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Enantioselective Recognition of Amino Alcohols and Amino Acids by Chiral Binol-Based Aldehydes with Conjugated Rings at the Hydrogen Bonding Donor Sites

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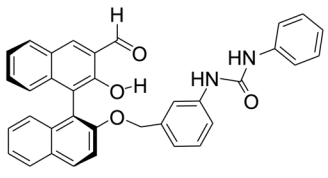
Novel binol-based uryl and guanidinium receptors having higher ring conjugation at the periphery of the hydrogen bonding donor sites have been synthesized and utilized to study the enantioselective recognition of 1,2-aminoalcohols and chirality conversion of natural amino acids via imine bond formation. There is a remarkable decrease in the stereoselectivites as the conjugation increases at the periphery of hydrogen bonding donor sites. The guanidinium-based receptors show more selectivity towards the amino alcohol than that of the uryl based ones due to its charge reinforced hydrogen bonds. The conversion efficiency of L-amino acids to D-amino acids by the uryl-based receptors is higher than that of the guanidinium-based ones.

Key Words : Chiral aldehyde, Chirality conversion, Enantioselective imine formation, Amino alcohols, Amino acids

Introduction

The exploration of stereoselective receptors, based on simple organic molecules, for chiral 1,2-aminoalcohols[1] and amino acids[2] is of great interest, as their structural motifs are found in many common drugs, chiral auxiliaries, and asymmetric catalysts.[3] The compounds **1**[4] and **2**[5] are binol-based aldehydes which bind enantioselectively amino acids and amino alcohols *via* reversible imine bond formation. The enantioselectivities arose due to the difference in steric hindrance around the imine bonds formed by enantiomeric amine couples (substrates) with the aldehydes (receptors).



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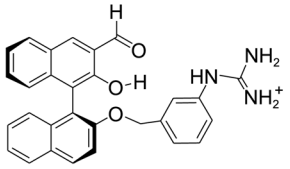

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The compound **1** is effective as Chirality Conversion Reagent (CCR), converting L-amino acids to D-amino acids, and **2** shows high stereoselectivity toward amino alcohols due to its charge-reinforced hydrogen bonding. The stereoselectivities are strongly associated with the hydrogen bonding power between Hydrogen Bonding Donors (HBDs) such as uryl and guanidinium groups at the receptors and carboxylate/hydroxy groups at the substrates. In efforts to acquire more effective enantiomeric selectivities, we modified the receptor's HBD to pyrroles, diuryls etc., which brought about versatile enantioselectivities for aminoalcohols and peptides besides amino acids.[6-10]

In this context, we tried to introduce conjugated ring systems at the periphery of the uryl and guanidium groups as shown in Figure 1 to alter the strength of the hydrogen bonding and to study its effect on the stereoselectivities of amine substrates. Here we report the detailed syntheses of new binol-based aldehydes with ring conjugated systems along with comparison of receptors **1**-**6** for their stereoselectivities to amino alcohols and amino acids as CCRs.

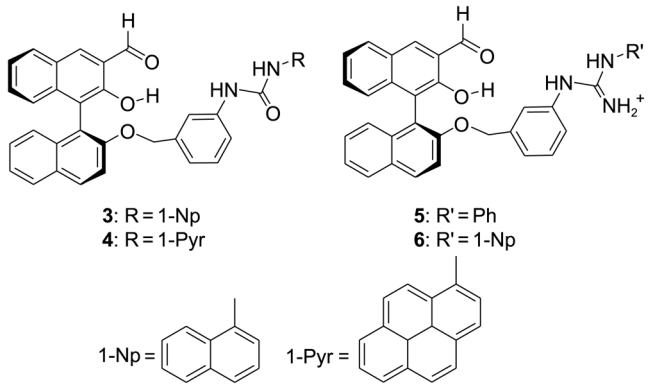
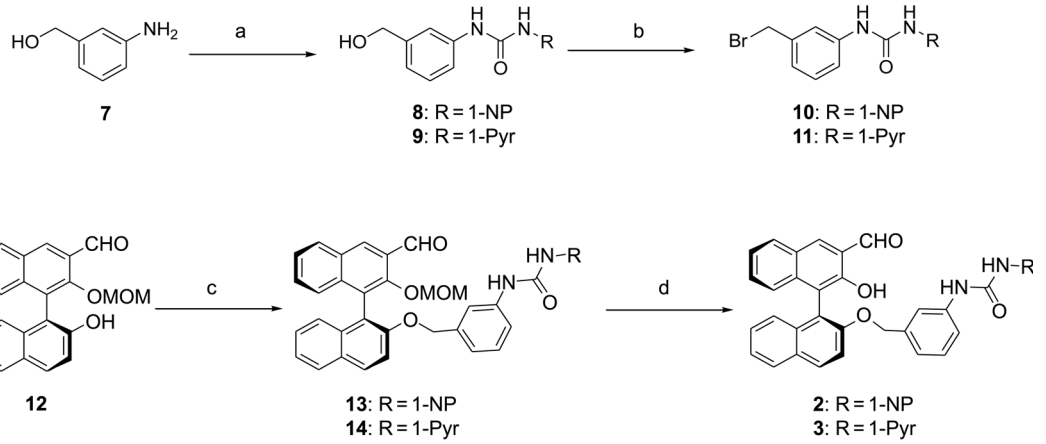


