Chirality Conversion of Dipeptides in the Schiff Bases of Binol Aldehydes with Multiple Hydrogen Bond Donors

Hyunjung Park, Jooyeon Hong,[†] Sihyun Ham,[†,*] Raju Nandhakumar, and Kwan Mook Kim[*]

Bio-Chiral Lab, Department of Chemistry and Nano Sciences, Ewha Womans University, Seoul 120-750, Korea
[*]E-mail: kkmook@ewha.ac.kr
[†]Department of Chemistry, Sookmyung Women's University, Seoul 140-742, Korea. [*]E-mail: sihyun@sookmyung.ac.kr
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Novel binol aldehydes derivatized at 2' hydroxy position with both uryl and acetamide groups (**2**), and diuryl groups (**3**) have been synthesized. Both were designed for streospecific binding and chirality conversion of general dipeptides with support of multiple hydrogen bonding donor sites in the receptors. The receptors, **2** and **3**, converted the chirality of *N*-terminal amino acids of peptides such as Ala-Gly, Met-Gly, Leu-Gly and His-Gly with stereoselectivity on D-form over L-form. The stereoselectivity ratios were in the range of 5-11, somewhat higher than those of the binol receptor with mono uryl group (**1**). The DFT calculation at the B3LYP/6-31G*//MPWB1K/6-31G* level revealed that **3**-D-Ala-Gly was 2.2 kcal/mol more stable than **3**-L-Ala-Gly. The considerable steric hindrance between the methyl group of the alanine and the imine CH moiety of the receptor seems to be the main contributing factor for the thermodynamic preference.

Key Words: Deracemization, Schiff base, Dipeptide, Stereoselective recognition, DFT calculation

Introduction

The development of new stereoselective receptors for amino acids[1] and aminoalcohols[2] which are important materials in chirotechnology[3] continues to be an active area of research in pharmaceutical and chemical industries. Pyridoxal 5'-phosphate (PLP), vitamin B6, plays a vital role as the cofactor of the enzymes that racemize amino acids.[4] The racemization is due to the acidification of α proton of the amino acid on the imine formed between the PLP and an amino acid.[5] Compound **1** is an effective enantioselective receptor for general amino acids and amino alcohols.[6] This receptor binds the substrates by the Schiff base formation like PLP but deracemizes amino acids unlike PLP. As a practical chirality conversion reagent (CCR),[7] high stereoselectivities and facile reusability are attractive advantages of compound **1.** Therefore, studies on novel derivatives of compound **1** are required for the development of more efficient receptor.

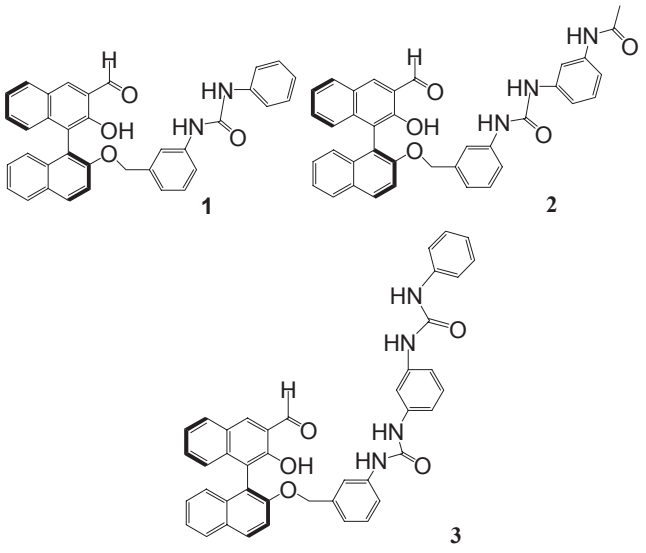


Figure 1. Binol aldehyde receptors.

