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Synthesis of Chiral Phenolic 1,1′-Binaphthocrown Ethers and Some Proton-ionisable Chromogenic Derivatives

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Synthesis of mono- and bis(1,1′-bi-2-naphthocrown) ethers containing bis(2,6-methylene)anisyl subunit in the crown ring were developed. These chiral macrocycles are suitable precursors to introduce a chromogenic function, as exemplified by two novel crowned azophenol chromoionophores. Their coloration process induced by various achiral and chiral amines was studied by UV–vis spectrophotometry.

Keywords: BINOL; Crowned azophenols; Amine recognition; UV–vis spectroscopy

INTRODUCTION

Over the last few decades 1,1′-bi-2-naphthyl derivatives have received constantly growing interest as chiral catalysts, mediators and chelators in asymmetric syntheses and chiral recognition processes [1–3]. BINOL (1,1′-bi-2-naphthol) has become one of the best known and utilized atropisomer possessing axial chirality due to its easy availability and versatile chemical modifications on the aromatic core and on the phenolic OH groups as well [2,3]. The replacement of the latter with *C*, *S*, *N* and *P* functionalities further expand the versatility of chiral ligands based on BINOL. The *O*,*O*-cyclized derivatives and related macrocycles also represent an important family of chiral receptors [4]. (*S*,*S*)-bis(1,1′-Bi-2-naphtho)-22-crown-6, reported first by Cram *et al.* in 1973 [5], was disclosed to exhibit remarkable chiral discrimination between the enantiomers of organic ammonium salts since the receptor possesses C_{2v} axis of symmetry due to the steric effect between the naphthalene rings. So far the choice of binaphthocrowns have scarcely been widened, only modifications on the crown ether ring size and some combination with calix[4]arenes were reported [6,7]. In the mean time, the number of chiral crown ethers based on natural chiral sources or constructed by introduction of asymmetric elements in the crown rings, have significantly increased [8]. However, some recent publications revealed that binaphthocrowns with auxiliary binding sites attached to the crown ether ring may have potential in various recognition processes [9–11]. Another way to modify the binding characteristics of binaphthocrowns is to insert a bis(2,6-methylene)anisyl subunit in the crown ring (**I**), which provides an easy access to proton-ionisable chromogenic chelators (type **II**) (Fig. 1). This approach has been frequently used for the synthesis of chiral phenolic crown ethers capable of discriminating amine eneantiomers by UV–vis spectroscopy [12–14], but hitherto this attractive way of detection has been limited to one example in the binaphthocrown series ((*R*,*R*-and *S*,*S*)-**III**) for the optical recognition of chiral amines [15].

As part of our ongoing program to synthesize chromoionophores for developing optical sensors, we have studied the optical properties of different chromophore groups (2,4-dinitrophenylazo, indophenol, etc.) introduced to various calix[4]arenes including bridged derivatives [16]. Recently, we published a facile method to prepare binaphthomonoazacrowns [17] and some novel photochromic conjugates thereof [18]. Herein, we report on the synthesis, characterization and recognition properties of novel binaphthocrown ethers **1**, **2** (Fig. 2), which can be utilized as precurors for the synthesis of chromoionophores type **II** and **III**, e.g., by dealkylation and subsequent nitration or oxidation

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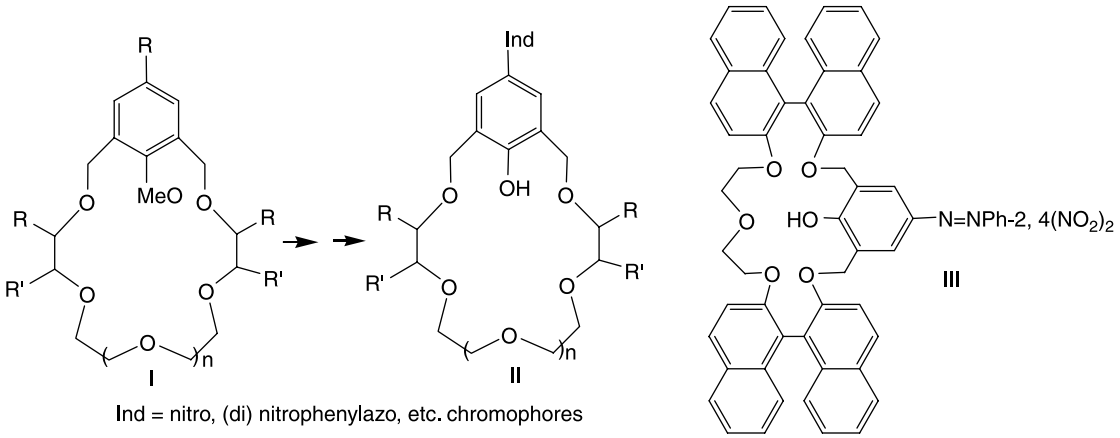


