Pergamon

Tetrahedron, Vol. 53, No. 13, pp. 4769-4778, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00160-9

Synthesis of Novel C_2-symmetric and Pseudo C_2-symmetric Based Diols, Epoxides and Dideoxy Derivatives of HIV Protease Inhibitors

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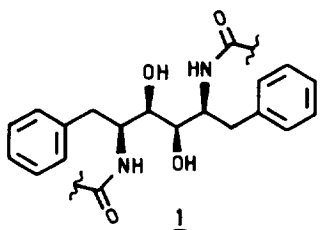
Abstract: The Julia's olefination reaction between the sulfone derivative (**10**) and the aldehyde (**13**) (both obtained from L-phenylalanine) followed by debenzylation led to the formation (2S,5S,3E)-2,5-bis-[(1,1-dimethyl ethoxy)-carbonyl]amino-1,6-diphenylhex-3-ene (**4a**). Similarly (2S,5S,3E)-2,5-bis-[(1,1-dimethylethoxy)-carbonyl]amino-1-phenyl-6-(p-methoxy)phenylhex-3-ene (**4b**) was also synthesised from the sulfone (**10**) and L-tyrosine derived aldehyde (**21**). These novel intermediates (**4a** and **4b**) were subjected to epoxidation, hydrogenation, hydroboration-oxidation and dihydroxylation reactions. These modifications resulted in the synthesis of known and unknown, C_2-symmetric and pseudo-C_2-symmetric diamino-epoxides, dideoxy derivatives, diols and deoxy diols based HIV protease inhibitors. © 1997 Published by Elsevier Science Ltd.

INTRODUCTION

Proteolytic processing of the *gag* and *gag-pol* polyproteins to form mature virions is performed by HIV-1 encoded protease[1]. Therefore, if one could antagonise this enzyme, it could constitute an ideal strategy to combat AIDS disease. A number of potent and selective HIV protease inhibitors which incorporate dihydroethylene, hydroxyethylamine and dihydroxyethylene isosteres as non-hydrolysable dipeptide residues, have been reported in literature[2]. However, protease inhibitors **1** containing a C_2-axis of symmetry are the most favoured targets because axes of symmetry of both inhibitors and enzyme could coalign during their interactions[3]. The deoxygenated analogue **2** of the diaminodiol derivative also show pronounced activity[4].



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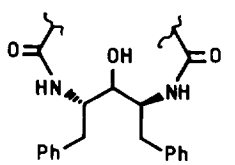

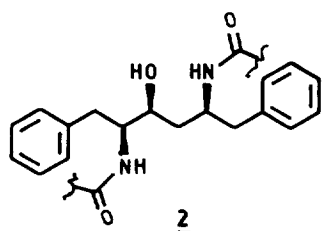

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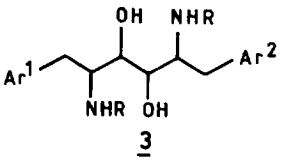
C_2-symmetrical diaminodiol based HIV-protease inhibitors **1** have been obtained either by dimerisation of aromatic aminoaldehydes[5] or from C_2-symmetrical substrates[6] such as D-mannitol in which the C_3-C_4 glycol unit correlates with that of HIV-protease inhibitors. A limitation of these methodologies is their inability to incorporate different aromatic substituents at the ends while keeping intact the diaminodiol and other structural

parameters. We envisaged that the latter compounds (**3**) may contribute interesting analogues for studying structure-activity relationships. We realised that (2S,5S,3E)-2,5-bis[(1,1-dimethylethoxy)-carbonyl]amino-1,6-diarylhex-3-ene (**4**) forms a unique starting material for this endeavour. We present in this report the synthesis of (2S,5S,3E)-2,5-bis-[(1,1-dimethyl ethoxy)-carbonyl]amino-1,6-diphenylhex-3-ene (**4a**) and (2S,5S,3E)- 2,5-bis-[(1,1-dimethylethoxy)-carbonyl]amino-1-phenyl-6-(p-methoxy)phenylhex-3-ene (**4b**) *via* Julia's olefination[7] strategy. We have also investigated chemical modifications of these intermediates in preparing known and unknown analogues of HIV-protease inhibitors.[8]



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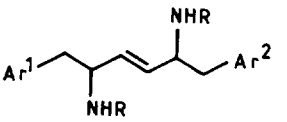

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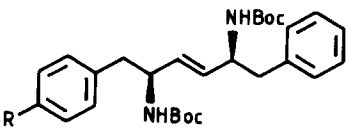


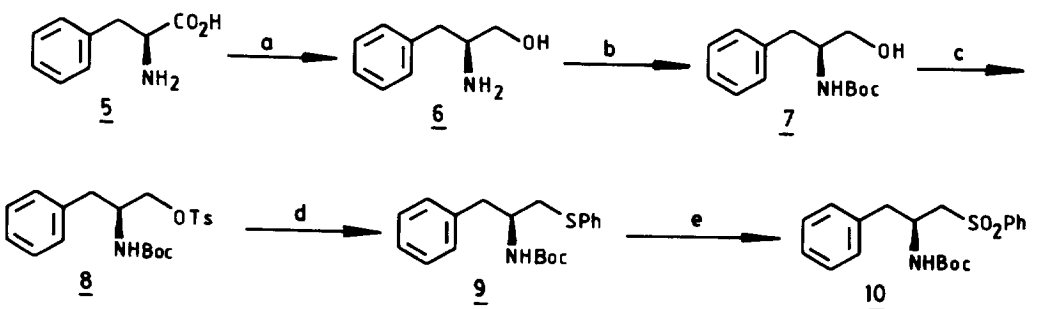
4a R = H

4b R = OMe

RESULTS AND DISCUSSIONS

Although several methods of converting phenylalanine (**5**) to phenylalanilol (**6**) were reported, the recently published[9] methodology of using sodium borohydride-iodine, in refluxing tetrahydrofuran was by far the most convenient in our hands for large scale preparation. Treatment of **6** with Boc anhydride in tetrahydrofuran-water mixture gave the N-Boc derivative (**7**). In order to obtain the requisite sulfone derivative (**10**), compound **7** was first tosylated by treating with 1.2 eq. of p-toluenesulfonyl chloride in pyridine to give **8**. Subsequent nucleophilic displacement of the tosylate group with sodium thiophenolate in methanol-tetrahydrofuran at ambient temperature furnished the sulfide derivative (**9**) which was subjected to oxidation with m-chloroperbenzoic acid in methylene chloride at room temperature for 1 h to obtain the sulfone derivative (**10**) (Scheme 1).