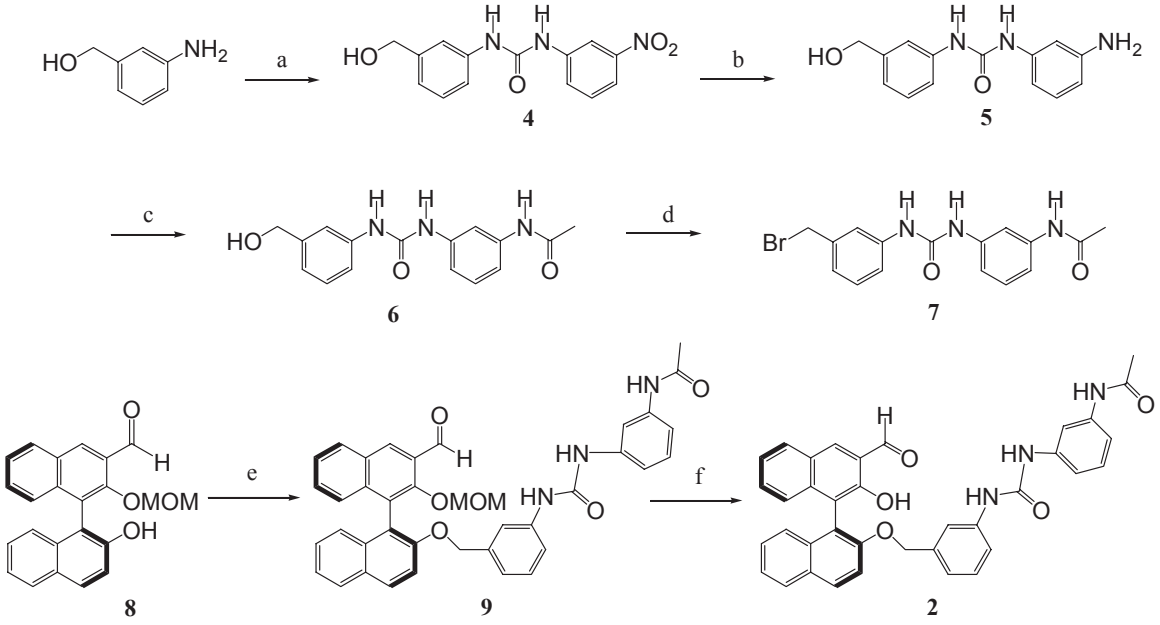
Peptides are important building blocks of high intensity sweeteners, peptide drugs, antibodies and drug delivery systems.[8] Any change in the chirality of an amino acid in a peptide may affect the total biological activity of the peptide. Recently, we have observed that compound **1** convert the chirality of *N*-terminal amino acids in peptides,[9] via reversible imine formation aided with hydrogen bonding. The stereoselectivity of the imine of **1** with an amino acid is associated with the hydrogen bond donating sites (HBD), which plays a decisive role. In order to enhance the stereoselectvity of dipeptides, we speculated that additional HBD's are required along with the uryl group, for effective hydrogen bonding with both the amide and carboxylate group of the peptides. Hence, we designed compound **2** with amide and uryl groups, and compound **3** with two uryl groups (Figure 1). Herein, we report their syntheses and capability as CCR's for peptides.