FIGURE 1 Anisyl-appended crown ethers and proton-ionizable chromoionophores.

to quinones followed by condensation with hydrazines [13,14]. In this paper, the latter route is demonstrated by the preparation of novel chromogenic azophenols (*S*)-**3a** and (*S*,*S*)-**3b** and their optical recognition ability toward achiral and chiral amines is also presented.

RESULTS AND DISCUSSION

The synthesis of **1a–c** consists of three steps: first, bis(2,6-bromomethyl)anisols **4a** [19], **b**,**c** [20] were condensed with diethylene glycol under strongly basic condititons [21] affording diols **5a–c**, which

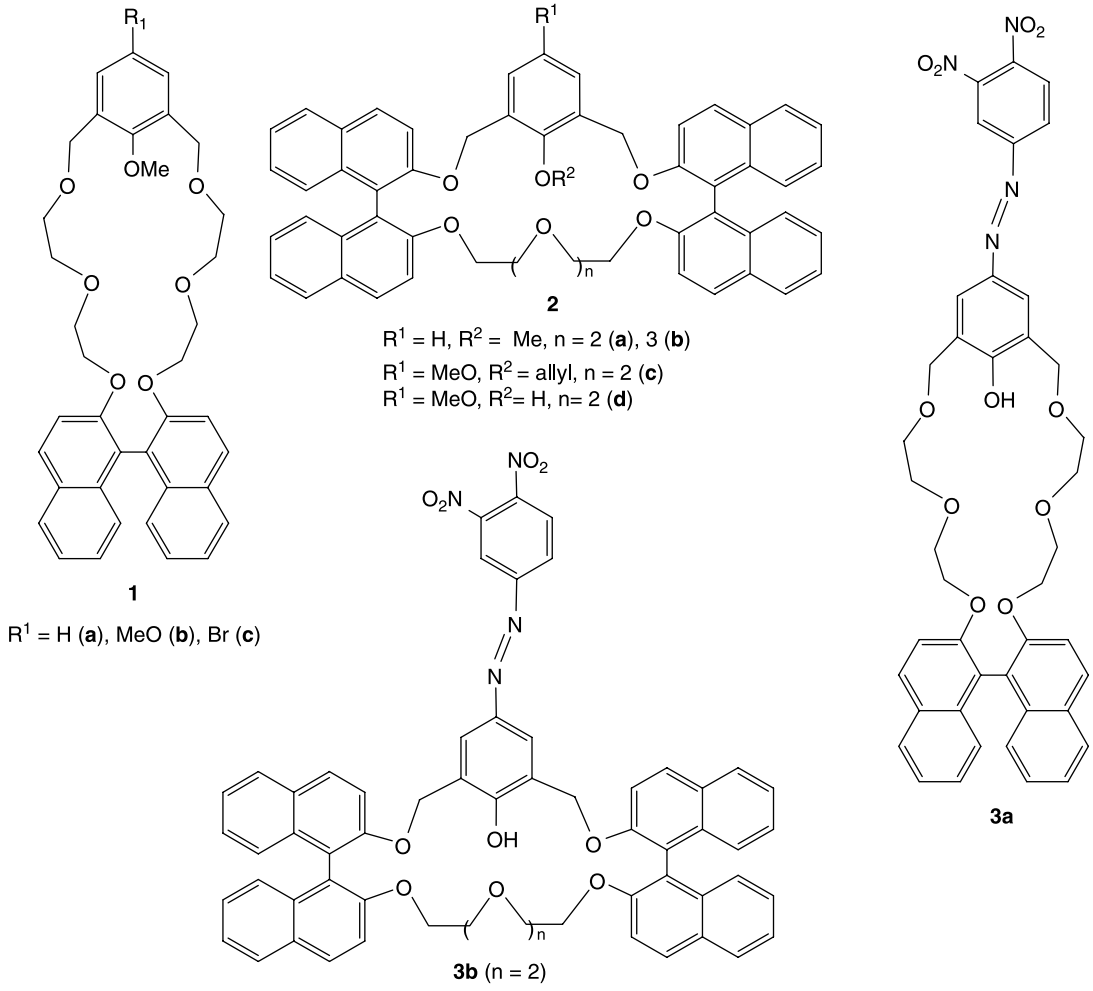


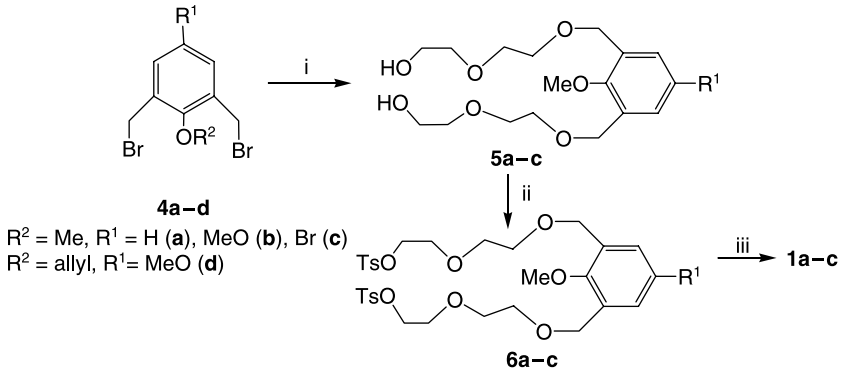
FIGURE 2 Mono-and bis(binaphthocrown)ether target molecules **1** and **2** and chromoionophores **3a**,**b** derived from them.