Scheme-1



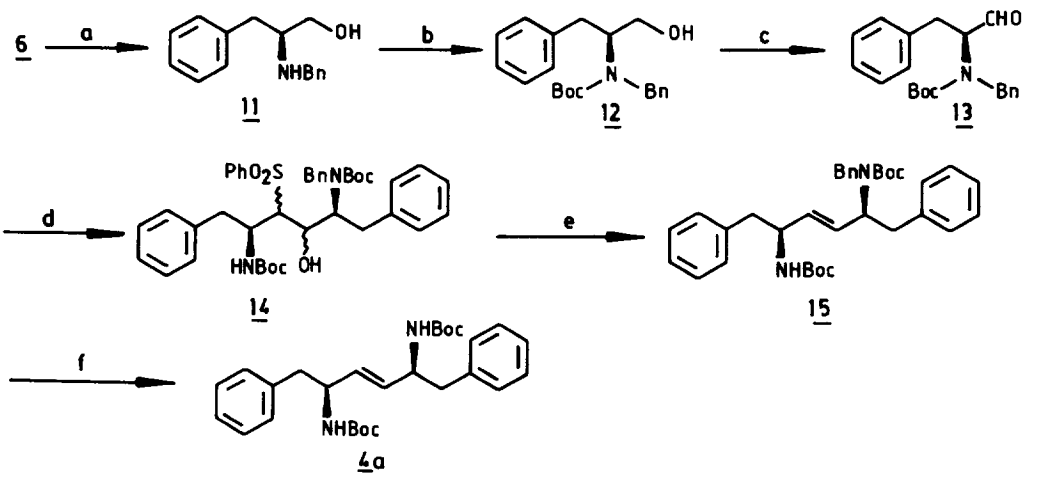
5 **6** **7** **8** **9** **10**

Reagents: (a) $NaBH_4/I_2$, THF, 18h, Δ ; (b) $(Boc)_2O$, THF:H_2O, 1h, RT, 95%; (c) TsCl, Py, CH_2Cl_2, 12h, RT, 90%; (d) NaSPh, MeOH:THF, 3h, RT, 83%; (e) MCPBA, CH_2Cl_2, 1h, RT, 95%.

Simultaneously, compound **6** was benzylated by first treating with benzaldehyde in methanol to furnish the Schiff's base followed by *in situ* reduction with sodium borohydride. The resulting compound (**11**) was protected as N-Boc derivative **12** by treatment with Boc anhydride in tetrahydrofuran-water mixture. Oxidation of **12** with sulfur trioxide pyridine complex in dimethylsulfoxide furnished the aldehyde (**13**) in high yield. The coupling between **10** and **13** in the presence of n-butyllithium in dry tetrahydrofuran at -78°C gave **14** as a mixture of diastereomers. **14** was first acetylated by treatment with acetic anhydride-pyridine and then subjected to reductive elimination reaction with freshly prepared 6% sodium amalgam in presence of disodiumhydrogenphosphate buffer in methanol at room temperature for 12 h to give **15** (overall

37% yield from **13**). Removal of benzyl group by Na in liq ammonia at -33°C provided **4a**. The structure of **4a** was confirmed by ^{1}H-NMR and high resolution mass spectral analysis (Scheme - 2).

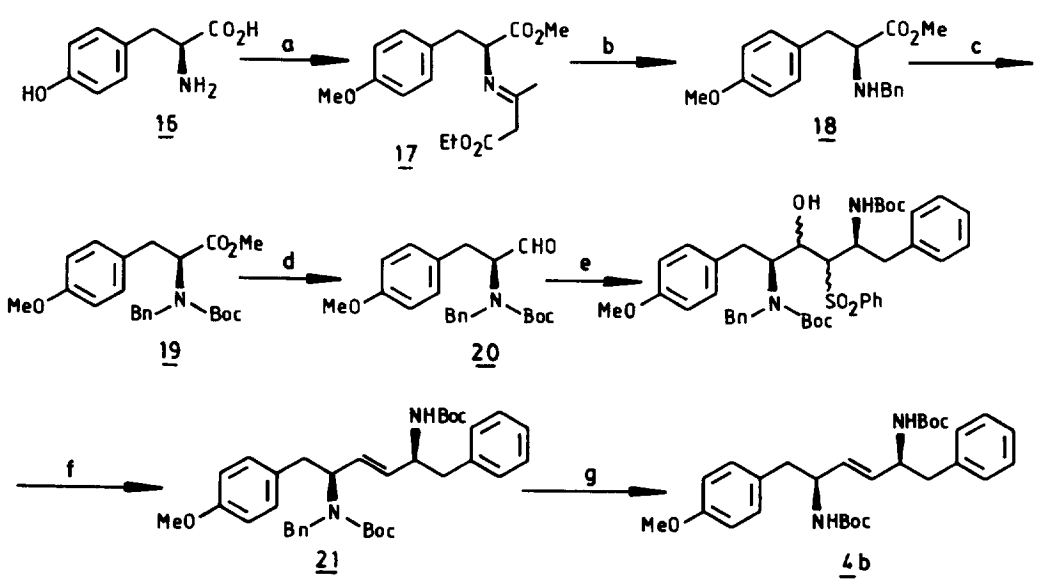
Scheme - 2



(a) PhCHO, $NaBH_4$, MeOH, 3h, RT, 77%; (b) $(Boc)_2O$, THF:H_2O, 1h, RT, 95%; (c) SO_3-Py, Et_3N, DMSO, 0°-RT, 1h; (d) n-BuLi, THF, -78°C, 1h; (e)(i) Ac_2O, Py, CH_2Cl_2, 12h, RT; (ii) 6% Na-Hg, Na_2HPO_4, MeOH, 12h, RT, 37% overall; (f) Na/liq. NH_3, THF, -33°C, 53%.

