Stereoselective Recognition of Amino Alcohols and Amino Acids by Carbonylurea- and Carbonyguanidinium-based Imine Receptors

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Received July 30, 2009, Accepted October 14, 2009

New receptors **1-3** that bind stereoselectively amino alcohols and convert chirality of amino acids via imine bond formation were synthesized. The receptors have uryl (**1**), thiouryl (**2**) and guanidinium (**3**) groups all with additional phenylcarbonyl motifs, which are effective hydrogen bonding donors and play a key role in the stereoselective recognitions. The stereoselectivities were measured from the integration of ^{1}H NMR peaks. Compound **1** and **2** showed the stereoselectivities for the imine formation with amino alcohols (K_R/K_S) in the range of 2 ~ 4, and compound **3** in the range of 4 ~ 8. Chirality conversion efficiencies of **1-3** for amino acids, i.e. D/L ratio at equilibrium, are in the range of 1.5 ~ 5.6, showing a little higher efficiency with **3**. The additional phenylcarbonyl motifs in **1-3** were revealed not to contribute to significant enhancement of the selectivities.
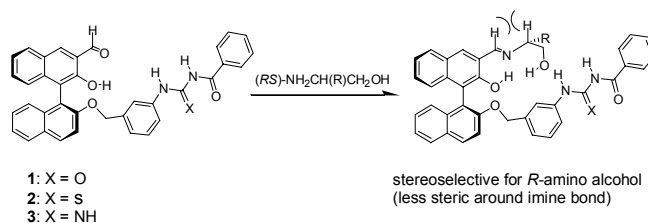
Key Words: Stereoselective recognition, Imine receptor, Chirality conversion, Amino alcohol, Amino acid

Introduction

Molecular recognition, especially chiral recognition, is one of the significant processes for diverse chemical and biological phenomena. The study of synthetic modeling systems for chiral recognition of amino alcohols,[1] amino acids[2] and amines[3] is an area of ever increasing research activity.[4] Although much progress has been made, it remains a challenge to develop highly stereoselective receptors for these substrates based on simple organic molecules.

We have developed a simple organic receptor with a uryl pending group that enantioselectively binds an amino acid and converts L-amino acid to D-amino acid.[5,6] The receptor binds the substrate *via* imine bond which is well known to be reversible.[7] Resonance Assisted Hydrogen Bonding (RAHB)[8] stabilizes the imine bond formed between the aldehyde of the receptor and amino group of the substrate. The uryl group in the receptor binds carboxylate group of the substrate by another hydrogen bonding. The complementarity and directionality of those hydrogen bondings contribute substantially to the enantioselectivity. Hence we modified the uryl group to provide efficient hydrogen bonding. The modified receptors contain guanidinium, pyrrole, imidazolium and diuryl groups instead of the uryl group, which demonstrated high enantioselectivities for aminoalcohols and peptides besides amino acids.[9-12] Furthermore, these receptors are efficient chiral selectors that are useful in an extractive resolution process which is an industrially cost-effective and time-saving one.[9,11,13]

In this context, we designed new receptors **1-3** based on uryl, thiouryl and guanidinium groups with additional phenylcarbonyl motif (Scheme 1). The carbonyl group provides the additional hydrogen bonding acceptor site and modify the hydrogen bonding donor capability of the uryl or guanidinyl group by electronic effect. Here we report the synthesis and enantioselectivities of those receptors for amino alcohols and amino acids.
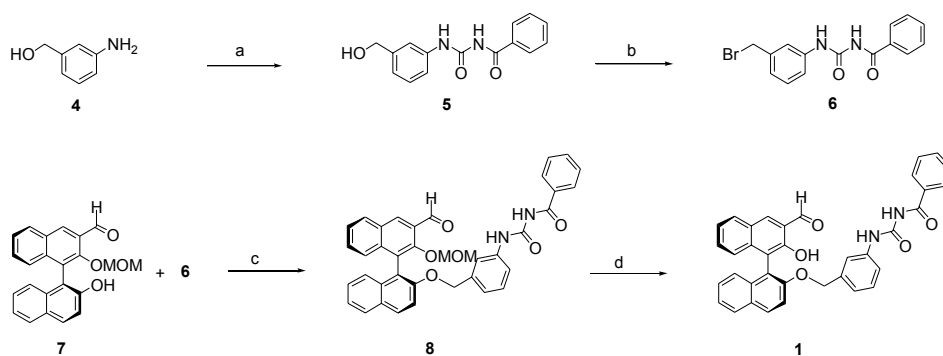