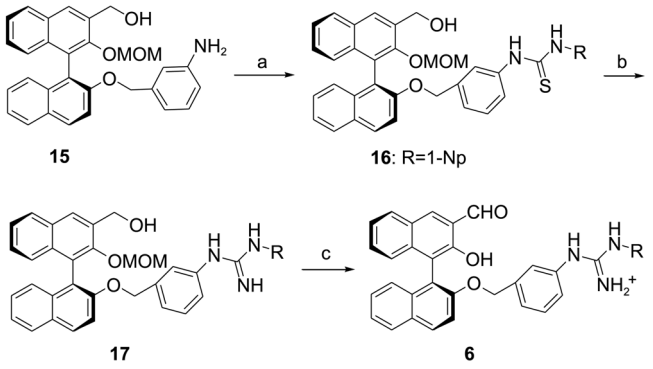
Figure 1. Compounds **3**-**6**. The synthesis of compound **5** and its enantioselectivity to amino acids were reported in the literature.[8]

Results and Discussion

Binol receptors **3** and **4** were synthesized according to Scheme 1 following the method to synthesize **1**.[4c] Respective substituted isocyanates and 3-aminobenzyl alcohol **7** were reacted in THF to form the substituted uryl-benzyl alcohols, which on further treatment with phosphorous tribromide gave substituted uryl-benzyl bromides **8** and **9**. Addition of these respective bromides to mono methoxymethyl (MOM) protected binol aldehyde **12** in DMF under



Scheme 1. Reagents and Conditions: (a) isocyanates, THF, rt, 5 h; (b) PBr_3, THF, rt, 2 h; (c) NaH, DMF, rt, 12 h; (d) conc. HCl, EtOH, reflux, 0.5 h.



Scheme 2. Reagents and Conditions: (a) THF, naphthalene-1-isothiocyanate, rt, 5 h; (b) mercuric chloride, liq. ammonia, EtOH, rt, 2 h (c) i. PCC, CH_2Cl_2, rt, 1-5 h, ii. conc. HCl, EtOH, reflux, 0.5 h.

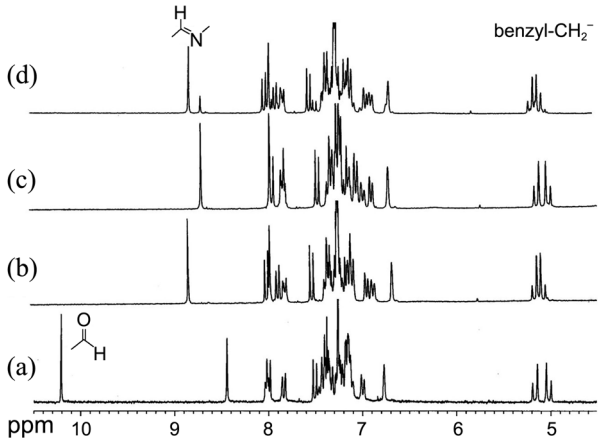


Figure 2. Partial ^{1}H-NMR spectra in $CDCl_3$ of (a) **5**, (b) **5**-R-ap, (c) **5**-S-ap and (d) mixture of **5**-S-ap and **5**-R-ap formed from addition of 2 equiv. of racemic *ap* to **5**.

the presence of sodium hydride led to the formation of the MOM protected uryl-based binols **13** and **14** in good yields, which upon hydrolysis under acidic condition gave the optically pure substituted uryl-based binol receptors **3** and **4** in quantitative yield.