Essentially a similar route was followed for synthesis of **4b**. For instance, L-tyrosine **16** was first

Scheme - 3

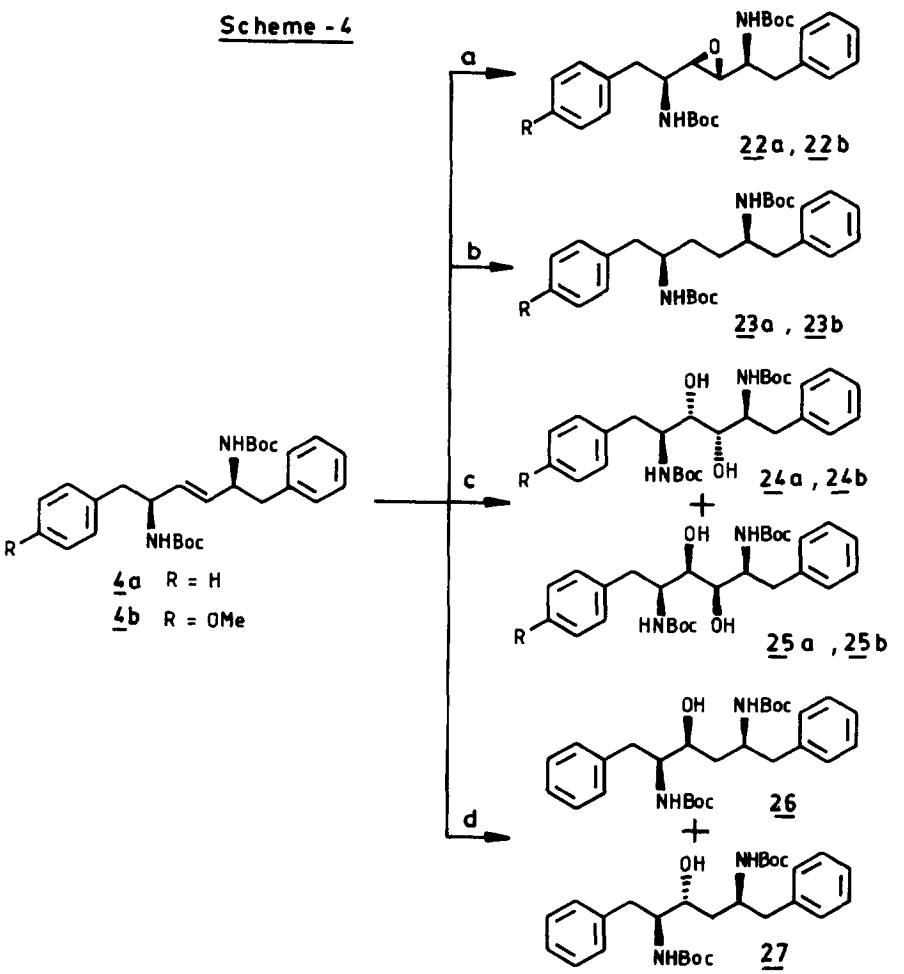


(a)(i) $CH_3COCH_2CO_2Et$, KOH, MeOH, 3h, Δ ; (ii) DMS-K_2CO_3, Me_2CO, 6h,Δ; (b)(i) 2M HCl, 4N NaOH; (ii) PhCHO, $NaBH_4$, MeOH, 3h, RT, 83%; (c) $(Boc)_2O$, THF:H_2O 2h, RT, 86%; (d)(i) $LiBH_4$, MeOH, 3h, RT, 81%; (ii) SO_3-Py, DMSO, Et_3N, 1h, RT; (e) n-BuLi, THF, -78°C; (f)(i) Ac_2O, Py, CH_2Cl_2, 12h, RT; (ii) 6% Na-Hg, Na_2HPO_4, MeOH, 12h, RT, 35% overall; (g) Na/Liq. NH_3, -33°C, 65%

converted into its Dane's salt and then methylated by using dimethylsulfate-acetone under reflux to give the dimethylated derivative **17.** The hydrolysis of Schiff's base was effected by using 2N-hydrochloric acid and then the free amino group was benzylated with benzaldehyde-sodium borohydride in methanol as described above to afford **18**. It was converted into the N-Boc derivative **19** by a conventional method. The direct transformation of **19** into the aldehyde (**20**) with diisobutylaluminium hydride was fraught with many side-reactions and therefore, a two step process was evolved. Reduction of **19** with lithium borohydride in tetrahydrofuran at room temperature gave the primary alcohol which was oxidized with sulfur trioxide pyridine complex in dimethylsulfoxide to give **20** in 80% yield. The Juila olefination of **20** with **10** yielded **21** which was debenzylated to afford **4b** (Scheme - 3).