were then tosylated to give the cyclizing agents **6a**–**c**. The ring closure reaction was carried out with (*R*) or (*S*)-BINOL promoted by K_2CO_3 in boiling MeCN to give binaphthocrowns **1a**–**c** in yields of 30–70% (Scheme 1).

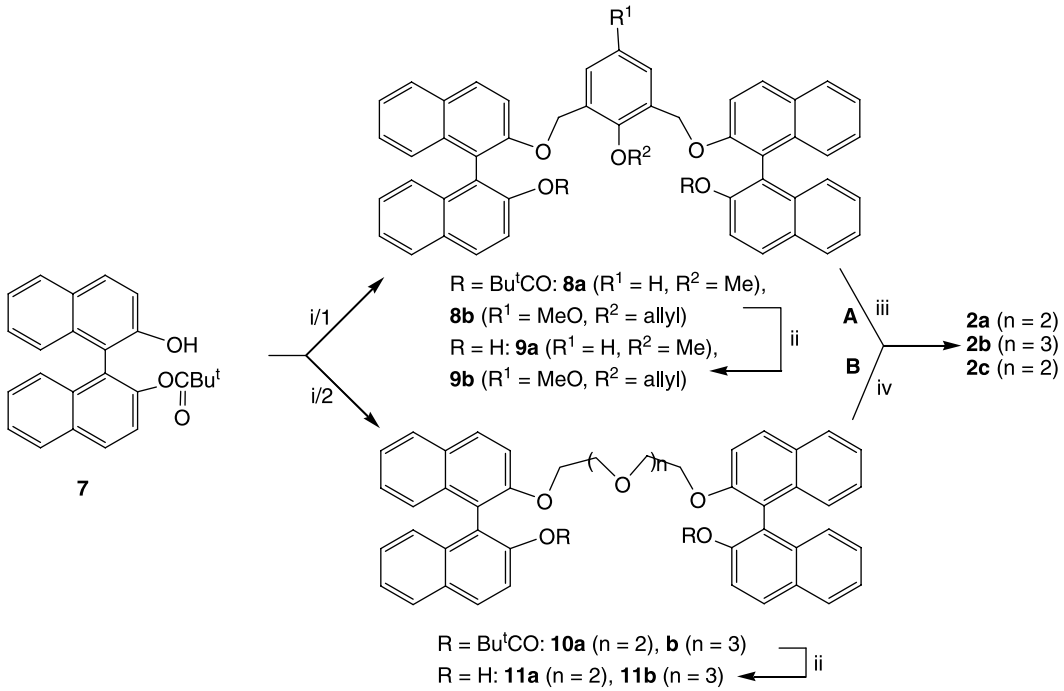
The synthesis of bis(binaphthocrown)ethers **2a**–**c** required first the protection of one OH group of BINOL, which was easily achieved by acylation with pivaloyl chloride to give monoester **7** [22]. This compound was then smoothly alkylated with **4a** and **4c** to give **8a** and **8b**, respectively, followed by deprotection with aq. NaOH furnishing the precursors **9a**,**b**. The cyclizations were then performed with tri- and tetraethylene glycol ditosylates (route **A**) and **2a**–**c** were obtained in 20–25% overall yields. Another approach, when intermediate **11a**,**b** were cyclized with **4a** using Cs_2CO_3 base as described in ref. [15] (route **B**), was also successful giving the same products in comparable yields (Scheme 2).

