A NEW STEREOSELECTIVE SYNTHETIC STRATEGY FOR β-HYDROXY-α-AMINO ACIDS OF VANCOMYCIN

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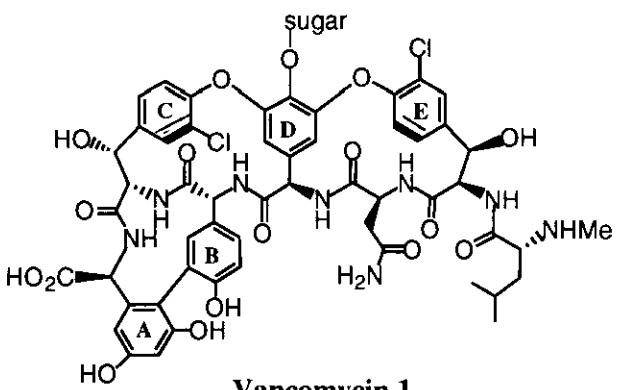
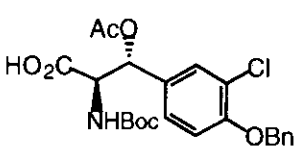
Abstract - The synthesis of *syn* and *anti* β-hydroxy-α-amino acids representing rings C and E of vancomycin has been achieved starting from (*R*)- and (*S*)-Garner's aldehydes by a stereocontrolled Grignard arylation reaction.

β-Hydroxy-α-amino acids are the primary constituents of many bioactive natural products.[1] Many brilliant approaches have been developed to synthesise them in enantiomerically pure forms.[2] Vancomycin (**1**), a glycopeptide antibiotic,[3] is increasingly becoming a drug of choice, particularly against penicillin resistant *Staphyloccii strain*. The complexity of vancomycin has preluded its total synthesis and many schools including ours have embarked on this endeavour.[4] Apart from many unprecedented structural features,



Vancomycin 1

vancomycin has unique *syn*- and *anti*- β-hydroxy-3-chlorotyrosine units representing rings C and E of **1**. The absolute configuration of ring C was established as 2*S*,3*R* while that of ring E as 2*R*,3*R*. Although, some elegant approaches[5] for both these segments of vancomycin have been reported, we believe that scope still existed in developing new stereoselective synthetic strategies based on highly stereocontrolled Grignard addition to the Garner's aldehyde. This paper reveals our efforts to synthesise



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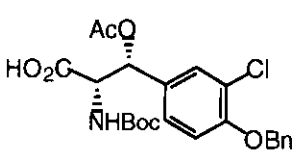

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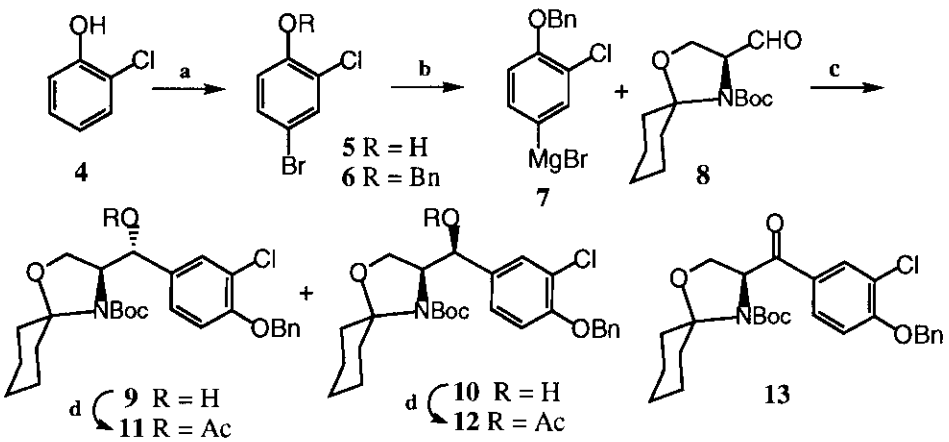
suitably substituted ring E (**2**) and ring C (**3**) derivatives of vancomycin (**1**) based on the above protocol. 2-Chlorophenol (**4**) was brominated using Br_2-CCl_4 to afford 4-bromo-2-chlorophenol (**5**).[6] Subsequent benzyl protection of the phenolic group with BnBr-K_2CO_3 in acetone gave **6** (Scheme 1). Treatment of **6** with magnesium in THF led to the formation of the Grignard reagent (**7**) exclusively, whose reaction[7] with (*S*)-Garner's aldehyde (**8**)[8] led to the formation of 8:1 diastereomeric mixture of **9** + **10** in which the *anti* product (**9**) predominated.[9] Acetylation of the mixture with Ac_2O-pyridine followed by chromatography gave the diastereomerically pure isomers (**11**) and (**12**). The absolute stereochemistry of **11** was established by its transformation into the known molecule (**15**). The stereoselective formation of the *anti* product (**9**) was explained by involving Felkin-Anh model according to which nucleophilic addition occurred from the least hindered face as shown in Figure A.[10]