Receptor **6** was synthesized following the procedures described in Scheme 2 which was used to synthesize **5**.[8] The binol amine **15** was reacted with naphthyl-1-isothiocyanate in tetrahydrofuran to obtain the corresponding MOM-protected alcohols **16** in good yield. Treatment of compounds **16** with mercuric chloride and liquor ammonia in ethanol yielded the guanidinum based compound **17**, which on pyridinium chlorochromate (PCC) oxidation in methylene chloride and upon hydrolysis under acidic condition gave the optically pure phenyl and naphthalene based guanidinium binol receptor **6** respectively. All the final compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS, which are in good agreement with the presented structures. All the receptors are freely soluble in solvents such as DMSO, $CHCl_3$ and benzene.

We have studied enantioselectivities of **3**-**6** toward amino alcohols by ^{1}H NMR in $CDCl_3$ following the protocols reported previously.[4a,5] As a representative, Figure 2 shows partial ^{1}H NMR spectra demonstrating the stereoselective imine formation of **5** with 2-aminopropanol (*ap*). Figure 2(a) indicates the ^{1}H NMR spectrum of **5** in $CDCl_3$, where the peak at 10.20 is due to -CHO and the doublet of doublet centered at 5.10 is due to the diastereotopic benzylic CH_2. The addition of (*S*)-*ap* to the $CDCl_3$ solution of **5** results in complete formation of the imine, **5**-S-ap, within minutes. This can be clearly noted by the appearance of the imine proton peak at 8.85 ppm and the disappearance of the aldehyde peak (Fig. 2b). Similarly, but in different position, the imine proton peak of **5**-R-ap appears at 8.75 ppm on addition of (*R*)-*ap* (Fig. 2c). A noticeable discrimination between **5**-S-ap and **5**-R-ap is observed on diastereotopic benzylic -CH_2- signals; more prominent doublet of doublet splitting pattern for **5**-R-ap centered at 5.08 ppm is observed. This implies that **5**-R-ap is more rigid than **5**-S-ap, i.e., stronger hydrogen bonding interaction is assumed for **5**-R-ap between alcoholic -OH and guanidinium moiety. Figure 2d shows the ^{1}H NMR spectrum for a mixture of **5**-R-ap and **5**-S-ap formed by the addition of 2 equiv of racemic *ap* to the $CDCl_3$ solution of **5**. The ratio of **5**-R-ap and **5**-S-ap is conveniently obtained from the signals of the sharp singlet imine peaks. Integration of the two peaks provides the ratio

Table 1. Stereoselective imine formation (K_R/K_S) between the receptors and amino alcohols as determined by ^{1}H NMR in $CDCl_3$

Amino alcohols	Uryl-based			Guanidinium-based		
	1[a]	**3**	**4**	**2**[b]	**5**	**6**
Ap	3.7	2.7	1.1	11	7.4	3.6
Ab	3.1	2.1	1.0	15	9.0	3.5
App	3.7	1.6	1.1	8.3	4.0	4.1
Ape	4.8	3.4	1.2	9.8	11.1	3.7
Amb	–	2.8	1.0	12	9.2	2.7
Amp	–	2.0	1.2	7.4	10.2	2.5

[a]Data from reference 4a. [b]Data from reference 5.

of **5**-R-ap/**5**-S-ap as 2.5:1 at equilibrium. The same ratio has been obtained when either (*R*)-*ap* was added to **5**-S-ap or (*S*)-*ap* was added to **5**-R-ap. These indicate that the imine formation is a reversible thermodynamic process, and the imine formation constant for **5**-R-ap (K_R) is larger than that for **5**-S-ap (K_S) by a factor of $2.72^2 = 7.4$.[4a,5]

The stereoselectivities of imine formation (K_R/K_S) between the receptors **1**-**6** and six representative 1,2-amino alcohols, 2-aminopropanol (*ap*), 2-amino-1-butanol (*ab*), 2-amino-3-phenyl-1-propanol (*app*), 2-amino-2-phenylethanol (*ape*), 2-amino-3-methyl-1-butanol (*amb*) and 2-amino-4-methyl-1-pentanol (*amp*) have been obtained following the above mentioned protocol. The results are tabulated in Table 1. In general, the stereoselectivities of guanidinium-based receptors are higher than those of the uryl-based ones, which is due to the charge reinforced hydrogen bonding between the guanidinium group and the amino alcohols.[5] Another noticeable point is that, as the conjugation increases at the periphery of the uryl and guanidinium groups, the stereoselectivities tend to decrease.