1: X = O
2: X = S
3: X = NH

stereoselective for *R*-amino alcohol
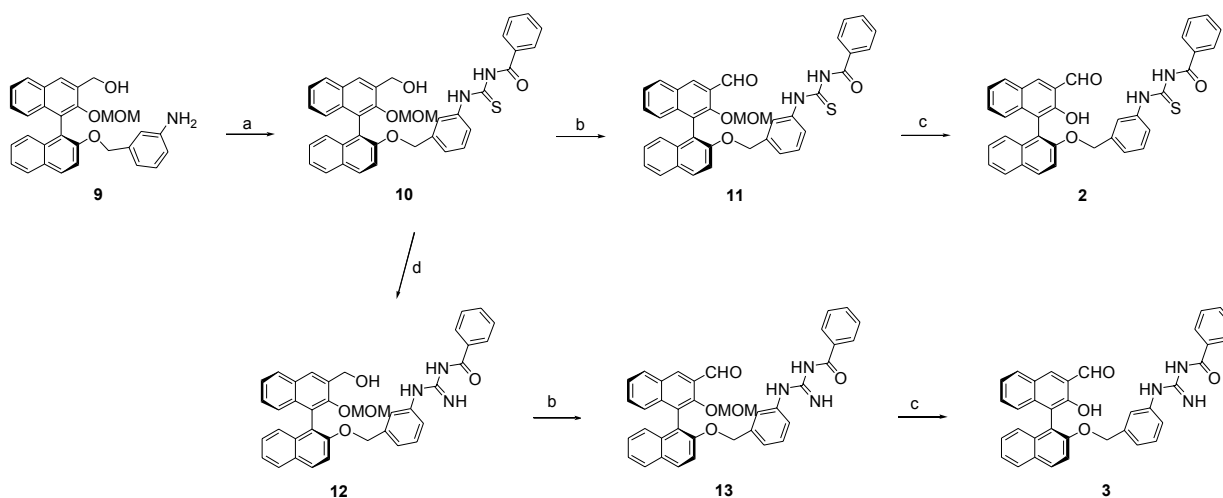(less steric around imine bond)

Scheme 1

Results and Discussion

Compound **1** was synthesized according to Scheme 2. Benzoyl isocyanate and 3-aminobenzyl alcohol **4** were reacted in THF to form 3-benzoyluryl-benzyl alcohol **5**, which on further treatment with phosphorous tribromide gave 3-benzoyluryl-benzyl bromide **6**. Addition of **6** to mono methoxymethyl (MOM) protected binol aldehyde **7**[6a] in DMF under the presence of sodium hydride led to the formation of the MOM protected benzoyluryl-based binol **8** in 82% yield, which upon hydrolysis under acidic condition gave the optically pure benzoyluryl-based binol receptor **1** in quantitative yield.

Unlike compound **1**, compound **2** was synthesized following the procedures described in Scheme 3, because 3-benzoylthiouryl-benzyl alcohol on treatment with PBr$_3$ yields a mixture of compounds which decomposes so rapidly and cannot be isolated as pure form nor reacted directly with mono-MOM-protected binol aldehyde. The binol amine **9**[9] was reacted with benzoyl isothiocyanate in tetrahydrofuran to obtain the corresponding MOM-protected alcohol **10** in good yield. The alcohol **10** was treated with pyridinium chlorochromate (PCC) in methylene chloride and upon hydrolysis under acidic conditions gave the optically pure thiouryl-based binol receptor **2**. Compound **3** was synthesized starting from compound **10** as shown in Scheme 3. Treatment of compound **10** with mercuric chloride and liquor ammonia in ethanol yielded the guanidinium based com-

Scheme 2. Reagents and Conditions: (a) Benzoyl isocyanate, THF, rt, 5 h; (b) PBr₃, THF, rt, 2 h; (c) NaH, DMF, rt, 12 h; (d) conc.HCl, EtOH, reflux, 0.5 h.