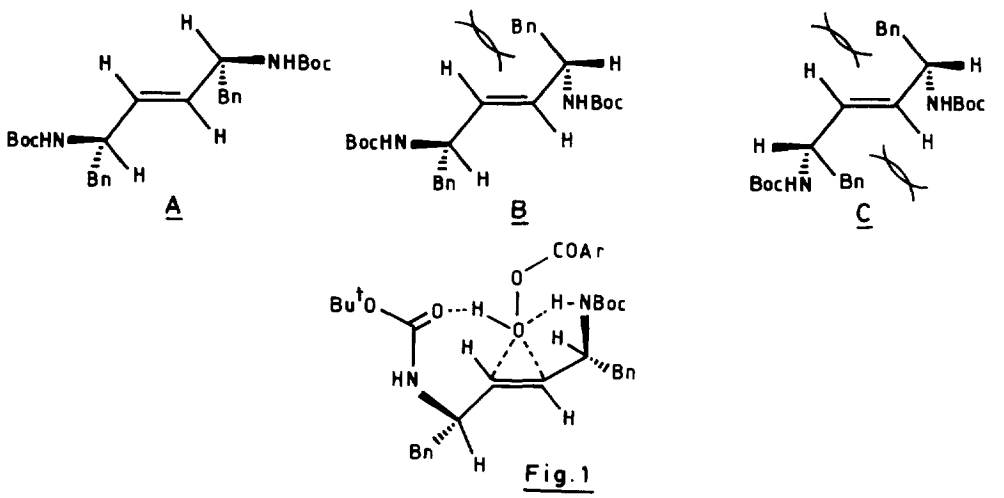
Having completed the syntheses of **4a/4b,** the first phase of our investigation had been accomplished. In second phase, compounds **4a/4b** were subjected to various chemical modifications in order to prepare known and unknown analogues of HIV-protease inhibitors, thus demonstrating the versatility of these intermediates

Scheme - 4



(a) m-CPBA, CH_2Cl_2, 48h, RT; (b) 10% Pd-C, MeOH, 45 psi, 12h, RT; (c) OsO_4, NMO, t-BuOH:H_2O (1:1), 12h, RT; (d) BH_3-Me_2S, NaOH, H_2O_2, THF, 4h, 0°-RT.

(Scheme - 4). For example, epoxidation of **4a** with m-chloroperbenzoic acid in methylene chloride at room temperature provided **22a** as an exclusive product (33:1) as judged by HPLC. Although the ^{1}H NMR spectrum of **22a** was comparable with the structure the stereochemical configuration was proposed based on ample of literature precedents. For instance the high degree of *threo*-stereoselectivity was explained in term of cooperative effect and stability difference of three conformations[10]. The conformation A is the most favoured one because in conformations B and C, there exists considerable steric compression due to olefinic proton and benzyl or carbamate groups. The cooperative coordination effect of peracid by carbamate groups as depicted in figure 1, explains the preferential β attack.



Hydrogenation of olefin function in **4a** was then carried out in the presence of 10% Pd-C in methanol at 45 psi. The dideoxygenated product **23a** was isolated in almost quantitative yield. The C_2-symmetrical structure of **23a** was indicated by the ^{1}H NMR spectrum in which resonances due to half the molecule were apparently observed. In the ^{1}H NMR spectrum of **23a**, the resonances due to methylene protons were located in the high field region between δ 1.2-1.6 ppm. Other characteristic signals due to benzylic protons at δ 2.72 ppm, methine protons at δ 3.75 ppm and NH at δ 4.18 ppm were in conformity with the assigned structure.

We have exploited the C_2-symmetrical nature of **4a** for obtaining (3R,4R) and (3S,4S)-diaminodiol inhibitors using catalytic osmylation reaction. It is pertinent to mention that all diastereomers of diaminodiol core unit are sufficiently active against HIV proteases[3]. The simple catalytic osmylation of **4a** with osmium tetraoxide in presence of N-methylmorpholine oxide in tert.butanol-water mixture at room temperature provided a chromatographically separable mixture of diols (**24a** and **25a**) in the ratio of 3:2 which were identical with reported samples[5].

The hydroboration/oxidation of **4a** was interesting from stereoselectivity point of view. For example, treatment of **4a** with 2M solution of borane-dimethyl sulfate in tetrahydrofuran at room temperature gave 4:1 diastereomeric mixtures of **26** and **27** which were conveniently separated by silica gel chromatography. Comparison of ^{1}H-NMR spectrum of **26** and **27** with those, reported[11] for authetic samples unambiguously confirmed their structure. The preferential formation of **26** could be explained by considering the possible bonding between boron and nitrogen. This coordination would effect the attack of borane on olefin from the same side as that of N-Boc group (fig-2).

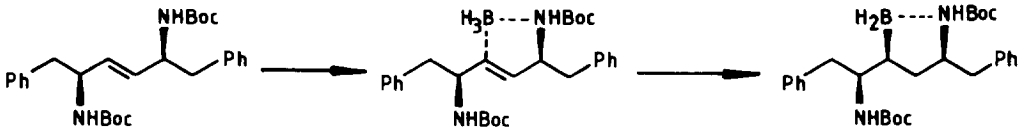
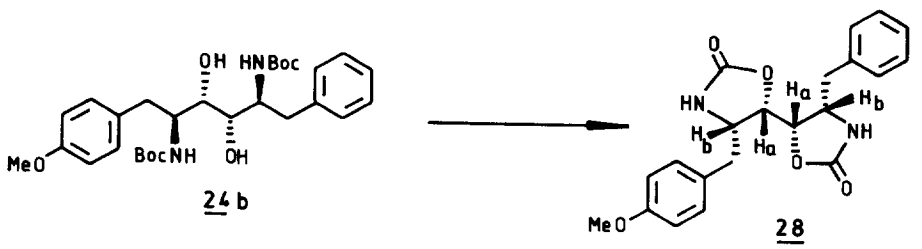


