteric moiety (scheme-1). The 2,3-dideoxypyranoside 4 was easily accessed from D-glucose by a known route in a six step sequence[6] (scheme-2). The selective monotosylation of this diol 4 was achieved using pyridine - tosylchloride to afford the monotosylated product 5 in over 80% yield. Facile nucleophilic displacement of the tosylate with an azide gave the azido compound 6 which was further subjected to benzylation in THF to give the O-benzylated product 7. Opening of the pyranoside ring with freshly distilled boron trifluoride ether complex gave the dithioacetal 8 in 80% yield.



Scheme-3

It became apparent at this stage that formation of aziridine at C6-C5 and regioselective opening of this ring would complete all the manipulations on the carbon chain except at C1. Thus the azido alcohol **8** on treatment with triphenylphosphine in refluxing benzene[7] gave the aziridine which was treated *in situ* with Boc_2O to get the Boc-protected aziridine **9**. The formation of the aziridine ring marked the inversion of the center C5. The regioselective opening of the aziridine ring[8] with PhMgBr in presence CuBr-Me_2S complex gave the required amino alcohol **10** thereby completing the transformations on C2-C6. What remained was the functional manipulation at C1. A number of methods were tried for

deprotection[9] but unfortunately the compound 10 did not give satisfactory dethioacetalization. An alternate scheme (scheme-3) was envisaged via the compound 8. In order to prevent the hemiacetal formation during the deprotection of the aldehyde the free alcohol of 8 was made into an acetate 12 and later the dethioacetalization was effected to give the aldehyde 13. Oxidation of the aldehyde and subsequent esterification led to compound 14. A simple hydrolysis of the acetate in dry MeOH using K_2CO_3 led to the formation of azido alcohol 15. Following similar steps as before the aziridine 16 was made. The formation of the aziridine was accompanied by the formation of N-Boc protected amino alcohol 17 which was converted to the required aziridine via an intramolecular Mitsunobu reaction using PPh_3-DEAD. Opening of the aziridine ring 16 was carried out regioselectively using PhMgBr in presence of $CuBr.Me_2S$. The amino acid 2 thus obtained could be used for further peptide coupling through appropriate functional group deprotections.

In conclusion, an efficient synthesis of the isostere has been achieved with a scope for introduction of various functionalities at C6 through cuprate based aziridine openings. The basic unit also offers easy formation of 5-membered lactone by deprotection of the hydroxy group which has been used in the alkylations at C2 positions[10].

EXPERIMENTAL

General Procedures. NMR spectra were recorded on Varian Gemini 200 instrument or Bruker WH 300Mhz instrument in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra were recorded on Shimadzu IR-470 and Perkin Elmer 283 B instruments. Electron impact and chemical ionization mass spectra were recorded on a Finnigan Mat 1210 spectrometer. Optical rotations were

measured on a JASCO DIP-360 instrument. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

Column chromatography was performed using silica gel (finer than 200mesh) supplied by Acme Synthetic Chemicals, India. 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 5% ethanolic phosphomolibdic acid-heat as developing agents.

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.

Ethyl 6-O-tosyl-2,3-dideoxy-α-D-erythro-pyranoside [5]. Pyridine (160ml) and p-toluenesulphonyl chloride (11.58g, 60.7mmol) were mixed and stirred for 30min. Compound 4 (8.95g, 55.22mmol) was added and the reaction mixture stirred overnight. It was then diluted with 500ml of EtOAc and washed with aq. $CuSO_4$ solution, water, brine and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was chromatographed (petroleum ether : EtOAc 7:3) to yield the monotosylate 5 (14.50g, 80%). EIMS (m/e) : 285 (M-45), 267, 215, 172, 156, 115, 99, 91, 87, 72. ^{1}H NMR ($CDCl_3$, 300MHz) :δ 1.15(t, 3H, $OCH_2\underline{CH}_3$ J=7Hz), 1.64-1.95(m, 4H, $-CH_2CH_2-$), 3.64(m, 3H), 4.14(d, 1H, J=10.9Hz), 4.35(dd, 1H, J=10.9Hz, J=3.6Hz), 4.72(s, 1H, anomeric) 7.32(d, 2H, J=8.2Hz), 7.78(d, 2H, J=8.2Hz). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 14.87, 21.66, 27.01, 29.06, 62.35, 65.49, 69.82, 71.36, 95.79, 127.80, 129.66, 132.88, 144.72.