Synthesis and Spectroscopic Characterization of Chiral Crowned Azophenols

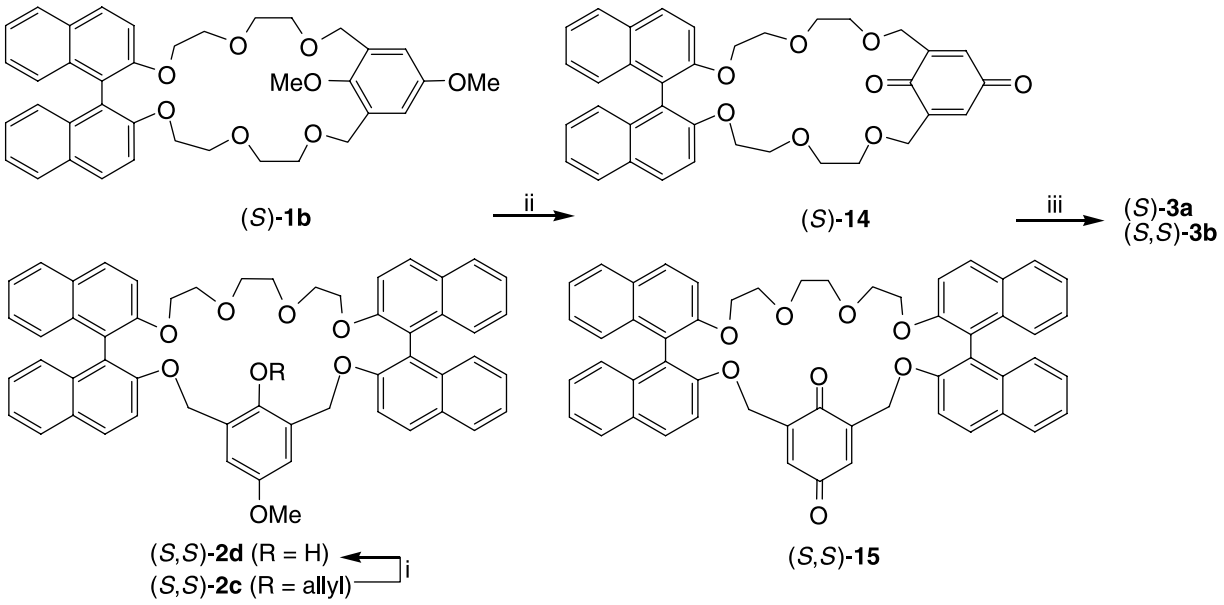
To demonstrate a way of chromogenization of anisyl-appended crown ethers **1** and **2**, proton ionisable receptors (*S*)-**3a** and (*S*,*S*)-**3b** were sythesized. The former was obtained from **1b** by oxidation with ammonium cerium(IV) nitrate (CAN) to quinone **14** followed by condensation with 2,4-dinitrophenylhydrazine (2,4-DNPH). Essentially this route was used for the preparation of (*S*,*S*)-**3b**, but the allyl protecting group of **2c** was removed prior