Scheme 1



Reagents and conditions: a) i) Br_2, CCl_4, rt, 12 h; ii) BnBr, K_2CO_3, Me_2CO, Δ, 2 h; b) Mg, THF, rt, 1 h; c) THF, 0 °C, 1 h; d) Ac_2O, Pyr, CH_2Cl_2, rt, 2 h.

Transformation of the undesired *syn* isomer (**12**) into the required *anti* isomer (**9**) was investigated. For example, hydrolysis of **12** with NaOMe-MeOH followed by oxidation with iodoxybenzoic acid (IBX)-DMSO provided the keto derivative (**13**). Compound (**13**) was reduced with $Zn(BH_4)_2$ in benzene-ether to provide exclusively the *anti* isomer (**9**)[11] which was acetylated to **11** and then correlated with previously prepared sample.

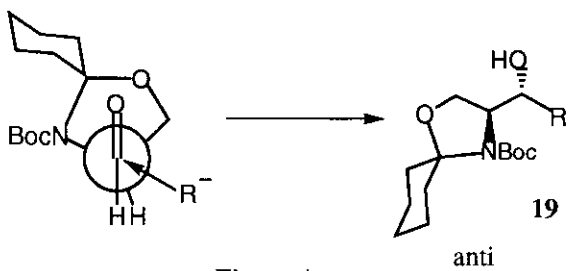
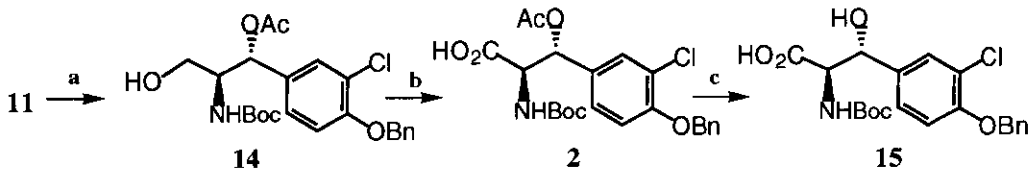


Figure A

Treatment of **11** with 98% aq. TFA at 0 °C smoothly cleaved the cyclohexylidene group to obtain **14**. The structure of **14** was compatible with the ^{1}H NMR spectrum whereas high resolution FABMS revealed molecular ion peak (M^+) at m/z : 449.1618 (calculated for $C_{23}H_{28}NO_6Cl$: 449.1605). The Jone's oxidation of **14** at 0 °C gave the required acid (**2**). For comparison, **2** was deacetylated with K_2CO_3-MeOH to furnish (2*R*,3*R*)-hydroxy-3-chlorotyrosine derivative (**15**). Compound (**15**) showed optical rotation, ^{1}H NMR and MS spectral values similar to the reported data[4d] (Scheme 2).