In addition, we have also studied the receptor's efficiency as CCR of amino acids from L-form to D-form. In nature, L-amino acids are converted to D-amino acids by pyridoxal phosphate (PLP) dependent enzymes that racemize amino acids.[11] These receptors **1**-**6** are chiral analogues of PLP.

The receptor's efficiency as CCR was determined by the diastereomeric ratio, (D-amino acid bound imine)/(L-amino acid bound imine), at equilibrium in the presence of base triethylamine and amino acids in DMSO-d_6. The detailed measurement methods are described in the literatures.[4b,4c] Table 2 compares the diastereomeric ratios of all the receptors **1**-**6** for representative eight amino acids, Leucine (Leu), Histidine (His), Tyrosine (Tyr), Phenyl Alanine (Phe), Serine (Ser), Glutamine (Glu), Asparagine (Asp), and Alanine (Ala), where those of **1**,[4b] **2**[8] and **5**[8] are quoted from the literatures.

The diastereomeric ratios of guanidinium-based receptors show decreased stereoselectivities compared to the uryl-based ones, which is probably due to the presence of triethylamine which decreases the cationic charge of the guanidiniums. The ratios also decrease as the number of conjugated rings increase at the periphery of HBD sites, which is a similar trend with the stereoselectivities of the same receptors for amino alcohols in Table 1.

Table 2. The diastereomeric ratio, (D-amino acid imine)/(L-amino acid imine), determined by ^{1}H-NMR in DMSO-d_6 at equilibrium

Amino acids	Uryl-based			Guanidinium-based		
	1[a]	**3**	**4**	**2**[b]	**5**[b]	**6**
Leu	9.0	3.8	2.4	5.5	2.6	3.1
His	13.0	8.0	11.0	9.6	3.0	3.9
Tyr	14.0	7.6	9.1	10.0	3.2	4.1
Phe	12.0	8.1	4.8	7.4	2.2	3.3
Ser	11.0	6.9	6.7	8.0	2.2	3.0
Glu	7.0	9.0	7.0	5.9	3.3	3.4
Asp	15.0	10.0	7.7	11.0	2.9	2.7
Ala	11.0	5.3	7.7	5.6	1.9	3.0

[a]Data from reference 4b. [b]Data from reference 8.

Conclusion

The enantioselective recognition of 1,2-aminoalcohols and chirality conversion of natural amino acids have been studied using uryl- and guanidinium-based chiral receptors with conjugated aromatic rings at the periphery of the HBD sites. The remarkable decrease in the stereoselectivites for the amino alcohols and amino acids on the increase of the conjugation numbers reveals that the change of electronic and steric environments around the HBD sites influences significantly on the stereoselectivities.

Experimental

General. Compounds **5**,[8] **12**[4c] and **15**[5] were prepared according to the literature procedures. Pyrene-1-isocyanate was prepared from 1-aminopyrene and triphosgene according to the literature method.[12] All other chemicals were commercially available and used without further purifications. The solvents for dry reactions were dried with appropriate desiccants and distilled prior to use. NMR spectra were recorded on a BrukerAM 250 spectrometer in $CDCl_3$ and DMSO-d_6 solutions containing tetramethylsilane as internal standard. Chemical shifts are reported in δ unit. Melting points were measured with Electrothermal IA 9000 digital melting point apparatus and are uncorrected. HRMS spectra were obtained on ESI. For column Chromatography silica gel of 230-400 mesh was used.

Compound 8: To a solution of 3-aminobenzyl alcohol **7** (0.500 g, 4.00 mmol) in THF (20 mL), naphthalene-1-isocyanate (0.60 mL, 4.00 mmol) was added and stirred at ambient temperature for 5 h. Evaporation of the solvent and addition of diethyl ether gave a white precipitate, which is filtered and dried in vacuum to obtain 1.16 g of 3-(naphthalene-1-uryl)benzyl alcohol **8**. Yield: 98%; mp 228 °C; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.11 (s, 1H), 8.73 (s, 1H), 8.12-6.90 (m, 11H), 5.21 (t, 1H), 4.48 (m, 2H).

Compound 9: It was prepared similar to **8** but with pyrene-1-isocyanate and stirred for 4 h to give 3-(pyrene-1-uryl)benzyl alcohol **9**. Yield: 88%; mp 222 °C; ^{1}H NMR (DMSO, 250 MHz) δ 9.17 (s, 1H), 9.16 (s, 1H), 8.12-6.90 (m, 13H), 4.49 (m, 2H).