Results and Discussion

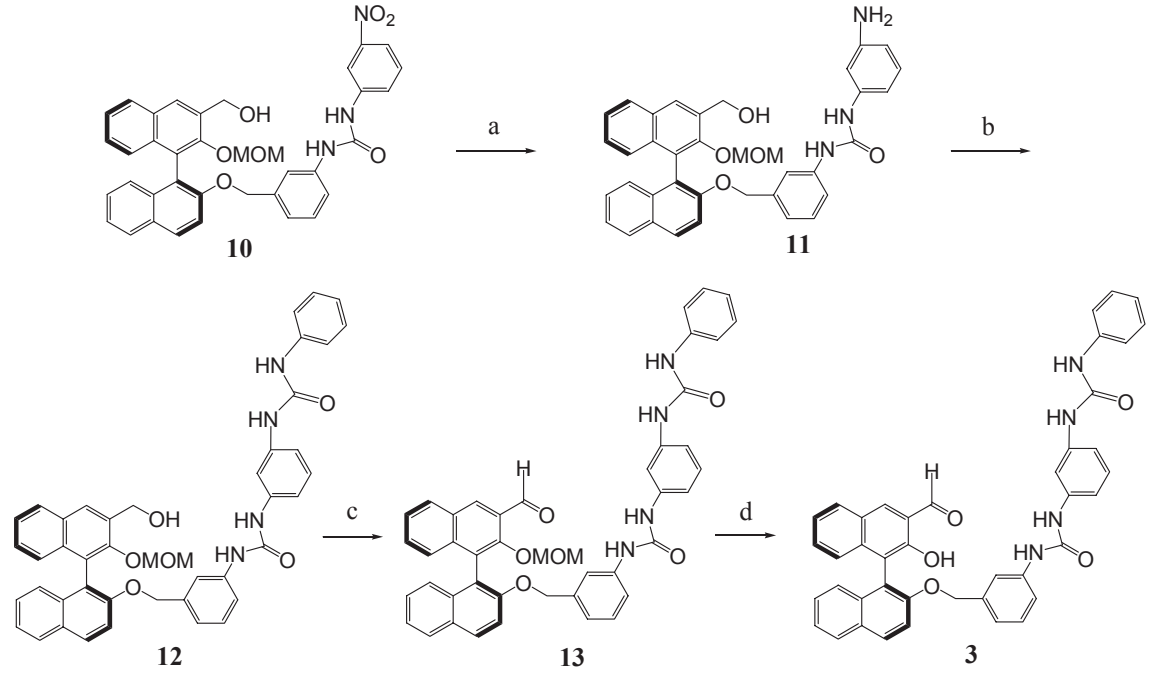
Synthesis of receptors **2** and **3** are described in schemes 1 and 2, respectively. The reaction of (*S*)-3-formyl-2'-hydroxy-2-methoxymethoxy-[1,1']binaphthalene (**8**)[10] with 3-(3'-acetylamino)-phenyluryl-benzyl bromide (**7**) (prepared from 3-aminobenzyl alcohol and 3-nitrophenyl isocyanate) in the presence of sodium hydride in dimethylformamide (DMF) gave MOM protected compound **9**. Subsequent hydrolysis of **9** under acidic condition gave the optically pure receptor **2**. A different synthetic methodology was adopted for the synthesis of receptor **3.** It is noteworthy to mention that the compound 3-(3'-phenyluryl)-phenyluryl-benzyl bromide (prepared from 3-(3'-phenyluryl)-phenyluryl-benzyl alcohol) was highly unstable. Therefore, reduction of (*S*)-3-hydroxymethyl-2-methoxymethoxy-2'-(3-(3-nitrophenyluryl)-benzyloxy)-[1,1']binaph-

thalene (**10**)[7b] with iron and ammonium chloride and subsequent treatment with phenylisocyanate in tetrahydrofuran (THF) gave the diuryl compound **12**. Pyridinium chlorochromate (PCC) oxidation in methylene chloride and acid hydrolysis gave the optically pure receptor **3**.

Chirality Conversion. Figure 2a shows the time-dependent partial ^{1}H NMR spectrum of DMSO-d_6 solution containing compound **3** (20 mM), dipeptide L-Ala-Gly (20 mM) and triethylamine (80 mM). The spectrum indicates the complete formation of imine by the disappearance of the aldehyde peak. The broad peak at 12.9 ppm is due to the phenolic OH of the imine formed between **3** and L-Ala-Gly, **3**-L-Ala-Gly. Two peaks at 10.65 and 10.05 ppm are due to two NHs of the uryl group of **3**-L-Ala-Gly. As time goes by, the intensities of those peaks decrease and new peaks at 12.7, 11.5 and 11.1 ppm increase, which are assigned to the peaks of OH and two NHs of **3**-D-Ala-Gly. These ^{1}H NMR spectra indicate clearly the chirality conversion (CC) of *N*-terminal L-alanine in the



Scheme 1. Reagents: (a) 3-nitrophenyl isocyanate, THF, 94 %; (b) Fe, NH_4Cl, C_2H_5OH/dioxane/H_2O, 83 %; (c) acetic anhydride, 91 %; (d) PBr_3, THF, 70 %; (e) 3-(3-acetylaminophenyluryl)-benzyl bromide, NaH, DMF, 62 %; (f) HCl, C_2H_5OH, 82 %



Scheme 2. Reagents: (a) Fe, NH_4Cl, C_2H_5OH/dioxane/H_2O, 92 %; (b) phenyl isocyanate, THF, 85 %; (c) PCC, CH_2Cl_2, 51%; (d) HCl, C_2H_5OH, 70%