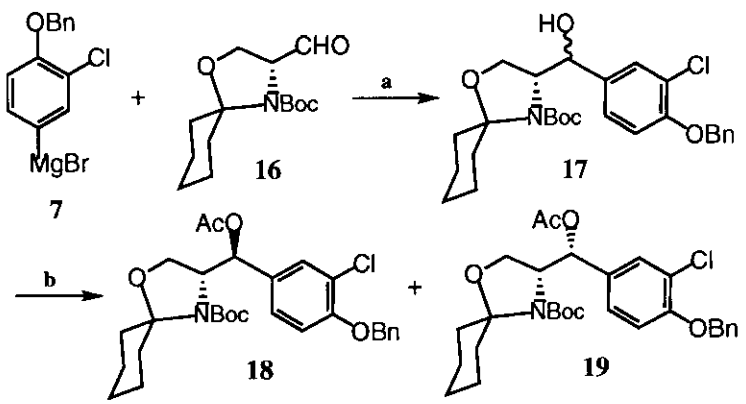
Scheme 2



Reagents and conditions : a) aq. TFA, CH_2Cl_2, 0 °C, 1 h; b) Jone's reagent, Me_2CO, 0 °C, 1 h; c) K_2CO_3, MeOH, rt, 30 min.

Having established an efficient protocol to obtain **2** (ring E), efforts were directed toward the synthesis of the corresponding (2*S*,3*R*)-β-hydroxytyrosine derivative (**3**), representing ring C of vancomycin (Scheme 3).

Scheme 3

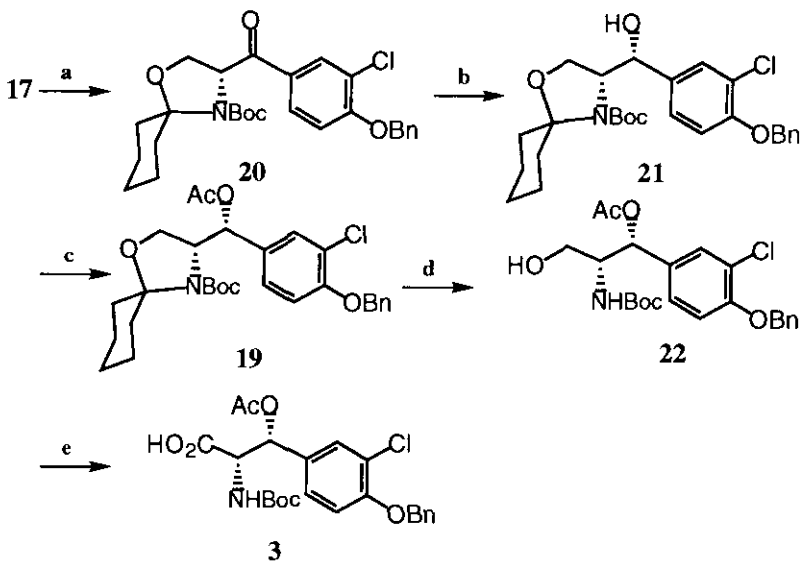


Reagents and conditions : a) THF, 0 °C, 1 h; b) Ac_2O, Pyr, rt, 2 h.

For example, the reaction of **7** with (*R*)-Garner's aldehyde (**16**) gave a mixture of diastereomers (**17**). As described earlier for separation of diastereomeric mixture (**9+10**), acetylation of **17** and chromatography likewise provided enantiomerically pure *anti* product (**18**) (89%) and *syn* (**19**) (11%). In order to directly convert **17** into the required *syn* isomer (**19**), its oxidation with iodoxybenzoic acid (IBX)-DMSO was carried out to give the ketone (**20**) whose stereoselective reduction with $NaBH_4$ - MeOH at 0 °C followed by acetylation provided the *syn* product (**19**) (92%).[12] Conversion of **19** into the final

product (**3**) (ring C) *via* **22** was carried out by the same sequence of reactions as reported for **2** (ring E) (Scheme 4).