SCHEME 1 Synthesis of binaphthomonocrowns **1a**–**c**. Reagents and conditions: (i) diethylene glycol, powdered NaOH, 100°C (**5a**–**c**), (ii) TsCl, THF, powdered KOH, 0°C, (iii) BINOL, K_2CO_3, MeCN, 80°C.



SCHEME 2 Synthesis of bis(binaphtho)crowns **2a**–**c**. Reagents and conditions: (i/1) **4a**,**d**, K_2CO_3, MeCN, 80°C (**8a**,**b**), (i/2) $TsO(CH_2CH_2O)_{3,4}Ts$, K_2CO_3, MeCN, 80°C (**10a**,**b**), (ii) aq. NaOH, EtOH, 80°C (**9a**,**b** **11a**,**b**); (iii) $TsO(CH_2CH_2O)_{3,4}Ts$, K_2CO_3 (**2a**,**b**) or Cs_2CO_3 (**2c**), MeCN, 80°C (route **A**); (iv) **4a**, Cs_2CO_3, MeCN, 80°C (**2a**) (route **B**).



SCHEME 3 Synthesis of chromogenic (*S*)-**3a** and (*S*,*S*)-**3b**. Reagents and conditions: (i) Pd/C, *p*-TsOH, EtOH/THF, Δ (**2d**); (ii) $Ce(NH_4)_2(NO_3)_6$, aq. MeCN, rt; (iii) 2,4-DNPH, EtOH/$CHCl_3$, H^+, rt.

to oxidation affording phenol **2d**, which was then treated in the same way (Scheme 3).

UV–vis Spectroscopic Investigation of (*S*)-3a and (*S*,*S*)-3b upon Addition of Amines

The visible spectrum of (*S*)-**3a** and (*S*,*S*)-**3b** taken in chloroform and MeCN exhibited absorption maxima around 380–390 nm, which were significantly red-shifted in both solvents (180–230 nm) upon addition of achiral 1° to 3° amines (1000 equiv.). The coloration process is due to the amine-based deprotonation of the azophenol moiety, affording a photoinduced charge transfer (PCT) [23]. The polar aprotic acetonitrile stabilizes the ammonium–phenolate ion pair more strongly than chloroform, accordingly band shifts to the lower energy region result, but without noteworthy discrimination in respect of the order of amines. In chloroform, however, **3a** responds to 1° and 2° amines, but a tertiary amine (Bu_3N) gives no coloration. Ligand **3b** behaves similarly with remarkably reduced discrimination (Figs. 3 and 4). The selectivity of **3a** toward 1°, 2° versus 3° amines is related to H-bonding interactions between the crown ring and the protons of ammonium ion formed. At the same time, none of ligands can discriminate among primary and secondary amines as reflected by the λ_{max} values of the new bands centered around 570–580 nm ($CHCl_3$) indicating complex stabilities irrespective of the number of NH^+ protons. Primary ammonium ions are enabled to form three-pointed H-bonds with the oxygen atoms of 18-crown-6, therefore their complexes are more stable than those of the secondary ammonium counterparts capable of only two-pointed H-bonding interactions [24]. Accordingly, $BuNH_2$ would have been expected to show larger red-shift than Bu_2NH or piperidine. We suppose, the lack of selectivity may be attributed to the less flexible conformation of the binaphthocrown ring that prevents all NH_3^+ protons to participate in binding. Obviously, the complexation selectivity is