Table 1. The stereoselective ratios(D/L) for *N*-terminal amino acid in peptide at equilibrium determined by the integration of ^{1}H NMR spectrum

	1	**2**	**3**
Ala-Gly	7.4/1	7.8/1	7.5/1
Met-Gly	8.1/1	7.9/1	5.8/1
Leu-Gly	11/1	5.1/1	4.4/1
His-Gly	8.5/1	6.8/1	5.7/1

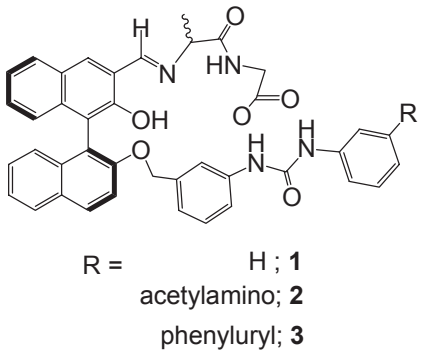


Figure 3. The proposed hydrogen bonding in the imines formed between the three aldehydes and Ala-Gly.

peptide. The solution reaches an equilibrium in 48 hrs. The signals of OH and uryl NH for **3**-L-Ala-Gly and **3**-D-Ala-Gly in the ^{1}H NMR spectrum are integrated, from which the stereoselectivity ([**3**-D-Ala] to [**3**-L-Ala]) is determined to be 7.5. The same CC is observed in the ^{1}H NMR spectra of the DMSO-d_6 solutions of **2** containing L-Ala-Gly and triethylamine shown in Figure 2b. Figure 2c depicts the CC of L-Ala-Gly by compound **1**.[9]

Similarly, we have tested the stereoselectivities of **2** and **3**

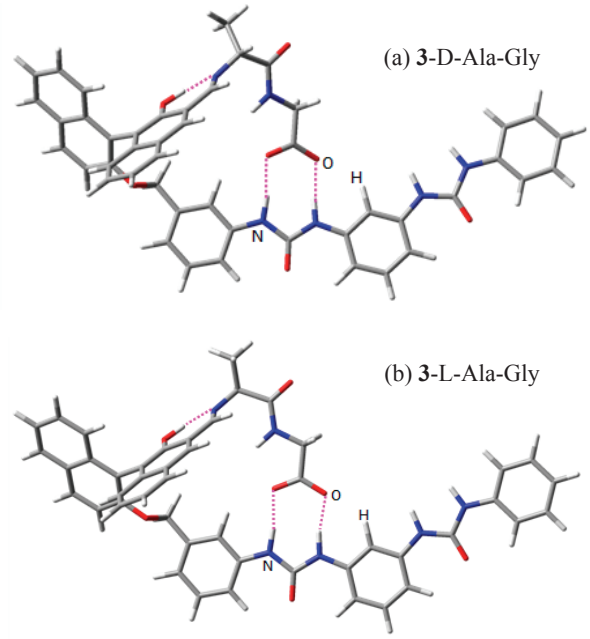


Figure 4. Energy-minimized structures for **3**-L-Ala-Gly and **3**-D-Ala-Gly at the B3LYP/6-31G* level. The pink dotted lines represent hydrogen bonding.

for CC of *N*-terminal amino acids for additional peptides such as Met-Gly, Leu-Gly and His-Gly, which are compared with those[9] of **1** in Table 1. It is rather disappointing that the stereoselectivities of **2** and **3** are in the same range with those of **1** for Ala-Gly, and even less for other peptides. As in Figure 2, the signals of OH and two NH protons appear in a very similar position for all three cases. This implies that the additional HBD's, amide for **2** and uryl group for **3**, are not involved in hydrogen bonding with the peptides. Thus we propose that the imines formed between the three aldehydes