Scheme 4



Reagents and conditions: a) IBX, DMSO, rt, 1 h; b) $NaBH_4$, MeOH, 0 °C, 30 min.; c) Ac_2O, Pyr, rt, 2 h; d) aq. TFA, CH_2Cl_2, 0 °C, 1 h; e) Jone's reagent, Me_2CO, 0 °C, 1 h.

In conclusion, we have demonstrated that a strategy involving stereocontrolled addition of arylmagnesium reagent on Garner's aldehyde forms an efficient approach for making both the diastereomers of β-hydroxy-α-amino acids associated with an important antibiotic-vancomycin.

EXPERIMENTAL

The reactions were monitored by TLC on Merck 0.25 mm precoated silica gel glass plate and detected by UV and molybdic acid spray. NMR spectra were recorded on Varian Gemini 200 instrument with TMS as an internal standard. MS spectra were recorded on VG Autospec (M-series). Evaporations were carried out below 40 °C. All the solvents were distilled before use and light petroleum refers to fraction, bp 60-80°C. Optical rotations were measured on JASCO DIP 370 digital polarimeter. Elemental analysis were carried out on Elementar Vario El.

4-Benzyloxy-3-chloro-1-bromobenzene (6)

Compound (**5**) (12.0 g, 58.0 mmol), benzyl bromide (9.91 g, 58.0 mmol), K_2CO_3 (11.4 g) in acetone (200 mL) was heated under reflux for 2 h and filtered. The filtrate was concentrated and the residue purified by column chromatography on silica gel by using ethyl acetate-light petroleum (1:20) as eluent to give **6** (15.5 g, 90%) as a white solid; ^1H NMR ($CDCl_3$): δ 5.26 (s, 2H), 6.80 (d, J=10 Hz, 1H), 7.20-7.45 (m, 6H), 7.50 (d, J=2.0 Hz, 1H). Anal. Calcd for $C_{13}H_{10}OBrCl$: C, 52.46; H, 3.36. Found : C,

52.03; H, 3.42.

(2*S*,3*R*)-3-Acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (11) and (2*S*,3*S*)-3-acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (12)

Grignard reagent (**7**) was prepared from Mg (0.9 g, 37.8 mmol) and 4-benzyloxy-3-chloro-1-bromobenzene (**6**) (11.0 g, 37.8 mmol) in dry THF (100 mL) at rt under nitrogen atmosphere in 1 h. The mixture was then cannulated to a flask containing the aldehyde (**8**) (2.5 g, 9.3 mmol) in THF at 0 °C. After 1 h at 0 °C, the reaction was quenched by the addition of saturated NH_4Cl solution and extracted with ethyl acetate (2 x 200 mL). The organic layer was dried (Na_2SO_4), concentrated and the residue purified by column chromatography over silica gel using ethyl acetate-light petroleum (3:7) as eluent to furnish a mixture of diastereomers (**9** + **10**) (3.4 g, 75%) as a syrup.