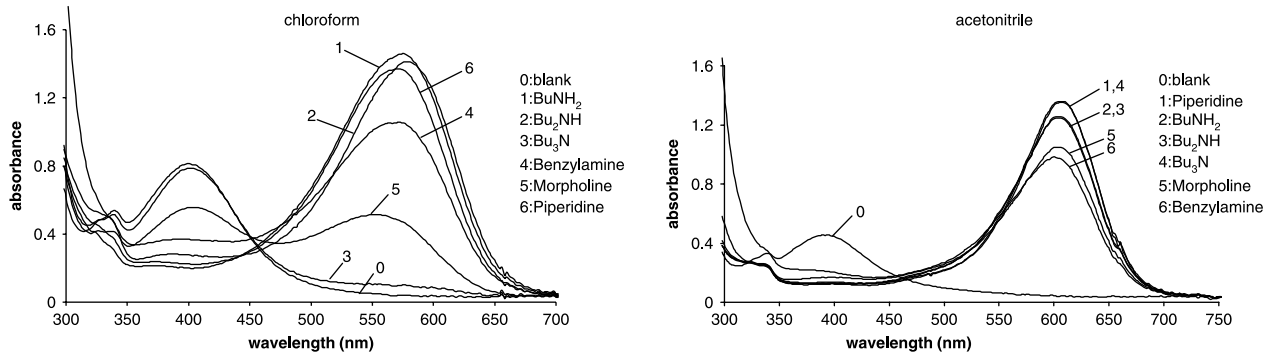


FIGURE 3 Spectral changes of (*S*)-**3a** upon addition of 1–3° amines. [**3a**] = 10^{-4} M, [amine] = 10^{-1} M, solvent: chloroform and acetonitrile.

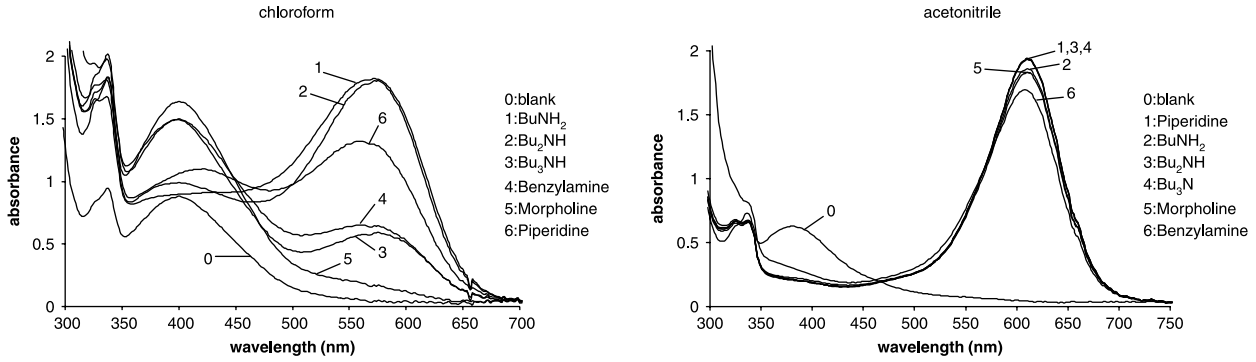


FIGURE 4 Spectral changes of (*S*,*S*)-**3b** upon addition of 1–3° amines. [**3b**] = 10^{-4} M, [amine] = 10^{-1} M, solvent: chloroform and acetonitrile.

affected by other factors, e.g., interactions (steric, CH–π, hydrophobic, etc.) between the substituents of the amine and the ligand. Recently, a selectivity enhancement of n-octylamine vs. di-n-octylamine was reported for an azophenol-crown ether ligand linked with permethylated α-cyclodextrin [25]. The critical role of the adjacent α-CD capable of interaction with the lipophilic alkyl chain by hydrophobic forces was emphasized.

The larger absorbances measured for $BuNH_2$, Bu_2NH and piperidine as compared to benzylamine and morpholine are in accord with the different basicities (the latter are ca. 2–3 orders of magnitude weaker bases). Nevertheless, the weak if any coloration with a strongly basic 3° amine (Bu_3N) underlines the role of the crown ring in the complexation-induced stabilization of the ammonium–phenolate ion pair possessing at least two NH^+ protons.