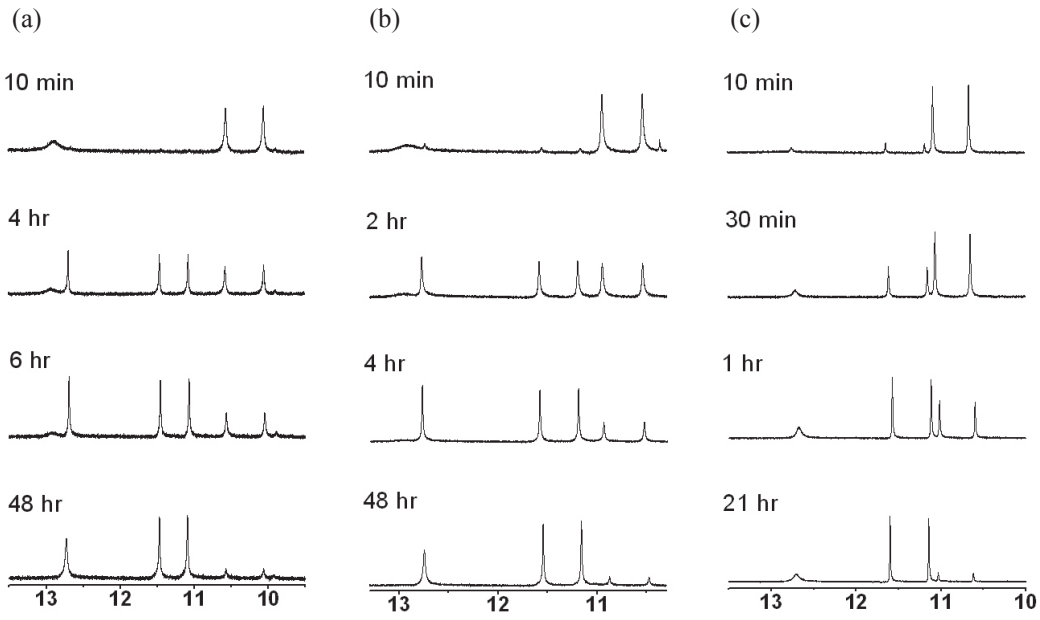


Figure 2. ^{1}H NMR spectra showing the chirality conversion of L-Ala-Gly in DMSO-d_6 containing triethylamine and (a) **3**, (b) **2** and (c) **1**. The spectra of (c) are reported ones.[7]

and the peptides in Table 1 takes the conformation shown in Figure 3 regardless of the additional R groups.

Furthermore, we have also studied the stereoselectivities of **2** and **3** for the CC of amino acids from L-form to D-form according to the reported procedures,[6a] which are compared with those[9] of **1** in Table 2. The same procedure as that of dipeptide CC is followed for the amino acids. The ^{1}H NMR spectra taken in the DMSO-d_6 solution containing **3** (20 mM), L-amino acid (20 mM) and triethylamine (80 mM) at equilibrium indicates the ratios of (D-amino acid bound imine)/(L-amino acid bound imine). The results of the stereoselectivities for the amino acids such as alanine, phenylalanine, histidine and glutamine are listed in Table 2. It indicates that the stereoselectivities of **2** and **3** are in similar range with those of **1** as that of dipeptides. In both cases of amino acid and peptides, it is clearly understood that the additional HBD's only affect the stereoselectivities through electronic effect.

The DFT calculations on 3-L-Ala-Gly and 3-D-Ala-Gly. In order to rationalize the fact that the streoselectivities of **2** and **3** are in the similar range with those of **1** for Ala-Gly and other peptides, we have employed the density functional theory (DFT) calculations to compute the relative thermodynamic stabilities of **3**-L-Ala-Gly and **3**-D-Ala-Gly. For each structure, geometry optimizations were performed at the B3LYP/6-31G* level[11] followed by the MPWB1K/6-31G*// B3LYP/6-31G* single point energy calculations[12] using Gaussian 03 package.[13] Frequency calculations were performed to verify the identity of each stationary point as a minimum. The energy-minimized structures for **3**-L-Ala-Gly and **3**-D-Ala- Gly are shown in Figure 4.

At the B3LYP/6-31G*//MPWB1K/6-31G* level, **3**-D-Ala-Gly was calculated to be 2.2 kcal/mol more stable than **3**-L-Ala-Gly. The considerable steric hindrance between the methyl group of the alanine and the imine CH moiety of the receptor seems to be the main contributing factor for the thermodynamic preference. This computational result indicates that the extra uryl group in **3** would not participate in recognizing the peptide due to its molecular orientation. It is in agreement with the experimental results that the stereoselectivities of **1**-**3** towards various peptides are very similar to each other.