The above mixture (**9** + **10**) (3.0 g, 6.16 mmol) was acetylated with acetic anhydride (1.25 mL, 12.32 mmol) and pyridine (1.22 mL, 15.40 mmol) in CH_2Cl_2 (15 mL) for 2 h at rt. The reaction was quenched with MeOH (2 mL) and evaporated to give a residue which was chromatographed on silica gel using ethyl acetate-light petroleum (1:9) as eluent. The first fraction gave *anti* product (**11**) (2.75 g, 84%) as a pale yellow syrup; $[\alpha]_D$ -7.5° (c 0.61, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3-1.8 (m, 16H), 2.0-2.45 (m, 3H), 2.14 (s, 3H), 3.70 (dd, J= 6.6 Hz, 8.8 Hz, 1H), 4.00 (m, 2H), 5.11 (s, 2H), 6.04 (d, J=4.4 Hz, 1H), 6.86 (d, J=8.8 Hz, 1H), 7.34 (m, 7H); FABHRMS: Calcd for $C_{29}H_{37}NO_6Cl$: 530.2204; Found: 530.2180 (M^++1). Anal. Calcd for $C_{29}H_{36}NO_6Cl$: C, 65.71; H, 6.85. Found : C, 65.92; H, 6.65. The second fraction provided *syn* product (**12**) (0.34 g, 10%); $[\alpha]_D$ -10° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3-1.7 (m, 17H), 2.0-2.3 (m, 2H), 2.02 (s, 3H), 3.70 (m, 2H), 4.20 (m, 1H), 5.09 (s, 2H), 5.86 (d, J=8.8 Hz, 1H), 6.86 (d, J=8.8 Hz, 1H), 7.36 (m, 7H); HRFABMS: Calcd for $C_{29}H_{37}NO_6Cl$; 530.2204; Found: 530.2189 (M^++1). Anal. Calcd for $C_{29}H_{36}NO_6Cl$: C, 65.71; H, 6.85. Found : C, 65.68; H, 6.75.

(2*S*)-3-(4-Benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidene-3-oxopropan-1-ol (13)

A solution of **12** (2.2 g, 4.16 mmol) in MeOH (15 mL), containing sodium (24 mg, 1.04 mmol) was stirred at rt for 30 min, deionised with Amberlite IR 120 (H^+) resin and concentrated to obtain **10** (2.04 g, 93%), used as such for next reaction.

A solution of iodoxybenzoic acid (IBX) (1.72 g, 6.16 mmol) in DMSO (5 mL), and **10** (2.0 g, 4.11 mmol) in THF (3 mL) was stirred at rt for 1 h. Ice was added, the solid filtered and washed with ethyl acetate. The aqueous layer was extracted, washed with 5% $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated. The residue was purified over silica gel by eluting with ethyl acetate-light petroleum (1:9) to furnish **13** (1.45 g, 73%) as a syrup; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 9H), 1.45-2.55 (m, 10H), 3.86 (m, 1H), 4.20 (m, 1H), 5.20 (s, 2H), 5.32 (m, 1H), 6.97 (d, J=8.1 Hz, 1H), 7.36 (m, 5H), 7.75 (dd, J=2.2 Hz, 8.1 Hz, 1H), 7.93 (s, 1H); HRFABMS: Calcd for $C_{27}H_{32}NO_5Cl$: 485.1969; Found 485.1964 (M^+). Anal. Calcd for $C_{27}H_{32}NO_5Cl$: C, 66.73; H, 6.64. Found : C, 66.69; H, 6.54.

(2*S*,3*R*)-3-Acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (11)

To the solution of **13** (1.2 g, 2.47 mmol) in (1:4) benzene-ether solvent mixture (10 mL), 0.66 M solution of $Zn(BH_4)_2$ in THF (5.6 mL, 3.7 mmol) was added. The reaction was stirred at rt for 1 h, decomposed with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and treated with acetic anhydride (0.5 mL, 4.95 mmol) and pyridine (0.5 mL, 6.18 mmol) at rt for 2 h. After usual workup, the residue was purified on silica gel with ethyl acetate-light petroleum (1:9) to give **11** (1.0 g, 77%) which was found to be identical with the compound obtained above.

(2*S*,3*R*)-3-Acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-propan-1-ol (14)

Compound (**11**) (1.0 g, 1.89 mmol) was dissolved in CH_2Cl_2 (10 mL) and 3 mL of 98% aq. TFA was added at 0 °C. The mixture was stirred at the same temperature for 1 h and excess TFA neutralised with satutated solution of $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the extract was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate - light petroleum (2:3) as eluent to furnish **14** (0.60 g, 70%) as a white solid mp 109-110 °C; $[\alpha]_D$ -27° (c 0.89, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 9H), 2.08 (s, 3H), 2.53 (br s, 1H), 3.62 (m, 2H), 3.93 (m, 1H), 4.84 (d, J=8.8 Hz, 1H), 5.08 (s, 2H), 5.73 (d, J=6.6 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 7.1-7.5 (m, 7H); HR-FABMS: Calcd for $C_{23}H_{28}NO_6Cl$: 449.1605; Found: 449.1618 (M^+). Anal. Calcd for $C_{23}H_{28}NO_6Cl$: C, 61.39; H, 6.27. Found : C, 61.40; H, 6.21.