Preliminary measurements on the chiral discrimination ability of (*S*)-**3a** and (*S*,*S*)-**3b** were performed in chloroform and acetonitrile at 25°C with α-phenylethylamine (PEA), ephedrine and D-threo-2-amino-1-*p*-nitrophenyl-1,3-propanediol (D-bases) enantiomers (Table I).

D-bases effected very weak coloration of each ligand, while (*S*,*S*)-**3b** did not show enantiomeric discrimination among any guests ($\Delta\lambda_{max} = 0$ nm). For chiral crown ether-appended azophenol–amine diastereomers, the blue-shift is indicative of the better host–guest complementarity. This prediction is consistent with the binding model, where hydrogen bonding between the phenolate oxygen of the host and an NH^+ hydrogen of the guest stabilizes the energy of the polar ground state more than the less polar excited state, thereby leading to a blue-shift [26]. Accordingly, (*S*)-**3a** exhibits some enantioselective coloration with (*R*)-PEA vs. (*S*)-PEA in MeCN ($\Delta\lambda_{max} = 2$ nm), in turn (+)-(1*S*,2*R*)-ephedrine is significantly discriminated over the (−)-(1*R*,2*S*)-enantiomer in both solvents ($\Delta\lambda_{max} = 8/12$ nm). This relatively high enantioselectivity can be ascribed to the (1*S*)—OH group of ephedrine which is supposed to be H-bonded with an oxygen atom of the ring, thereby providing an additional stability for this diastereomer complex.

These preliminary results encourage us to continue our studies with other chiral amines and aminoalcohols performing the spectroscopic measurements at 0°C to achieve better enantioselections [15].

CONCLUSIONS

A series of 1,1′-bi-2-naphthyl-appended mono- and biscrown ethers containing anisyl subunit in the

TABLE I Absorption maxima of the colored species of (*S*)-**3a** and (*S*,*S*)-**3b** with chiral amines

		λ_{max}/nm (ε)		
Host	Amine	$CHCl_3$	MeCN	$\Delta\lambda_{max}$ (nm)
(*S*)-**3a**	(*R*)-PEA	576 (18310)	600 (24020)	0/2
	(*S*)-PEA	576 (16550)	602 (25240)	
(*S*,*S*)-**3b**	(*R*)-PEA	576 (7740)	610 (33230)	0/0
	(*S*)-PEA	576 (9150)	610 (33340)	
(*S*)-**3a**	(+)-E	548 (20750)	592 (18260)	8/12
	(−)-E	556 (18000)	604 (28200)	
(*S*,*S*)-**3b**	(+)-E	572 (15360)	610 (36380)	0/0
	(−)-E	572 (16470)	610 (35510)	

t = 25°C, PEA: phenylethylamine, E: ephedrine, (+): 1*S*,2*R*; (−): 1*R*,2*S*

crown ring have been synthesized, which are considered to be useful precursors for the development of various chiral chromogenic receptors, as demonstrated by the synthesis of ligands (*S*)-**3a** and (*S*,*S*)-**3b** containing 2,4-dinitrophenylazo chromophore. The optical characteristics of the two azophenol ligands were studied by UV–vis spectroscopy, in addition the coloration process induced by various achiral and chiral amines was also investigated. Ligand (*S*)-**3a** was found to exhibit significant enantioselective coloration toward (+)-(1*S*,2*R*)-ephedrine over the (−)-(1*R*,2*S*)-enantiomer.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were taken in $CDCl_3$ at 500/125 MHz on a Bruker Avance DRX-500 spectrometer. UV–vis spectra of the chromoionophores were recorded on a HP 8452A spectrophotometer. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade and used without further purification. Compounds **4a–c** [19,20], **5a–c**, **6a–c** [21], and **7** [22] were prepared as reported. Deallylation of **2c** to **2d** was carried as described in ref. [27]. Quinones (*S*)-**14** and (*S*,*S*)-**15** were prepared following literature analogy [13].