Conclusions

We have designed and synthesized receptors **2** and **3**, with multiple hydrogen bond donating sites to enhance the stereoselectivities in chirality conversion of dipeptides. The stereoselectivities are in a similar range with those of the receptor **1**, which has one uryl site. The DFT calculation result provides the rational for the similar stereoselectivity ratios of receptors **1**-**3** towards various peptides that the additional uryl group in **3** does not participate in recognizing the dipeptide due to its molecular orientation.

Experimental Section

General. (*S*)-3-Formyl-2'-hydroxy-2-methoxymethoxy-[1,1']binaphthalene (**8**) and (*S*)-3-hydroxymethyl-2-methoxymethoxy-2'-(3-(3-nitrophenyluryl)-benzyloxy)-[1,1']binaphthalene (**10**) were prepared according to the previously reported procedures.[7b,10] Chemicals such as 3-nitrophenyl isocyanate, 3-aminobenzylalcohol, iron powder, ammonium chloride, acetic anhydride, phenyl isocyanate and pyridinium chlorochromate (PCC) were purchased from Aldrich and TCI Chemical Companies, and used without further purification. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. NMR spectra were recorded on a Bruker AM 250 spectrometer in $CDCl_3$, DMSO-d_6 and benzene-d_6 solutions containing tetramethylsilane as internal standard. Melting points were measured with Electrothermal IA 9000 digital melting point apparatus and are uncorrected. HRMS spectra were obtained on FAB mode. EA was determined using vario EL Elemental Analyzer. For column Chromatography, silica gel of 230-400 mesh was used.

Compound 4. 3-nitrophenyl isocyanate (2.62 ml, 16 mmol) was added to 3-aminobenzylalcohol (1.97 g, 16 mol) in THF (30 ml) and stirred. After 3hrs, the mixture was filtered and washed with chloroform and ether to give **4** (4.3 g, 94 %). mp 192 ^{o}C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.18 (s, 1H, -NH), 8.83 (s, 1H, -NH), 8.56 (s, 1H, -CH), 7.85-6.92 (m, 7H), 5.20 (t, 1H, -OH), 4.46 (d, 2H, -CH_2); ^{13}C NMR (63 MHz, DMSO-d_6) δ 152.3, 148.1, 143.3, 141.0, 139.0, 130.0, 128.4, 124.2, 120.3, 116.8, 116.5, 116.2, 112.0, 62.8.

Compound 5. Compound **4** (4.2 g, 15 mmol) was dissolved in a mixture of solvents (ethanol/dioxane/water; 1/1/1 ratio), iron powder (5.58 g, 0.1 mol) and ammonium chloride (1.44 g, 27 mmol) were added and refluxed for 15 hrs. The reaction mixture was then cooled to room temperature, filtered and extracted with MC. Silica gel column chromatography with EA and hexane (1:1) provided the compound **5** (3.1 g, 83 %). mp 167 ^{o}C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.52 (s, 1H, -NH), 8.30 (s, 1H, -NH), 7.39-6.15 (m, 8H), 5.17 (t, 1H, -OH), 5.01 (s, 2H, NH_2), 4.44 (d, 2H, -CH_2); ^{13}C NMR (63 MHz, DMSO-d_6) δ 152.8, 149.6, 7, 140.7, 140.2, 129.5, 128.9, 1, 116.7, 116.4, 108.5, 106.5, 104.1, 63.4, 31.1.

Compound 6. Acetic anhydride (0.7 ml, 7.38 mmol) was added to compound **5** (1.9 g, 7.38 mmol) in THF (80 ml). After 2 hrs, the mixture was filtered and washed with ether to give a white solid product (2.02 g, 91 %). mp 171 ^{o}C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.91 (s, 1H, -NH), 8.67 (s, 1H, -NH), 8.48 (s, 1H, -NH), 7.76-6.88 (m, 8H), 5.18 (t, 1H, -OH), 4.45 (d, 2H, -CH_2); ^{13}C NMR (63 MHz, DMSO-d_6) δ 168.8, 152.8, 143.7, 140.4, 140.2, 140.0, 129.4, 128.9, 120.3, 116.8, 116.5, 113.2, 113.0, 109.1, 63.3, 24.5.