(2*R*,3*R*)-3-(4-Benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-3-hydroxy-propionic acid (15)

To a solution of **14** (0.55 g, 1.22 mmol) in acetone (4 mL) at 0 °C, Jones reagent was added dropwise till the orange colour of the reagent retained. After 1 h, the reaction was quenched with i-PrOH and concentrated. The residue was extracted with ethyl acetate, the extract was dried (Na_2SO_4) and concentrated to yield a residue which was purified by column chromatography on silica gel using ethyl acetate : hexane (3:2) as eluent to afford **2** (0.31 g, 54%) as a oil; $[\alpha]_D$: -60° (c 1.14, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36 (s, 9H), 2.09 (s, 3H), 4.61 (br s), 4.91 (br s, 1H), 5.02 (m, 1H), 5.15 (s, 2H), 6.11 (m, 1H), 6.95 (d, J=8.5 Hz, 1H), 7.19 (d, J=8.5 Hz, 1H), 7.39 (m, 6H); HRFABMS: Calcd for $C_{23}H_{27}NO_7Cl$. 464.1416; Found 464.1405 (M^++1). Anal. Calcd for $C_{23}H_{26}NO_7Cl$: C, 59.55; H, 5.65. Found : C, 59.36; H, 5.66.

Compound (**2**) (0.25 g, 0.54 mmol), K_2CO_3 (20 mg, 0.16 mmol) and MeOH (5 mL) were stirred at rt for 30 min. It was evaporated, extracted with ethyl acetate and the extract was washed with aqueous 5% $KHSO_4$ solution, brine and dried (Na_2SO_4). Solvent removal provided a residue which was purified on silica gel using ethyl acetate:light petroleum (4:1) to furnish **15** (0.21 g, 91%); $[\alpha]_D$ -44° (c 0.53, $CHCl_3$),

lit.,[4d] $[\alpha]_D$ -45° (c 0.5, $CHCl_3$); ^1H NMR (DMSO-d_6, 200 MHz): δ 1.36 (s, 9H), 3.25 (br s), 4.36 (m, 1H), 4.93 (m, 1H), 5.14 (s, 2H), 5.85 (m, 1H), 6.97 (d, J=8.5 Hz, 1H), 7.25 (d, J=8.5 Hz, 1H), 7.3-7.5 (m, 5H), 7.75 (s, 1H); FABMS: 422 (M^++1).

(2*R*,3*S*)-3-Acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (18) and (2*R*,3*R*)-3-acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (19)

The Grignard reaction between **7** (9.95 g, 34.20 mmol) and aldehyde (**16**) (2.3 g, 8.55 mmol) was carried out by a similar procedure as described earlier, which gave a diastereomeric mixture of products (**17**) (3.1 g, 74.5%).

Acetylation of **17** (1.0 g, 2.05 mmol) with acetic anhydride (0.42 mL, 4.11 mmol) and pyridine (0.4 mL, 5.13 mmol) followed by column chromatography on silica gel using ethyl acetate - light petroleum (1:4) gave **18** (0.97, 89%) as a syrup, $[\alpha]_D$ 8.2° (c 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.4-1.7 (m, 17H), 2.10 (m, 5H), 3.80 (m, 1H), 4.1-4.2 (m, 2H), 5.11 (s, 2H), 6.10 (d, J=4.4 Hz, 1H), 6.87 (d, J=8.3 Hz, 1H), 7.05-7.4 (m, 8H); HRFABMS: Calcd for $C_{29}H_{37}NO_6Cl$: 530.2204; Found: 530.2198 (M^++1). Anal. Calcd for $C_{29}H_{36}NO_6Cl$: C, 65.71; H, 6.85. Found : C, 65.79; H, 6.66.