Scheme 3. Reagents and Conditions: (a) THF, benzoylisothiocyanate, rt, 5 h; (b) PCC, CH₂Cl₂, rt, 1 - 5 h; (c) conc. HCl, EtOH, reflux, 0.5 h; (d) mercuric chloride, liq. Ammonia, EtOH, rt, 2 h

pound **12**, which on PCC oxidation and acid hydrolysis produced the final receptor **3**.

The final compounds **1-3** were confirmed by ¹H NMR, ¹³C NMR and HRMS, which are in good agreement with the presented structures. All the receptors are freely soluble in solvents such as DMSO, CHCl₃ and benzene.

Figure 1 shows the stereoselective imine formation of the receptor **3** for 2-aminopropanol (*ap*) as a representative. Figure 1a indicates the ¹H NMR spectrum for **3** in CDCl₃, where the peak at 10.19 is due to -CHO and the doublet of doublet centered at 5.10 is due to the diastereotopic benzylic CH₂. The addition of (*S*)-*ap* to the CDCl₃ solution of **3** results in complete formation of the imine, **3**-S-ap, within minutes. This can be clearly noted by the appearance of the imine proton peak at 8.68 ppm and the disappearance of the aldehyde peak (Fig. 1b). Similarly, upon addition of (*R*)-*ap*, the imine proton peak of **3**-R-ap appears at different position at 8.62 ppm (Fig. 1c). A noticeable discrimination between **3**-S-ap and **3**-R-ap is observed on diastereotopic benzylic -CH₂- signals; more prominent doublet of doublet splitting pattern for **3**-R-ap centered at 5.15 ppm is observed. This implies that **3**-R-ap is more rigid than **3**-S-ap, i.e., stronger hydrogen bonding interaction is assumed for **3**-R-ap between alcoholic -OH and guanidinium moiety. Figure 1d shows the ¹H

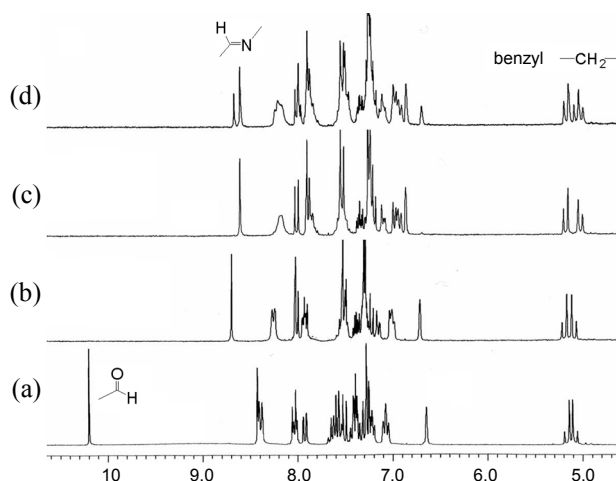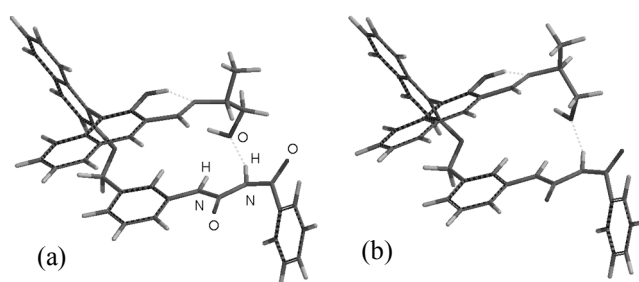**Figure 1.** Partial ¹H NMR spectra in CDCl₃ of (a) **3**, (b) **3**-S-ap, (c) **3**-R-ap, and (d) mixture of **3**-S-ap and **3**-R-ap formed by the addition of 2 equiv of racemic *ap* to **3**.