Compound 7. Compound **6** (1 g, 3.34 mmol) was dissolved in THF(100 ml) at 50 ^{o}C and Phosphorus tribromide (0.12 ml, 1.22 mmol) was added to this solution. After 2 hrs, the product formed was filtered and washed with THF and ether to give **7** (0.85 g, 70%). mp 274 ^{o}C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.92 (s, 1H, -NH), 8.72 (s, 1H, -NH), 8.66 (s, 1H, -NH), 7.77-6.97 (m, 8H), 4.66 (d, 2H, -CH_2); ^{13}C NMR (63 MHz, DMSO-d_6) δ 168.2, 152.3, 139.9, 139.8, 139.7, 138.5, 129.0, 128.9, 122.6, 118.7, 118.0, 112.7, 108.7, 34.7, 24.0.

Compound 9. NaH (123 mg, 3.07 mmol) was added to

DMF (10 ml) under ice cooled conditions. Compound **8** (1 g, 2.79 mmol) in DMF (20 ml) was dropped to this solution. After 1 hr, compound **7** (1.01 g, 3.07 mmol) was dropped to this solution and the reaction was monitored by TLC. After 5 hr stirring, crude products were isolated from the organic layer by extraction of the reaction mixture with EA and water, dried over anhydrous $MgSO_4$. Silica gel column chromatography with EA and hexane (1:1) provided the compound **9** (1.11 g, 63 %). mp 103 ^oC; ^1H NMR (250 MHz, DMSO-d_6) δ 10.43 (s, 1H, -CHO), 9.81 (s, 1H, -NH), 8.66-6.58 (m, 21H), 5.16 (s, 2H, -OCH_2-), 4.71 (dd, 2H, uryl-CH_2), 2.82 (s, 3H, OCH_3), 2.02 (s, 3H, -$COCH_3$); ^{13}C NMR (63 MHz, DMSO-d_6) δ 191.2, 168.9, 154.1, 153.6, 152.7, 139.9, 139.5, 137.6, 136.8, 133.6, 131.0, 130.2, 130.1, 130.0, 129.1, 129.0, 128.9, 128.6, 128.0, 126.9, 126.8, 125.9, 124.8, 123.9, 120.5, 118.4, 117.8, 117.0, 115.1, 113.3, 113.2, 109.4, 100.0, 70.9, 57.0, 24.3.

Compound 2. HCl (35 %, 0.13 ml, 1.56 mmol) was added to compound **9** (1g, 1.56mmol) in ethanol (100 ml) and the solution was heated to 70 ^oC for 30 min. The solution was evaporated to dryness and the product was purified by column chromatography with a hexane and EA (2:1) to give **2** (0.76 g, 82 %) mp 193 ^oC; ^1H NMR (250 MHz, DMSO-d_6) δ 10.36 (s, 1H, -CHO), 10.32 (s, 1H, -OH), 9.98 (s, 2H, -NH), 8.75-6.68 (m, 21H), 5.20 (s, 2H, -CH_2), 2.09 (s, 3H, -$COCH_3$); ^{13}C NMR (63 MHz, DMSO-d_6) δ 197.4, 168.8, 154.5, 153.4, 152.7, 140.4, 140.2, 139.9, 138.4, 137.4, 137.1, 133.7, 130.6, 130.5, 130.2, 129.4, 129.0, 128.6, 127.6, 127.1, 124.9, 124.8, 124.5, 124.1, 123.1, 120.7, 118.1, 117.9, 117.2, 116.2, 113.2, 113.0, 109.1, 72.7, 720.5, 60.7, 24.5. HRMS (FAB) calcd for $C_{37}H_{29}N_3O_5$: 595.2107; found: 595.2210.

Compound 11. It was prepared similar to compound **5** but with compound **10.** The product is yellow liquid (0.48 g, 92 %). mp 125 ^oC; ^1H NMR (250 MHz, $CDCl_3$) δ 8.06-7.05 (m, 21H), 6.67 (t,1H), 6.4 (d, 1H), 6.17 (s, 1H), 5.32-4.80 (m, 4H, -OCH_2), 4.70 (dd, 2H, -OCH_2O), 3.25 (s, 3H, -CH_3) ^{13}C NMR (63 MHz ,$CDCl_3$) δ 148.8, 147.6, 142.0, 134.8, 134.2, 132.3, 128.9, 128.6, 128.0, 125.7, 125.0, 124.5, 124.3, 123.6, 122.9, 121.8, 121.5, 120.9, 120.3, 120.0, 115.2, 112.4, 111.0, 110.7, 104.5, 104.2, 100.7, 93.7, 65.4, 57.7, 51.7.