Compound 10: Phosphorus tribromide (0.11 mL, 0.93 mmol) was added to slurry 3-(naphthalene-1-uryl)benzyl alcohol **8** (0.900 g, 3.10 mmol) in THF (40 mL) and allowed to stir at room temperature for 2 h. After evaporation of the solvent, the residue is washed with diethyl ether several times to give 0.63 g product as a white solid 3-(naphthalene-1-uryl)benzyl bromide **10**. Yield: 57%; mp 204 °C; ^{1}H NMR (DMSO, 250 MHz) δ 9.12 (s, 1H), 8.76 (s, 1H), 8.11-7.03 (m, 11H), 4.71 (m, 2H).

Compound 11: It was prepared similar to **10** but with 3-(pyrene-1-uryl)benzyl alcohol **9** and stirred overnight to give 3-(pyrene-1-uryl)benzyl bromide **12**. Yield: 85%; mp 202 °C; ^{1}H NMR (DMSO, 250 MHz) δ 9.22 (s, 1H), 9.19 (s, 1H), 8.61-7.06 (m, 13H), 4.70 (m, 2H).

Compound 13: To an ice cooled solution of (S)-2-methoxymethoxy-2'-hydroxy-1,1'-binaphthalene-3-carboxaldehyde **12** (0.200 g, 0.6 mmol) in 15 mL of DMF was added NaH (0.030 g, 0.90 mmol). After stirring for a while, 3-(naphthalene-1-uryl)benzyl bromide (0.200 g, 0.60 mmol) was added and the resulting mixture was stirred overnight at ambient temperature. After the reaction completed (monitored by TLC), water was added to quench the reaction. Extraction with ethylacetate, and silica column chromatography with EA/hexane (1:3, v/v) as eluent gave 0.260 g of **15**. Yield: 74%; mp 68 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.84 (s, 1H, -CHO), 8.77 (s, 1H), 7.91 (d, 2H), 7.87-6.88 (m, 20H), 6.74 (d, 1H), 4.92-4.86 (dd, 2H), 4.63 (m, 2H), 2.7 (s, 3H). ^{13}C NMR ($CDCl_3$, 63 MHz) δ 196.88, 155.83, 153.93, 138.57, 137.93, 138.92, 138.82, 133.30, 132.98, 130.33, 130.12, 129.46, 128.92, 128.69, 128.19, 127.20, 126.93, 126.68, 125.92, 125.53, 125.26, 124.76, 124.27, 124.01, 121.05, 121.42, 119.21, 71.69, 61.69, 56.24.

Compound 14: It was prepared similar to **13** but with 3-(pyrene-1-uryl)benzyl bromide. Yield: 53%; mp 129 °C; ^{1}H NMR (DMSO, 250 MHz) δ 10.44 (s, 1H, -CHO), 9.18 (s, 1H), 9.00 (s, 1H), 8.59 (d, 2H), 8.30-7.00 (m, 21H), 6.69 (d, 1H), 5.20 (m, 2H), 4.75-4.67 (m, 2H), 2.83 (s, 3H); ^{13}C NMR (DMSO, 63 MHz) δ 197.39, 155.63, 153.52, 138.93, 137.52, 134.67, 131.93, 130.55, 130.73, 129.92, 129.83, 128.65, 127.39, 127.14, 126.96, 126.39, 126.13, 124.41, 124.76, 121.58, 119.43, 118.46, 71.35, 61.29, 57.63.

Compound 16: A mixture of binol amine **15** (0.500 g, 1.10 mmol) and naphthalene-1-isothiocyanate (0.2 mL, 1.1 mmol) was dissolved in methylene chloride (15 mL) and stirred overnight at room temperature. Evaporation of the solvent and silica gel column chromatography with EA and hexane 1:2 mixture afforded 0.540 g of the desired product **16**. Yield: 59%; mp 70 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.3 (d, 2H), 7.99-7.93 (m, 4H), 7.71-7.14 (m, 18H), 6.62 (d, 1H), 6.62 (s, 1H), 5.04-4.99 (m, 2H), 4.98-4.48 (dd, 2H), 4.44 (m, 2H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 180.69, 153.85, 153.54, 152.93, 138.67, 137.12, 137.52, 134.23, 133.65, 133.89, 131.16, 130.66, 129.71, 129.43, 129.10, 128.80, 128. 46, 128.07, 126.31, 126. 82, 125.76, 125.53, 125.24, 125.06, 124.56, 124.81, 124.73, 121.28, 114.65, 100.47, 71.61, 60.89, 57.14.