NMR spectrum for a mixture of **3**-R-ap and **3**-S-ap formed by the addition of 2 equiv of racemic *ap* to the CDCl₃ solution of **3**. The ratio of **3**-R-ap and **3**-S-ap is conveniently obtained from

Table 1. The stereoselectivities (K_R/K_S) for the imine formation of receptors **1-3**

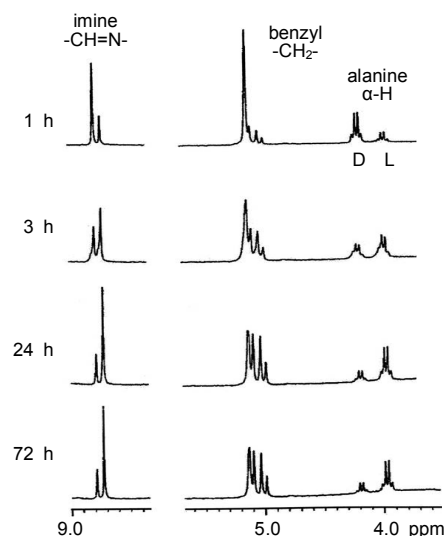| Amines	K_R/K_S		
	1	**2**	**3**
methylbenzylamine	1.00	1.00	1.00
2-amino-1-propanol	3.31	2.25	6.25
2-amino-1-butanol	2.82	2.31	5.06
Valinol	3.17	2.00	4.56
Phenylalaninol	4.12	3.06	7.29
Phenylglycinol	2.53	2.07	8.48
Leucinol	2.89	2.28	4.89

Figure 2. Energy-minimized structure of **3**-R-ap (a) and **3**-S-ap (b) calculated by Molecular Mechanics.

the signals of the sharp singlet imine peaks. Integration of the two peaks provides the ratio of **3**-R-ap/**3**-S-ap as 2.5:1 at equilibrium. The same ratio has been obtained when either (R)-*ap* was added to **3**-S-ap or (S)-*ap* was added to **3**-R-ap. These indicate that the imine formation is a reversible thermodynamic process, and the imine formation constant for **3**-R-ap (K_R) is larger than that for **3**-S-ap (K_S) by a factor of $2.5^2 = 6.25$.[14]

We have compared the stereoselectivities (K_R/K_S) for the imine formation between receptors **1-3** and six representative aminoalcohols, 2-aminopropanol, 2-amino-1-butanol, 2-amino-3-methyl-1-butanol (valinol), 2-amino-3-phenyl-1-propanol (phenylalaninol), 2-amino-2-phenylethanol (phenylglycinol), and 2-amino-4-methyl-1-pentanol (leucinol) following the above mentioned protocol.

Table 1 lists the values of K_R/K_S for six amino alcohols, which shows that the binol based receptors **1-3** bind all the amino alcohols with the same sense of stereoselectivity. The stereoselectivities of **1** and **2** are similar or slightly less than those of the previously reported uryl-based binol receptor. Those of **3** show higher values compared to **1** and **2**, however, they are similar or slightly less than those of the previously reported guanidinium-based binol receptor.[9] These guanidinium-based receptors have better selectivities due to the charge reinforced hydrogen bonding.[9,11]

Figure 2 illustrates energy-minimized structure of imines **3**-R-ap and **3**-S-ap which are calculated by Molecular Mechanics with Spartan Program.[15] Notable difference is the steric repulsion between imine proton and methyl group on *ap*. The repulsion of **3**-R-ap is less than that of **3**-S-ap, which is a key origin of the stereoselectivity as proposed in our previous works.

Figure 3. Time-dependent ^{1}H NMR of **3**-L-Ala in DMSO-d_6 in the presence of 4 equiv TEA.

Table 2. L to D conversion efficiency of the receptors for amino acid

Amines	D/L ratio		
	1	**2**	**3**
Ala	2.51	1.80	3.32
Gln	2.48	2.58	5.56
His	2.90	1.82	3.85
Phe	1.53	3.12	3.45
Ser	1.96	2.32	4.77
Tyr	2.68	2.86	4.83

Benzoyl carbonyl group seems not to be involved in the hydrogen bonding with alcoholic OH group of *ap*. Thus the additional carbonyl group did not contribute to enhancement of the selectivity.

Furthermore, we have also studied the receptor activities for the conversion efficiency of amino acids from L-form to D-form. In nature, L-amino acids are racemized by pyridoxal phosphate (PLP) dependent enzymes.[16] 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.[17] The receptors of this work form Schiff base like PLP, however, deracemize the bound amino acids unlike PLP due to the chirality of binol.