Fig. 2

We have also briefly examined chemical modification studies, as discussed above, with the intermediate **4b**. In the case of epoxidation reaction with m-perchlorobenzoic acid in methylene chloride, **4b** also provided the epoxide (**22b**) with excellent selectivity (HPLC). Likewise the preparation of dideoxygenated product (**23b**) from **4b** by catalytic hydrogenation was a straight forward excercise. However, the catalytic osmylation of **4b** provided two diastereomers **24b** and **25b** in the ratio of 3:2. On the basis of spectral data the stereochemistry of newly formed centres in **24b** and **25b** could not be ascertained. Based on stereochemical studies reported by Kempf[12] and Ghosh[6], we also investigated the transformation of the major bis-carbamate derivative (**24b**) into the corresponding bis-oxazolidinone derivative **28** by the treatment with sodium hydride in tetrahydrofuran at 60°C. The characteristic coupling constant J_{ab}= 8.3 Hz observed in the ^{1}H-NMR spectrum of was consistent with the reported value[11] thus providing confirmation to the assigned structre of **28** as well as to its parent diaminodiol derivative **24b**. Obviously the minor product was given the structure **25b**.



In the preceding lines we have investigated a novel strategy based on Julia's olefination to prepare actual and potential HIV protease inhibitors. This strategy allowed us to introduce substituent on aromatic ring while maining diaminodiol skeleton untouched, the existing methodologies do not offer these advantages.

EXPERIMENTAL

(2S)-2-[N-(1,1-Dimethylethoxycarbonyl)-N-benzyl]amino-3-phenylpropanaldehyde (13)

(S)-Phenylalanilol **6** (5.0 g, 33.0 mmol) and benzaldehyde (3.5 g, 33.0 mmol) in methanol (20 mL) were stirred for 1 h at room temperature and then cooled to 0°. $NaBH_4$ (1.3 g, 36.0 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, quenched with acetic acid and concentrated. The residue was partitioned between ethyl acetate-water. The ethyl acetate layer was dried, concentrated to afford a crude product which was suspended in 1:1 THF-water mixture (20 mL). $(Boc)_2O$ (8.0 g, 36.0 mmol) was introduced and stirred for 2 h at room temperature. THF was removed under vacuum, and extracted with ethyl acetate which was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography using ethyl acetate - light petroleum (3:20) as eluent to give **12** (10.0 g, 88%), $[\alpha]_D$ -75°

(c, 0.8, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.45 (s, 9 H), 2.97 (br s, 2 H), 3.63 (br s, 4 H), 4.36 (m, 1 H), 7.36 (m, 10 H).

Compound **12** (5.5 g, 16.1 mmol), dry DMSO (50 mL) and Et_3N (8 mL) were stirred for 30 min. and cooled to 0°. SO_3-Py complex (10.1 g) was added and after 30 min, the reaction mixture poured over ice-water and extracted with ethyl acetate. The ethyl acetate layer was successively washed with $NaHCO_3$, water, dried and concentrated. The crude aldehyde **13** (4.5 g, 82%) was used without further purification.

(2S,5S,3E)-2-[(1,1-Dimethylethoxy)carbonyl]amino-5-{[(1,1-dimethylethoxy)carbonyl]-N-benzyl}amino-1,6-diphenylhex-3-ene (15)

A suspension of the sulfone derivative[10i] **10** (5.5 g, 14.7 mmol) in dry THF (50 mL) was heated under reflux till a clear solution was obtained. The solution was cooled to -78° and 0.9M n-BuLi (32 mL, 28.5 mmol) was introduced. Meanwhile, the aldehyde (**13**) (4.5 g, 13.1 mmol) was activated by the treatment with DIBAL-methoxide solution [prepared by addition of MeOH (0.5 mL, 15.7 mmol) and THF (3 mL) to 1.65M solution of DIBAL-H in hexane (9.5 mL, 15.7 mmol)] at -78°. This solution was transferred *via* canula to the solution of sulfone dianion. After 30 min. at -78°, it was quenched by adding NH_4Cl solution, extracted with ethyl acetate, dried and concentrated. The crude hydroxysulfone was treated with acetic anhydride (3 mL) and pyridine (6 mL) in CH_2Cl_2 (50 mL) at room temperature overnight. Methanol (5 mL) was added to the reaction which was then washed with brine, dried and concentrated. The crude product was dissolved in methanol (60 mL) cooled to 0°. Na_2HPO_4 (9.8 g) and freshly prepared 6% Na-Hg (12 g) were added. After 12 h, water (5 mL) was added and solid filtered. The filtrate was concentrated and extracted with ethyl acetate which was washed with brine, dried and concentrated. The crude residue was chromatographed on silica gel by using ethyl acetate-light petroleum (1:15) as eluent to give **15** (2.7 g, 37%), $[\alpha]_D$ -39° (c, 0.9, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.34 (s, 18 H), 2.64 (d, J = 6.0 Hz, 2 H), 2.74 (dd, J = 6.0, 13.0 Hz, 1 H), 2.94 (dd, J = 8.0, 13.0 Hz, 1 H), 4 - 4.5 (m, 5 H), 5.28 (brd, J = 16.0 Hz, 1 H), 5.56 (dd, J = 6.0, 16.0 Hz, 1 H), 6.92 - 7.26 (m, 15 H).

(2S,5S,3E)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenylhex-3-ene (4a)

Compound **15** (2.7 g, 4.9 mmol), in dry THF (5 mL) was introduced to liq. ammonia (50 mL) at -33° followed by addition of sodium till the blue colour persisted. After 1 h, solid NH_4Cl was added and ammonia was allowed to escape at ambient temperature. The residue was extracted with ethyl acetate, washed with water, dried and concentrated. The chromatographic purification of the residue over silica gel by using ethyl acetate-light petroleum (1:9) gave **4a** (1.2 g, 53%), m.p. 133°, $[\alpha]_D$ -14° (c, 1.0, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.40 (s, 18 H), 2.74 (bs, 4 H), 4.32 (bs, 4 H), 5.42 (s, 2 H), 7.0 - 7.3 (m, 10 H), HRMS : Found : 467.2909 (M+1), calc. for $C_{28}H_{39}N_2O_4$: 467.2909.