Ethyl 6-azido-2,3,6-trideoxy-α-D-erythro-hexopyranoside [6]. To a solution of compound 5 (12g, 36.36mmol) in DMF (100ml), NaN_3 (11.8g, 181.8mmol) was added and the reaction mixture was maintained at 60°C for *ca* 5h (t.l.c monitoring). The reaction mixture was cooled to r.t. and diluted with 500ml of EtOAc and washed

with water and brine. The EtOAc layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed over silica gel to yield the pure azide **6** (6.9g, 95%) as a colorless oil. IR (neat) : 3445, 3390, 3330, 2910, 2070, 1435, 1345, 1270, 1120, 1030, 970 cm^{-1}. CIMS (m/e) : 201 (M^+). ^1H NMR ($CDCl_3$, 200MHz) :δ 1.19(t, 3H, $OCH_2C\underline{H}_3$ J=7Hz), 1.62-1.96(m, 5H, one D_2O exchg.), 3.34-3.8(m, 6H), 4.78(bs, 1H, anomeric). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 14.95, 27.38, 29.21, 51.86, 62.48, 67.12, 72.62, 95.71.

Ethyl 6-azido-2,3,6-trideoxy-4-O-(phenylmethyl)-α-D-erythro-hexopyranoside [7]. To a solution of compound **6** (4.11g, 20.45mmol) in dry THF (50ml), cooled to 0°C, NaH (1.11g, 25.56mmol, 55% dispersion in paraffin oil) was added and stirred for 15min. Bu_4NI (0.75g, 2.04mmol) and BnBr (2.8ml, 23.52mmol) were added successively and the reaction mixture was allowed to attain r.t and stirred for 2h. The excess NaH was quenched by dropwise addition of ice cold water. After washing with water and brine, the THF layer was dried (Na_2SO_4) and concentrated. The syrupy liquid so obtained was chromatographed (EtOAc : petroleum ether 1:9) to yield 5.96g (100%) of the product. $[\alpha]_D$ +70.32 (C 3.43, $CHCl_3$). IR (neat) : 2895, 2075, 1435, 1355, 1280, 1260, 1210, 1100, 1060, 965, 895, 800, 720 cm^{-1}. CIMS (m/e) : 291 (M^+). ^1H NMR ($CDCl_3$, 200MHz) :δ 1.2(t, 3H, $OCH_2C\underline{H}_3$, J=7Hz), 1.64-1.82(m, 3H), 2.0-2.22(m, 1H), 3.28-3.56(m, 4H), 3.63-3.87(m, 2H), 4.42 & 4.64(2xd, 2H, $PhC\underline{H}_2$, J=12Hz), 4.8(d, 1H, anomeric, J=2Hz), 7.32(m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 14.98, 23.48, 28.91, 51.89, 62.38, 70.38, 71.11, 73.76, 95.78, 127.66, 128.34, 138.04.

6-Azido-2,3,6-trideoxy-4-O-(phenylmethyl)-D-erythro-hexose-(propane-1,3-diyl)dithioacetal [8]. To a mixture of compound **7** (5.55g, 19.09mmol) and 1,3-propane dithiol (2.3ml, 22.92mmol) in 100ml of dry CH_2Cl_2, $BF_3.Et_2O$ (2.64ml, 21.01mmol) was added dropwise. The reaction mixture was stirred for 45min and quenched with solid $NaHCO_3$. The CH_2Cl_2 layer was washed with aq.$NaHCO_3$, water and brine. After drying (Na_2SO_4), the solvent

was evaporated under reduced pressure and the residue chromatographed (EtOAc : petroleum ether 2:8) to give the pure product 8 (5.4g, 80%). IR (neat) : 3440, 2880, 2075, 1425, 1275, 1070 cm^{-1}. EIMS (m/e) : 355 (M+2), 354, 268, 262, 205 187, 145, 132, 119, 106, 99, 91, 87, 65. ^{1}H NMR ($CDCl_3$, 200MHz) :δ 1.70-2.20(m, 6H), 2.38(d, 1H, OH, D_2O exchg.), 2.75-2.80(m, 4H), 3.38-3.52(m, 3H), 3.85(m, 1H), 3.98(t, 1H), 4.57(A_2B_2, 2H, J=11.4Hz), 7.35(m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 20.80, 26.29, 30.20, 30.51, 47.28, 53.48, 71.35, 72.02, 78.68, 127.90, 128.42, 137.71.