Partial ^{1}H NMR spectra in Figure 3 demonstrate the chirality conversion of **3**-L-Ala (the imine formed between **3** and L-Alanine) to **3**-D-Ala in the presence of triethylamine in DMSO-d_6. The imine CH signals are conveniently monitored as it is free from other signals. The singlet peak at 8.78 ppm assigned to the imine CH proton of **3**-L-Ala decreases, and the singlet peak at 8.72 ppm ascribed to the imine CH of **3**-D-Ala increases concomitantly. Besides imine -CH peak, benzyl -CH₂- peaks centered at 5.12 for **3**-L-Ala and 5.07 ppm for **3**-D-Ala, and alanine α proton peaks centered at 4.15 for **3**-L-Ala and 3.95 ppm for **3**-D-Ala are also helpful to determine the chirality conversion. The intensities of the peaks reach the equilibrium at ~

48 h. The stereoselectivity, which is defined by the ratio of (**3**-D-Ala)/(**3**-L-Ala), is measured by the integration of the corresponding signals.

Table 2 compares the stereoselectivities of the receptors **1-3** for representative six amino acids, alanine (Ala), Glutamine (Gln), histidine (His), phenyl alanine (Phe), serine (Ser) and tyrosine (Tyr).The stereoselectivities show a similar pattern with those of the amino alcohol case. While all the receptors show similar efficiencies, receptor **3** exhibits better efficiency. The selectivities are not satisfactory compared to those of our previously developed receptors.

Conclusions

In summary, we have designed and synthesized receptors **1-3** with an additional carbonyl motif along with uryl, thiouryl and guanidinium moieties with the idea to enhance the hydrogen bonding thereby obtaining higher stereoselectivities in chiral recognition of amino alcohols and chirality conversion in amino acids. However, the additional carbonyl group is not helpful as expected in obtaining higher enantioselectivity in both amino alcohols and amino acids.

Experimental Section

General. Compounds **7** and **9** were prepared according to the literature procedure.[6,9] 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 recordedon a Bruker-AM 250 spectrometer in CDCl$_3$ & 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 EI or FAB mode. For column Chromatography silica gel of 230-400 mesh was used.

Compound 5: To a solution of 3-aminobenzyl alcohol (0.45 g, 3.74 mmol) in THF (30 mL), benzoylisocyanate (0.50 g, 3.40 mmol) was added and stirred at ambient temperature for 5 h. Evaporation of the solvent and addition of chloroform gave a white precipitate, which is filtered and dried in vacuum to obtain 0.92 g of **5**. Yield: 92%. m.p. 171 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 11.07 (s, 1H, NH), 10.85 (s, 1H, NH), 8.03 (d, 2H), 7.61-7.38 (m, 5H), 7.22 (t, 1H), 7.05 (d, 1H), 5.23 (t, 1H, OH), 4.47 (d, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 168.73, 150.99, 143.57, 137.74, 136.77, 132.98, 132.24, 129.13, 128.66, 128.25, 121.75, 119.55, 118.00, 117.64, 62.67.

Compound 6: Phosphorus tribromide (0.084 mL, 0.89 mmol) was added to slurry of 3-benzoyluryl-benzyl alcohol **5** (0.20 g, 0.74 mmol) in THF (20 mL) and allowed to stir at room temperature for 2 h. After evaporation of the solvent, the residue is washed with chloroform and ether several times to give 0.24 g product as a white solid Yield: 97%. m.p. 183 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 11.06 (s, 1H, NH), 10.88 (s, 1H, NH), 7.99 (d, 2H), 7.70-7.50 (m, 5H), 7.33 (t, 1H), 7.16 (d, 1H), 4.70 (d, 2H, CH$_2$); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 168.70, 151.13, 138.84, 138.49, 137.81, 133.05, 132.11, 129.33, 128.53,

128.27, 124.60, 122.67, 120.34, 119.66, 34.27.