(2S)-2{[(1,1-Dimethylethoxy)carbonyl]-N-benzyl}amino-3-(p-methoxy)phenylpropionic acid methyl ester (19)

(S)-Tyrosine **16** (6.0 g, 36.3 mmol), ethyl acetoacetate (5.2 g) and potassium hydroxide (4.0 g) in MeOH (25 mL) were heated under reflux for 3 h. The reaction mixture was filtered to remove solid impurities. MeOH was evaporated and the residue heated under reflux with dimethylsulfate (5.2 mL), K_2CO_3 (6.7 g) and acetone (50 mL) for 6 h. Solid was filtered, concentrated to give **17** which was stirred with 2M hydrochloric acid (15 mL) for 30 min. and washed with $CHCl_3$. The aqueous layer was neutralised with 4N NaOH hydroxide, extracted with ethyl acetate and concentrated. The resulting amine (2.7 g) and PhCHO (1.4 mL,

12.9 mmol) in MeOH (15 mL) were stirred at room temperature for 1 h and then $NaBH_4$ (0.53 g, 14.3 mmol) added. After stirring for 2 h at room temperature, the reaction was quenched with dil. acetic acid and concentrated. The residue was extracted with ethyl acetate, washed with water, dried, concentrated and purified by column chromatography using ethyl acetate-light petroleum (1:4) as eluent to give **18** (3.2 g, 83%), ^{1}H-NMR data ($CDCl_3$) : δ 2.87 (d, J = 6.25 Hz, 2 H),), 3.45 (t, J = 6.25 Hz, 1 H), 3.58 (d, J = 13.3 Hz, 1 H), 3.60 (s, 3 H), 3.72 (s, 3 H), 3.79 (d, J = 13.3 Hz, 1H), 6.77 (d, J = 8.3 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 2 H), 7.25 (m, 5 H).

Compound **18** (3.2 g, 10.7 mmol) and $(Boc)_2O$ (2.5 g, 11.8 mmol) in (1:1) THF-water (20 mL), were stirred for 2 h after which time THF was removed, extracted with ethyl acetate, dried and concentrated. The residue on chromatographic purification over silica gel using ethyl acetate-light petroleum (3:17) gave **19** (3.7 g, 86%), $[\alpha]_D$ -107° (c, 1.5, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : (NCO bond restriction) δ 1.47, 1.50 (2s, 9 H), 3.0 (dis dd, J = 14.6 Hz, 1H), 3.22 (dd, J = 6.25 Hz, 14.6 Hz, 1H), 3.58, 3.79 (2s, 6 H), 3.6 - 4.05 (m, 2 H), 4.2 - 4.6 (m, 1 H), 6.75 (d, J = 8.3 Hz, 1H), 6.8 - 7.25 (m, 8 H), HRFABMS: Found : 400.2129 (M^++1), calcd. for $C_{23}H_{30}NO_5$: 400.2123.

(2S)-2{[(1,1-Dimethylethoxy)carbonyl]-N-benzyl}amino-3-(p-methoxy)phenylpropanaldehyde (20)

Compound **19** (4.0 g, 10.5 mmol) and $LiBH_4$ (0.26 g, 12.1 mmol) in THF (10 mL) was stirred at room temperature for 3 h and quenched with saturated solution of NH_4Cl. The reaction mixture was concentrated, extracted with ethyl acetate and dried. Removal of solvent and column chromatography of the residue over silica gel using ethyl acetate-light petroleum (1:4) as eluent afforded the alcohol (3.0 g, 81%), which was oxidised with dry DMSO (15 mL), Et_3N (2.2 mL) and SO_3-Py (2.6 g) as described above to give **20** (1.7 g, 85%), used as such for the next reaction.

(2S,5S,3E)-2,5-bis-[(1,1-dimethylethoxy)-carbonyl]amino-1-phenyl-6-(p-methoxy)-phenylhex-3-ene (4b)

The sulfone **10** (1.8 g, 4.7 mmol) and the aldehyde **20** (1.7 g) were converted into **21** (0.94 g, 35%) (according to the procedure reported above for compound **15**), $[\alpha]_D$ -23° (c 0.39, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.39 (s, 18 H), 2.6 - 2.95 (m, 4 H), 3.8 (s, 3 H), 4.21 (m, 5 H), 5.3 (br s, 1 H), 5.65 (dd, J = 6.5, 15.2 Hz, 1 H), 6.76 (d, J = 8.5 Hz, 2H), 6.85 - 7.35 (m, 12 H).

As described for **4a**, compound **21** (0.9 g, 1.53 mmol) was debenzylated with sodium in liquid ammonia to yield **4b** (0.5 g, 65%), $[\alpha]_D$ -19° (c, 1.2, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.4 (s, 18 H), 2.72 (m, 4H), 3.76 (s, 3 H), 4.32 (m, 4 H), 5.42 (br s, 2 H), 6.72 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 2 H), 7.04 (dd, J = 2.0, 8.0 Hz, 2H), 7.2 (m, 3 H), HRFABMS: Found : 497.3029 (M^++1), calcd. for $C_{29}H_{41}N_2O_5$: 497.3015.