Compound 12. Phenyl isocyanate (0.09 ml, 0.8 mmol) was added to compound **11** (0.47 g, 0.8 mmol) in THF (80 ml). After 2 hrs the mixture was evaporated under reduced pressure. The residue was extracted with EA, dried over anhydrous sodium sulfate and evaporation under vacuum to give **12** (0.47 g, 85 %). mp 145 ^oC; ^1H NMR (250 MHz, DMSO-d_6) δ 8.68 (s, 2H, -NH), 8.58 (s, 1H, -NH), 8.48 (s, 1H, -NH), 8.08-6.64 (m, 23H), 6.64 (d, 1H, -CH), 5.36 (t, 1H, -OH), 5.16 (s, 2H, -OCH_2), 4.82 (d, 2H, -CH_2OH), 4.55 (dd, 2H, -OCH_2O-), 2.82 (s, 3H, -CH_3); ^{13}C NMR (63 MHz, DMSO-d_6) δ 153.9, 152.4, 152.2, 151.1, 140.1, 139.6, 139.5, 137.9, 135.9, 133.3, 132.3, 130.5, 129.7, 129.1, 128.8, 128.6, 128.0, 127.8, 126.6, 125.7, 125.0, 124.8, 124.5, 123.5, 121.8, 120.4, 118.6, 118.1, 117.4, 116.9, 115.1, 111.6, 107.7, 98.4, 79.1, 69.9, 64.9, 58.9, 56.0, 15.1.

Compound 13. Pyridinium chlorochromate (0.36 g, 1.69 mmol) was added to compound **12** (1 g, 1.41 mol) in MC. After stirred overnight, the mixture was filtered and extracted with EA, dried over anhydrous sodium sulfate. Silica gel column chromatography with EA and hexane 1:1 mixture provided the compound **13** (0.52 g, 51 %). mp 211 ^oC; ^1H NMR (250 MHz, DMSO-d_6) δ 10.43 (s, 1H, -CHO), 8.69 (s, 2H, -NH), 8.60-6.95 (m, 25H), 6.61 (d, 1H, -CH), 5.17 (s, 2H, -OCH_2O-) 4.71 (dd, 2H, -OCH_2), 2.83 (s, 3H, -CH_3); ^{13}C NMR (63 MHz, DMSO-d_6) δ 153.8, 152.4, 152.2, 151.1, 140.1, 139.6, 139.5, 137.9, 135.9, 136.3, 132.3, 130.5, 129.7, 129.1, 128.8, 128.6, 128.0, 128.5, 127.8, 126.6, 125.7, 125.0, 124.8, 124.5, 125.0, 124.8, 124.5, 123.5, 121.8, 120.4, 118.6, 1128.1, 117.4, 116.9, 115.1, 111.6, 107.7, 98.4, 79.1, 69.9, 64.9, 58.8, 56.0, 15.1.

Compound 3. It was prepared similar to compound **2** but with compound **13.** (0.66 g, 70 %). mp 292 oC; ^1H NMR (250 MHz, DMSO-d_6) δ 10.30 (s, 1H, -CHO), 10.22 (s,1H, -OH), 8.68 (s, 2H, -NH), 8.61-6.98 (m, 25H), 6.61 (d, 1H, -CH), 5.13 (dd, 2H, -OCH_2); 13C NMR (63 MHz, DMSO-d_6) δ 154.0, 152.8, 152.4, 152.2, 140.1, 139.6, 139.5, 137.9, 136.8, 136.6, 133.3, 130.1, 129.7, 129.0, 128.8, 128.7, 128.5, 128.1, 127.1, 126.6, 124.4, 124.3, 124.1, 123.6, 122.6, 121.7, 120.2, 118.0, 117.6, 117.3, 116.7, 115.6, 111.6, 107.7, 69.9. HRMS (FAB) calcd for $C_{42}H_{32}N_4O_5$: 672.2373; found: 672.2381.

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