Compound 8: To an ice cooled solution of MOM protected binol aldehyde **6** (0.36 g, 1.00 mmol) in 25 mL of DMF was added NaH (0.027 g, 1.10 mmol). After stirring for a while, 3-benzoyluryl benzyl bromide **6** (0.37 g, 1.10 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 0.50 g of **8**. Yield: 82 %. m.p. 210 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 10.88 (s, 1H, NH), 10.59 (s, 1H, -CHO), 10.09 (s, 1H, NH), 8.59 (s, 1H), 8.07-7.98 (m, 5H), 7.49-7.15 (m, 13H), 6.82 (d, 1H), 5.15 (dd, 2H, benzyl CH$_2$), 4.71 (dd, 2H, -OC*H$_2$*OCH$_3$), 2.97 (s, 3H, -OCH$_2$OC*H$_3$*); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 191.36, 169.60, 155.78, 154.49, 152.41, 142.39, 138.84, 133.67, 131.43, 130.93, 129.75, 129.42, 128.86, 128.39, 127.54, 127.21, 126.43, 125.76, 124.56, 124.03, 122.53, 120.52, 119.42, 116.93, 69.79, 59.83, 54.38; HRMS (EI) calcd for C$_{38}$H$_{30}$N$_2$O$_6$ 610.2104; found: 610.2109.

Compound 10: A mixture of binol amine **9** (2.0 g, 4.30 mmol) and Benzoyl isothiocyanate (0.78 g, 4.73 mmol) was dissolved in THF (75 mL) and stirred for 5 h at room temperature. Evaporation of the solvent and silica gel column chromatography with EA and hexane 1:3 mixture afforded 2.2 g of the desired product **10**. Yield: 81%. m.p. 185 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 12.32 (bs, 1H, NH), 9.11 (s, 1H, NH), 8.01-7.87 (m, 6H), 7.62-7.16 (m, 13H), 6.92 (d, 1H), 5.15 (q, 2H, -OCH$_2$-), 4.95 (d, 2H, -C*H$_2$*OH), 4.55 (dd, 2H, -OC*H$_2$*OCH$_3$), 4.12 (t, 1H, -CH$_2$O*H*), 3.17 (s, 3H, -OCH$_2$OC*H$_3$*); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 168.74, 152.57, 152.02, 150.42, 141.35, 138.69, 135.78, 133.20, 131.28, 129.54, 128.94, 128.23, 127.60, 126.45, 125.80, 124.82, 124.48, 123.71, 123.25, 122.12, 120.56, 117.36, 70.24, 56.28, 52.03; HRMS (EI) calcd for C$_{38}$H$_{32}$N$_2$O$_5$S 628.2032; found: 628.2024.

Compound 11: A mixture of **10** (2.7 g, 4.33 mmol) and pyridinium chlorochromate (PCC) (1.38 g, 6.49 mmol) was dissolved in methylene chloride and stirred for 1 h. The reaction mixture was filtered and the filtrate after evaporation, on column chromatography with EA and hexane 1 : 2 mixture provided 1.37 g of **11**. Yield: 51%. m.p. 165 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 12.36 (s, 1H, NH), 10.67 (s, 1H, -CHO), 9.10 (s, 1H, NH), 8.59 (s, 1H), 8.00-7.95 (m, 5H), 7.62-7.20 (m, 13H), 6.95 (d, 1H), 5.15 (dd, 2H, benzyl CH$_2$), 4.70 (dd, 2H, -OC*H$_2$*OCH$_3$), 2.94 (s, 3H, -OCH$_2$OC*H$_3$*); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 192.23, 163.33, 151.46, 151.36, 151.12, 138.29, 137.49, 134.38, 131.26, 129.86, 129.11, 128.87, 128.34, 126.60, 125.37, 125.03, 124.40, 124.15, 123.51, 123.32, 121.32, 119.62, 115.68, 69.93, 55.26, 51.94; HRMS (EI) calcd for C$_{38}$H$_{30}$N$_2$O$_5$S 626.1875; found: 626.1867.

Compound 12: The thio compound **11** (1.2 g, 2.04 mmol) taken in ethanol, mercuric chloride (0.67 g, 2.5 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 1.10 g of **12**. Yield: 95%. m.p. 173 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 8.25-8.21 (m, 2H), 8.01-7.95 (m, 2H), 7.90-7.73 (m, 3H), 7.43-6.95 (m, 14H), 6.80 (d, 1H), 6.55 (s, 1H), 5.03 (m, 2H, benzyl CH$_2$), 4.85 (d, 2H, -C*H$_2$*OH), 4.55 (dd, 2H, -OC*H$_2$*OCH$_3$), 2.96 (s, 3H, -OCH$_2$OC*H$_3$*); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 171.43, 156.61, 154.70, 152.51, 140.64,

139.61, 138.19, 135.50, 131.60, 130.92, 129.91, 129.30, 128.65, 128.25, 128.94, 127.84, 127.14, 126.06, 125.29, 124.83, 122.60, 118.66, 69.14, 56.92, 53.46; HRMS (EI) calcd for $C_{38}H_{33}N_3O_5$ 611.2420; found: 611.2413.