(2S,3R,4R,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenyl-3,4-epoxy-hexane (22a)

To a solution of **4a** (0.1 g, 0.21 mmol) in CH_2Cl_2 (3 mL), m-CPBA (0.1 g, 0.64 mmol) was added. After 48 h of stirring at room temperature, the reaction mixture was worked-up in usual manner and the residue purified by column chromatography on silica gel by using ethyl acetate-light petroleum (1:9) as eluent to give **22a** (0.07 g, 70%), $[\alpha]_D$ +25° (c, 0.3, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.32 (s, 18 H), 2.65 - 2.95 (m, 6 H), 3.91 (bs, 2 H), 4.38 (d, J = 9.6 Hz, 2 H), 7.1 -7.3 (m, 10 H), FABMS: 371 (M^++1 - 2 ^{t}Bu).

(2S,5S)-2,5-Bis[(1,1-dimethoxy)carbonyl]amino-1,6-diphenyl-3,4-dideoxyhexane (23a)

Compound **4a** (0.05 g, 0.11 mmol) was hydrogenated over 10% Pd/C (10 mg) in MeOH (4 mL) at 45 psi for 6 h. The solution was filtered through celite, concentrated and purified by column chromatography using ethyl acetate-light petroleum(1:9) to obtain **23a** (0.05 g, 100%), mp 141°C, $[\alpha]_D$ -11° (c, 0.3, $CHCl_3$), ^{1}H-NMR data ($CDCl_3$) : δ 1.2 - 1.6 (m, 4 H), 1.38 (s, 18 H), 2.72 (d, J = 6.8 Hz, 4 H), 3.75 (bs, 2 H), 4.18 (d, J = 9.0 Hz, 2 H), 7.0 -7.35 (m, 10 H), HRFABMS: Found : 468.2990 (M^+), calcd. for $C_{28}H_{40}N_2O_4$: 468.2988.

(2S,3S,4S,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenyl-3,4-dihydroxyhexane (24a) and (2S,3R,4R,5S)-2,5-bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenyl-3,4-dihydroxyhexane (25a)

Compound **4a** (0.1 g, 0.22 mmol) was taken in (1:1) t-BuOH: H_2O mixture (2 mL) and catalytic OsO_4 and NMO (0.05 mL) were added and stirred at room temperature for 12 h. To the reaction mixture solid $NaHSO_3$ was added, concentrated and then extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography with ethyl acetate-light petroleum (1:2) to give **24a** (0.052 g, 49%), ^{1}H-NMR data ($CDCl_3$) : δ 1.43 (s, 18 H), 2.91 (dd, J = 4.3 , 13.0 Hz, 2 H), 3.15 (dd, J = 2.1, 8.7 Hz, 2 H), 3.30 (dd, J = 4.3 , 13.0 Hz, 2 H), 4.02 (m, 2 H), 4.4 (m, 4 H), 7.3 (s, 10 H), HRFABMS: Found : 502.3031 (M^++1), calcd. for $C_{28}H_{42}N_2O_6$: 502.3042.

Further elution afforded compound **25a** (0.036 g, 33%), ^{1}H-NMR data ($CDCl_3$) : δ 1.29 (s, 18 H), 2.85 (dd, J = 7.4, 14.0 Hz, 2H), 2.95 (dd, J = 8.5, 14.0 Hz, 2H), 3.38 (br s, 2 H), 3.74 (m, 2 H), 3.95 (br s, 2 H), 4.76 (d, J = 8.5 Hz, 2 H), 7.2 (m, 10 H), HRFABMS: Found : 502.3040 (M^++1), calcd. for $C_{28}H_{42}N_2O_6$: 502.3042.

(2S,3R,4R,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1-phenyl-6-(p-methoxy)phenyl-3,4-epoxyhexane (22b)

Yield - 65%, ^{1}H-NMR data ($CDCl_3$) : δ 1.3 (s, 18 H), 2.6 - 2.8 (m, 6 H), 3.74 (s, 3 H), 3.94 (brs, 2 H), 4.32 (m, 2 H), 6.72 (d, J = 8.0 Hz, 2 H), 7.02 (d, J = 8.0 Hz, 2 H), 7.08 - 7.22 (m, 5 H), FABMS : 401 (M^++1 - 2 ^{t}Bu).

(2S,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1-phenyl-6-(p-methoxy)phenyl-3,4-dideoxyhexane (23b)

Yield - 100%, ^{1}H-NMR data ($CDCl_3$) : δ 1.38 (s, 18 H), 1.47 (m, 4 H), 2.7 (m, 4 H), 3.75 (m, 2 H), 3.8 (s, 3H), 4.22 (d, J = 7.5 Hz, 2 H), 6.84 (d, J = 8.0 Hz, 2 H), 7.06 (d, J = 8.0 Hz, 2 H), 7.1 - 7.3 (m, 5 H), FABMS : 499 (M^++1).

(2S,3S,4S,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1-phenyl-6-(p-methoxy)phenyl-3,4-dihydroxyhexane (24b) and (2S,3R,4R,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]-amino-1-phenyl-6-(p-methoxy)phenyl-3,4-dihydroxyhexane (25b)

24b : Yield - 48%, ^{1}H-NMR data ($CDCl_3$) : δ 1.32 (s, 18 H), 2.72 (dd, J = 4.0, 14.0 Hz, 1 H), 2.82 (dd, J = 4.4, 14.0 Hz, 1H), 2.95 - 3.25 (m, 4 H), 3.62 (s, 3 H), 3.85 (m, 2 H), 4.25 (m, 4 H), 6.64 (d, J = 8.0 Hz, 2 H), 7.0 (d, J = 8.0 Hz, 2 H), 7.0 - 7.15 (m, 5 H), HRFABMS : Found 531.3053 (M^++1), calc. for $C_{29}H_{43}N_2O_7$: 531.3070.