Further elution provided compound (**19**) (0.12 g, 11%) as a syrup; $[\alpha]_D$ 16.9° (c 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.3-1.75 (m, 17H), 2.00 (m, 5H), 3.72 (m, 2H), 4.15-4.4 (m, 1H), 5.11 (s, 2H), 5.84 (d, J=7.7 Hz, 1H), 6.86 (d, J=8.3 Hz, 1H), 7.05-7.4 (m, 8H); HRFABMS: Calcd for $C_{29}H_{37}NO_6Cl$: 530.2204; Found 530.2188 (M^++1). Anal. Calcd for $C_{29}H_{36}NO_6Cl$: C, 65.71; H, 6.85. Found : C, 65.82; H, 6.53.

(2*R*,3*R*)-3-Acetoxy-3-(4-benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-1,2-cyclohexylidenepropan-1-ol (19)

Oxidation of **17** (2.0 g, 4.10 mmol) was carried out with iodoxybenzoic acid (IBX)-DMSO as described earlier to give **20** (1.43 g, 72%). $NaBH_4$ (0.23 g,6.18 mmol) was added in portions to a solution of (**20**) (2.0 g, 4.12 mmol) in MeOH (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min after which time excess $NaBH_4$ was quenched with dil. CH_3COOH and concentrated. It was extracted with ethyl acetate and the extract was washed with brine, dried (Na_2SO_4) and concentrated to afford the residue which was purified on silica gel using ethyl acetate - light petroleum (3:7) as eluent to furnish **21** (1.7 g, 85%) as a semi solid. Conventional acetylation of **21** (1.7 g, 3.49 mmol) with acetic anhydride (0.71 mL, 6.98 mmol) and pyridine (0.6 mL, 8.73 mmol) gave **19** (1.7 g, 92%). The ^1H NMR and optical rotation data of **19** was found to be identical to the product obtained above.

(2*R*,3*R*)-3-Acetoxy-3-(4-benzylocy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-propan-1-ol (22)

Compound (**22**) as a thick syrup was obtained by the similar procedure as described earlier for **14**; $[\alpha]_D$ -52.2° (c 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) : δ 1.73 (s, 9H), 2.14 (s, 3H), 3.52 (m, 2H), 3.97 (s, 1H), 4.95 (br d, 1H), 5.16 (s, 2H), 5.91 (d, J=6.8 Hz, 1H), 6.93 (d, J=8.3 Hz, 1H), 7.20 (dd, J=2.2, 8.3 Hz, 1H), 7.38 (m, 6H); HRFABMS: Calcd for $C_{23}H_{29}NO_6Cl$: 450.1683; Found 450.1688

(M+-+1). Anal. Calcd for $C_{23}H_{28}NO_6Cl$: C, 61.39; H, 6.27. Found : C, 61.44; H, 6.12.

(2*S*, 3*R*)-3-(4-Benzyloxy-3-chlorophenyl)-2-*tert*-butoxycarbonylamino-3-acetoxy-propionic acid (3)

Compound (**3**) as a semi solid was obtained in a similar manner as described for **2**; $[\alpha]_D$: -75° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.39 (br s, 9H), 2.11 (s, 3H), 3.40 (br s), 4.91 (m, 2H), 5.11 (s, 2H), 6.02 (br s, 1H), 6.90 (d, J=8.1 Hz, 1H), 7.14 (dd, J=2.1, 8.1 Hz, 1H), 7.3 (m, 6H); HRFABMS: Calcd for $C_{23}H_{27}NO_7Cl$. 464.1416; Found 464.1401 (M+-+1). Anal. Calcd for $C_{23}H_{26}NO_7Cl$: C, 59.55; H, 5.65. Found : C, 59.59; H, 5.61.

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