Compound 17: To thio compound **16** (1.4 g, 2.30 mmol) taken in ethanol, mercuric chloride (0.74 g, 2.8 mmol) and 2 mL of ammonium hydroxide solution are added. The resulting solution was stirred for 2 h and after filtration, evaporation of the solvent yielded 0.47 g of **21**. Yield: 91%; mp 92 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.98-7.72 (m, 4H), 7.48-6.12 (m, 18H), 6.81 (d, 2H), 6.47 (s, 1H), 4.82-4.37 (m, 4H), 4.32 (dd, 2H), 2.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 155.41, 153.85, 152.32, 139.65, 134.29, 134.63, 133.93, 133.87, 130.73, 130.39, 130.24, 129.92, 129.46, 128.82, 128.30, 128.01, 127.76, 127.28, 126.83, 125.81, 125.64, 125.55, 125.37, 124.39, 124.02, 122.24, 116.36, 100.25, 71.24, 62.35, 57.02.

Compound 3: MOM protected compound **13** (0.600 g, 0.9 mmol) taken in ethanol and conc. hydrochloric acid (0.17 mL, 1.8 mmol) was mixed and refluxed for 30 minutes. The solvent was evaporated and washed with EA several times and finally recrystallized from ethanol to afford the desired product **2** in quantitative yield. mp 84 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.48 (s, 1H, -CHO), 10.00 (s, 1H), 8.05 (s, 1H), 7.94 (d, 2H), 7.92-6.70 (m, 20H), 6.34 (d, 1H), 5.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) 196.88, 154.03, 153.25, 138.22, 137.99, 138.88, 138.80, 133.54, 130.30, 130.09, 129.64, 128.92, 128.20, 126.63, 126.38, 125.78, 125.32, 124.83, 124.17, 121.96, 121.52, 118.21, 70.79; $[\alpha]_D = -75$ ($CHCl_3$); HRMS (ESI) calcd for $C_{39}H_{28}N_2O_4$: 588.2049; found: 588.2038.

Compound 4: It was prepared similar to receptor **2** but with compound **14**. mp 148 °C; ^{1}H NMR (DMSO, 250 MHz) δ 10.88 (s, 1H, -CHO), 10.30 (s, 1H), 9.19 (s, 1H), 9.07 (s, 1H), 8.63 (d, 2H), 8.61-6.64 (m, 20H), 5.16 (m, 2H); ^{13}C NMR (DMSO, 63 MHz) δ 196.86, 154.03, 152.82, 138.06, 136.90, 133.25, 132.99, 131.05, 130.53, 129.98, 129.70, 128.89, 127.32, 127.10, 126.90, 126.52, 126.33, 125.28, 124.44, 121.04, 119.96, 117.48, 70.02; $[\alpha]_D = -69$ ($CHCl_3$); HRMS (ESI) calcd for $C_{45}H_{30}N_2O_4$: 662.2206; found: 662.6198.

Compound 6: A mixture of **17** (0.300 g, 0.47 mmol) and pyridinium chlorochromate (PCC) (0.16 g, 0.70 mmol) was dissolved in methylene chloride and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate is evaporated. The crude residue was refluxed in ethanol with conc. hydrochloric acid (0.05 mL, 0.35 mmol) for 30 minutes. The solvent was evaporated and the silica gel column chromatography with EA:MeOH (97:3) as eluent afforded the desired product **6**. Yield: 0.22g (73%); mp 102 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.10 (s, 1H, -CHO), 8.17 (s, 1H), 8.02 (d, 2H), 7.91-7.12 (m, 17H), 6.74 (d, 1H), 5.09-5.00 (dd, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 191.78, 148.42, 147.97, 133.66, 132.80, 132.54, 128.22, 125.15, 124.90, 124.51, 124.34, 123.04, 122.79, 122.21, 121.50, 120.61, 119.99, 119.62, 119.03, 118.89, 116.61, 113.8, 110.87, 65.76; $[\alpha]_D = -64$ ($CHCl_3$); HRMS (ESI) calcd for $C_{39}H_{29}N_3O_3$: 587.2209; found: 587.2201.

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