6-Azido-2,3,6-trideoxy-5-acetoxy-4-O-(phenylmethyl)-D-erythro-hexose-(propane-1,3-diyl)dithioacetal [12]. To a solution of compound 8 (5.3g, 15mmol) in pyridine (50ml), Ac_2O (2.12ml, 22.5mmol) was added dropwise and the reaction mixture allowed to stir for 12h. Excess pyridine was removed under reduced pressure. The residue was taken up in EtOAc (50ml) and washed with water and brine and dried (Na_2SO_4). Concentration under reduced pressure gave the product 12 (5.93g, 100%). $[\alpha]_D$ = 1.65 (C 2.9, $CHCl_3$). IR (neat) : 2100, 1740cm^{-1}.^{1}H NMR ($CDCl_3$, 200MHz) :δ 1.66-2.00(m, 5H), 2.00-2.24(m, 4H), 2.72-2.96(m, 4H), 3.40-3.75(m, 3H), 3.94(m, 1H), 4.56(m, 2H, $C\underline{H}_2Ph$), 5.06(m, 1H), 7.33(m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 20.69, 25.58, 26.92, 29.90, 30.37, 46.86, 50.21, 72.04, 72.90, 76.54, 127.73, 128.15, 137.43, 169.70.

(4S,5R)-5-Acetoxy-6-azido-4-(phenylmethoxy) hexanal [13]. HgO (red, 0.58g, 2.6mmol) and $BF_3.Et_2O$ (0.38g, 2.6mmol) taken in 2ml of 15% aq.THF were stirred vigorously in a three necked flask equipped with a $CaCl_2$ gaurd tube, N_2 inlet tube and a dropping funnel. Dithiane 12 dissolved in 2ml of THF was added via the dropping funnel in 15mins under N_2 flow with vigorous stirring. The stirring was continued for additional 15min. 8ml of ether was added and the precipitated salts were filtered. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield the aldehyde (0.38g, 93%) as a colorless oil. CIMS (m/e) :

305 (M^+). ^1H NMR ($CDCl_3$, 200MHz) :δ 1.71-2.07(m, 2H), 2.13(s, 3H, OAc), 2.54(t, 2H, $C\underline{H}_2COOMe$ J=8Hz), 3.53(m, 2H, CH_2N_3), 3.67(m, 1H, $C\underline{H}OBn$), 4.50 & 4.61(2xd, 2H, $PhC\underline{H}_2$, J=11.95Hz), 5.11(m,1H), 7.33(m, 5H, Ar), 9.73(s, 1H, $C\underline{H}O$). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 20.69, 22.33, 38.99, 50.28, 72.20, 72.67, 76.33, 127.88, 128.27, 137.27, 169.86.

Methyl (4S,5R)-5-acetoxy-6-azido-4-(phenylmethoxy) hexanoate [14]. To a solution of aldehyde 13 (0.35g, 1.1mmol) in 3ml of DMF, PDC (1.0g, 2.8mmol) was added and stirred for 4h. The reaction mixture was diluted with ether (10ml) and filtered. The insoluble brown mass was extracted repeatedly with ether (3x10ml) and the combined ether extracts were washed with water (2x20ml) and dried (Na_2SO_4). The ether layer was concentrated under reduced pressure to yield the crude acid which was redissolved in dry ether and treated with an etheral solution of diazomethane. On completion (t.l.c monitoring) air was bubbled for 5mins through the reaction mixture. The crude residue obtained on evaporating the etheral layer was chromatographed to afford the ester 14 (0.23g, 60%). IR (neat) : 2943, 2090, 1724, 1428, 1358, 1224, 1062, 731, 689 cm^{-1}. EIMS (m/e) : 307 (M-28), 306, 220, 207, 160, 148, 132, 731, 98, 92, 91, 82, 65. ^1H NMR ($CDCl_3$, 200MHz) :δ 1.68-1.96(m, 2H, $C\underline{H}_2CH_2COOMe$), 2.04 (s, 3H, OAc), 2.36(t, 2H, $CH_2C\underline{H}_2COOMe$), 3.44(m, 2H, CH_2N_3), 3.57(s, 3H, COOMe), 3.50-3.68(m, 1H, $C\underline{H}OBn$), 4.44 & 4.55(2xd, 2H, $OC\underline{H}_2Ph$, J=11Hz), 5.02(dt, 1H, J=5Hz), 7.26 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50MHz) :δ 20.5, 25.0, 28.9, 50.1, 51.2, 72.1, 72.6, 76.2, 127.6, 128.0, 137.3, 169.6, 173.2.