Compound 13: It was prepared similar to **11** by PCC treatment of **12** and stirring for 5 h. Yield: 82%. m.p. 167 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 10.05 (s, 1H, -CHO), 8.53 (s, 1H), 8.17-7.86 (m, 5H), 7.43-6.73 (m, 17H), 5.05 (s, 2H, benzyl CH$_2$), 4.69 (dd, 2H, -OC*H*$_2$OCH$_3$), 2.86 (s, 3H, -OCH$_2$O*CH*$_3$); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 192.46, 169.95, 154.57, 153.50, 153.14, 139.91, 138.15, 137.59, 134.03, 130.71, 130.23, 129.87, 129.64, 129.15, 128.35, 127.94, 127.32, 126.34, 125.56, 124.48, 124.03, 121.71, 116.36, 71.07, 56.63, 52.78; HRMS (EI) calcd for $C_{38}H_{31}N_3O_5$ 609.2264; found: 609.2257.

Compound 1: MOM protected benzoyluryl based binol aldehyde **8** taken in ethanol and a few drops of conc. Hydrochloric acid was added and refluxed for 30 minutes. The solvent was evaporated and recrystallized from ethanol to afford the desired receptor **1** in quantitative yield. m.p. 255 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 11.04 (s, 1H, NH), 10.72 (s, 1H, -OH), 10.33 (s, 1H, -CHO), 10.28 (s, 1H, -NH), 8.65 (s, 1H), 8.08-7.94 (m, 5H), 7.67-6.99 (m, 13H), 6.83 (d, 1H), 5.19 (s, 2H, -OCH$_2$-); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 196.88, 168.33, 153.94, 153.48, 151.60, 138.39, 138.07, 132.03, 130.31, 130.03, 129.75, 128.92, 128.86, 128.19, 127.84, 127.51, 126.70, 125.34, 124.94, 124.22, 122.03, 119.62, 118.72, 115.73, 70.84; HRMS (EI) calcd for $C_{36}H_{26}N_2O_5$ 566.1842; found: 566.1836.

Compound 2: It was prepared similar to **1** by MOM deprotection of **11**. m.p. 210 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 12.35 (s, 1H, NH), 10.51 (s, 1H, -OH), 10.20 (s, 1H, -CHO), 9.07 (s, 1H, -NH), 8.33 (s, 1H), 7.96-7.93 (m, 5H), 7.61-7.17 (m, 13H), 6.92 (d, 1H), 5.14 (s, 2H, -OCH$_2$-); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 196.82, 166.53, 152.74, 152.25, 151.21, 137.93, 136.27, 133.81, 130.11, 129.73, 129.30, 128.67, 128.21, 127.48, 125.34, 125.17, 124.93, 124.21, 124.01, 123.27, 120.72, 119.22, 115.77, 70.75; HRMS (EI) calcd for $C_{36}H_{26}N_2O_4S$ 582.1613; found: 582.1607.

Compound 3: It was prepared similar to **1** by MOM deprotection of **13**. m.p. 223 °C. ^{1}H NMR (CDCl$_3$, 250 MHz) δ 10.19 (s, 1H, -CHO), 8.42-8.37 (m, 3H), 8.05-7.91 (m, 5H), 7.59-6.85 (m, 14H), 6.64 (s, 1H), 5.19 (q, 2H, -OCH$_2$-); ^{13}C NMR (CDCl$_3$, 63 MHz) δ 197.22, 172.59, 156.67, 153.49, 153.24, 138.36, 137.76, 133.49, 133.43, 130.56, 130.33, 130.20, 129.95, 129.72, 129.05, 128.75, 128.24, 127.52, 126.98, 125.15, 124.99, 124.43, 121.84, 115.76, 70.60; HRMS (EI) calcd for $C_{36}H_{27}N_3O_4$ 565.2002; found: 565.1996.

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