25b : Yield - 35%, ^{1}H-NMR data ($CDCl_3$) : δ 1.25 (s, 18 H), 2.8 (m, 4 H), 3.27 (br s, 2 H), 3.59 (m,

2 H), 3.65 (s, 3 H), 3.87 (m, 2 H), 4.74 (d, J = 8.5 Hz, 2 H), 6.68 (d, J = 8.5 Hz, 2H), 7.0 (d, J = 8.5 Hz, 2H), 7.06 - 7.17 (m, 5 H), HRFABMS : Found 531.3079 (M+1), calc. for $C_{29}H_{43}N_2O_7$: 531.3070.

(2S,4S,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenyl-4-hydroxy-hexane (26) and (2S,4R,5S)-2,5-Bis[(1,1-dimethylethoxy)carbonyl]amino-1,6-diphenyl-4-hydroxyhexane (27)

To an ice cooled solution of compound **4a** (0.1 g, 0.22 mmol) in THF (2 mL) was added 2M solution of borane - dimethylsulfate in THF (0.4 mL, 0.67 mmol). After stirring for 2 h at room temperature a saturated solution of sodium acetate (0.2 mL) was added followed by 30% H_2O_2 (0.1 mL). The stirring was continued for another 1.5 h and extracted with ethyl acetate which was washed with brine, dried and concentrated. The residue was chromatographed on silica gel using ethyl acetate-light petroleum (1:3) as eluent to give **26** (0.063 g, 59%), ^{1}H-NMR data ($CDCl_3$) : δ 1.38 (s, 18 H), 1.65 (m, 2 H), 2.67 - 2.90 (m, 4 H), 3.55 - 3.7 (m, 2 H), 3.85 (m, 1 H), 4.55 (d, J = 8.1 Hz, 1H), 4.8 (d, J = 8.0 Hz, 1H), 7.1 -7.3 (m, 10 H), HRFABMS : Found 485.2973 (M+), calc. for $C_{27}H_{40}N_2O_5$: 485.2970.

Further elution with the same solvent system afforded **27** (0.018 g, 17%), ^{1}H-NMR data ($CDCl_3$) : δ 1.35 (s, 9 H), 1.4 (s, 9 H), 1.6 - 1.7 (m, 2 H), 2.7 - 2.9 (m, 4 H), 3.50 (m 1 H), 3.8 (m, 1 H), 4.1 (m, 1 H), 4.38 (d, J = 9.1 Hz, 1H), 4.51 (d, J = 8.0 Hz), 7.1 -7.3 (m, 10 H), HRFABMS : Found 485.2985 (M+), calc. for $C_{27}H_{40}N_2O_5$: 485.2970.

References

1. Huff, J.R. *J. Med. Chem.* **1991**, 34, 2305.
2. (i) Erickson, J.; Neidhart, D.J.; Van Drie, J.; Kempf, D.J.; Wang, X.C.; Norbeck, D.W.; Plattner, J.J.; Ritenhouse, J.W.; Turon, M.; Wideburg, N.; Kohlbrenner, W.E.; Limmer, R.; Helfrich, R.; Paul, D.A.; Knigge, M. *Science*, **1990**, 249, 527. (ii) Kempf, D.J.; Marsh, K.C.; Fino, L.C.; Bryant, P.; Craig-Kennard, A.; Sham, H.L.; Zhao, C.; Vasavanonda, S.; Kohlbrenner, W.E.; Wideburg, N.; Saldivar, A.; Ween, B.E.; Herrin, T.; Norbeck, D.W. *Biorg. Med.Chem.* **1994**, 2, 847.
3. Hosur, M.V.; Bhat, T.N.; Kempf, D.J.; Baldwin, E.T.; Lui, B.; Gulnik, S.; Wideburg, N.E.; Appelt, N.K.; Erickson, J.W. *J. Am. Chem. Soc.*, **1994**, 116, 847.
4. Kempf, D.J.; Norbeck, D.W.; Codacovi, L.; Wang, X.C.; Kohlbrenner, W.E.; Wideburg, N.E.; Saldivar, A.; Craig-Kennard, A.; Vasavanonda, S.; Clement, J.J.; Erickson, J. *Recent Advances in the Chemistry of Anti-infective Agents*, Cambridge Press : Cambridge, **1993**, p.247.
5. Kempf, D.J.; Codacovi, L.M.; Norbeck, D.W.; Plattner, J.J.; Sham, H.L.; Wittenberger, S.J.; Zhao, C . *European Patent* **1991** 0 48 6948 A2
6. Ghosh, A.K.; McKee, S.P.; Thompson, W.J. *Tetrahedron Lett.* **1991**, 32, 5729.
7. Julia, M.; Paris, J.M.; Tetrahedron Lett. **1993**, 34, 4833; Trost, B.M.; *Bull. Chem. Soc. Jpn.* **988**, 61, 107.
8. Rama Rao, A.V.; Gurjar, M.K.; Pal, S.; Pariza, R.J. Chorghade, M.S. *Tetrahedron Lett.* **1995**, 36, 2505.
9. Kanth, J.V.B.; Periasamy, M. *J. Org. Chem.* **1991**, 56, 5964.
10. (i) Jemalam, A.; Berts, W.; Li, Y-L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, 56, 1139. (ii) Johnson, M.R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347; Kogan, H.; Nishi, T. *JCS Chem. Comm.* **1987**, 311.
11. Ghosh, A.K.; McKee, S.P.; Thompson, W.J.; Darke, P.L.; Zugay, J.C. *J. Org. Chem.* **1993**, 58, 1025.
12. Kempf, D.J.; Norbeck, D.W.; Codacovi, L.; Wang, X.C.; Kohlbrenner, W.E.; Wideburg, N.E.; Paul, D.A.; Knigge, M.F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook Jr. W.; Clement, J.J.; Plattner, J.J.; Erickson, J. *J. Med. Chem.* **1990**, 33, 2687.

(*Received in UK* 28 *November* 1996; *revised* 11 *February* 1997; *accepted* 13 *February* 1997)