Methyl (4S,5R)-6-Azido-5-hydroxy-4-(phenylmethoxy) hexanoate [15]. To a solution of compound 14 (0.25g, 0.75mmol) in dry MeOH (3ml), catalytic amount of K_2CO_3 (20mg) was added and stirred for 10min. The solvent was removed under reduced pressure and the residue was extracted with EtOAc. Combined extracts were washed with water and dried (Na_2SO_4) and concentrated under reduced pressure to yield the pure compound 15 in quantitative yield

(0.22g). CIMS (m/e) : 293 (M^+). IR (neat) : 3436, 2929, 2090, 1731, 1442, 1259, 1062, 738, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 200MHz) :δ 1.97(m, 2H, $C\underline{H}_2CH_2COOMe$), 2.31-2.62 (m, 2H, $C\underline{H}_2COOMe$), 2.72(d, 1H, OH, D_2O exchg.), 3.40-3.57(m, 3H), 3.66(s, 3H, COOMe), 3.80(m, 1H), 4.53(2xd, 2H, $OC\underline{H}_2Ph$, J=11.2Hz), 7.35(m, 5H, Ar).

Methyl(4S)-4-benzyloxy-4-[(2S)-N-Boc-aziridin-2-yl]-butanoate [16]. Azidoalcohol 15 (0.6g, 2mmol) and PPh_3(0.59g, 2.2mmol) were mixed in benzene (10ml) and refluxed under nitrogen for 10h. The solution was cooled and Boc_2O (0.67g, 1.5eq) was added and stirred for 12h. Chromatography of the residue obtained after removal of benzene afforded the product 16 (0.5g, 70%) as a colorless oil. CIMS (m/e) : 349 (M^+). ^1H NMR ($CDCl_3$, 200MHz) :δ 1.41(s, 9H), 1.77-1.84(m, 2H), 1.86 (d, 1H, J=3.75Hz), 2.23(d, 1H, J=6.59), 2.30-2.50(m, 3H), 3.01 (q, 1H, J=7Hz), 3.54(s, 3H, COOMe), 4.53 & 4.92(2xd, 2H, $OC\underline{H}_2Ph$), 7.20-7.35(m, 5H, Ar).

Methyl N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoate [2]. To a solution of $CuBr.Me_2S$ (11mg, 0.2eq) in dry toluene (1.5ml), a 1M solution of PhMgBr (0.32ml, 1.1eq), in THF was added and stirred for 5min at -10°C (ice-salt). The aziridine 16 (0.1g, 0.28mmol) in toluene (0.5ml) was added to this mixture. After stirring for 10min the reaction was quenched with aq.NH_4Cl, the organic layer was washed with water, brine and dried (Na_2SO_4). After concentrating under reduced pressure the crude was chromatographed (EtOAc : Benzene 1:9) to afford the product 2 (0.85g, 70%) m.p : 63°C. $[\alpha]_D$ +3.75 (C 0.4, $CHCl_3$). IR (KBr) τ_{max} : 3390, 1725, 1685, 1500, 1150, 730cm^{-1}. CIMS (m/e) : 427 (M^+). ^1H NMR ($CDCl_3$, 200MHz) : 1.37(s, 9H), 1.79(m, 1H, $C\underline{H}_2CH_2COOMe$), 1.98(m, 1H, $C\underline{H}_2CH_2COOMe$), 2.30(m, 2H, $C\underline{H}_2COOMe$), 2.82(d, 2H, J=7.4Hz), 3.36(m, 1H, $C\underline{H}$-OBn), 3.57(s, 3H, -$COO\underline{Me}$), 3.91(m, 1H), 4.45 & 4.62(2xd, 2H, - $OC\underline{H}_2Ph$, J =11.2Hz), 4.87(d, 1H, -$N\underline{H}$, J=9.53Hz), 7.04-7.40(m, 10H, Aromatic).

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