General Procedure for the Synthesis of 1,1′-Binaphthocrown Ethers 1a–c and 2a–c

The mixture of BINOL (0.57 g, 2 mmol), ditosylate **6a–c** (2.2 mmol) and K_2CO_3 (1.12 g, 8 mmol) in MeCN (20 ml) was vigorously stirred under reflux for 20 h. The reaction mixture was eveporated to dryness and the residue was dissolved in $CHCl_3$ (20 ml), washed with water and dried. The volatile was distilled off in vacuo and the residue was purified by column chromatography on silica to give **1a–c** as white amorph solids.

The same procedure was used for the alkylation of BINOL-monopivalate **7** (2 mmol) with **4a,d** or tri- and tetraethylene glycol ditosylates (1 mmol each) in the presence of K_2CO_3 (2 mmol) followed by basic deprotection of **8a,b** and **10a,b** thus formed, according to ref. [20], affording bis-BINOL precursors **9a,b** and **11a,b**, respectively. The ring closure of **9a,b** (1 mmol) with ditosylates (1.1 mmol) was carried out similarly but 10 fold excess of K_2CO_3 was required in 48 h reaction (route **A**) affording bis(binaphthocrowns) **2a–d** as white solids after column chromatography.

Compound (*S*)-**1a** (79%, eluent: AcOEt), $[\alpha]_D^{20} = -118.0$ (c 1, THF); ^{1}H NMR δ 7.80 (m, 4H, Ar*H*), 7.27–7.37 (m, 6H, Ar*H*), 7.18 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.12 (d, 3H, $J = 6.0$ Hz, Ar*H*), 4.54 (d, 2H, $J = 11.0$ Hz, ArCH_2O), 4.47 (d, 2H, $J = 11.0$ Hz, ArCH_2O), 3.96 (m, 2H, OCH_2), 3.83 (m, 2 + 3H, OCH_2, OCH_3), 3.46 (m, 2H, OCH_2), 3.39 (m, 4H, OCH_2), 3.27 (m, 4H, OCH_2), 3.20 (m, 2H, OCH_2); ^{13}C NMR δ 158.75, 154.92, 134.21, 131.95, 131.63, 129.78, 129.45, 128.02, 126.29, 125.71, 123.90, 123.82, 121.18, 117.38, (Ar), 70.79, 70.70, 69.88, 69.43 (O*C*H_2), 68.80 (Ar*C*H_2O), 63.97 (O*C*H_3); Anal. calcd. for $C_{37}H_{38}O_7$ (594.69): C 74.73, H 6.44, found C 74.52, H 6.41%.

Compound (*S*)-**1b** (39%, eluent: hexane-AcOEt = 1:1), mp: 112–116°C, $[\alpha]_D^{20} = -113.5$ (c 1, THF); ^{1}H NMR δ 7.82 (m, 4H, Ar*H*), 7.36 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.29 (t, 2H, $J = 6.5$ Hz, Ar*H*), 7.18 (t, 2H, $J = 7.0$ Hz, Ar*H*), 7.12 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.88 (s, 2H, Ar*H*), 4.55 (d, 2H, $J = 11.5$ Hz, ArCH_2O), 4.45 (d, 2H, $J = 11.5$ Hz, ArCH_2O), 3.97 (m, 2H, OCH_2), 3.84 (m, 2 + 3H, OCH_2, OCH_3), 3.73 (s, 3H, OCH_3), 3.47-3.37 (m, 6H, OCH_2), 3.31 (m, 2H, OCH_2), 3.26 (m, 2H, OCH_2), 3.19 (m, 2H, OCH_2); ^{13}C NMR δ 155.6, 154.9, 151.9, 134.2, 132.7, 129.7, 129.4, 128.0, 126.3, 125.7, 123.9, 121.1, 117.2, 116.1, (Ar), 70.8, 10.6, 69.8, 69.4, 68.6, (O*C*H_2), 63.8, 55.9, (O*C*H_3); Anal. calcd. for $C_{38}H_{40}O_8$ (624.72): C 73.06, H 6.45, found C 72.87, H 6.51%.

Compound (*S*)-**1c** (34%, eluent: hexane-AcOEt = 1:1), mp 136–139°C (CH_3OH), $[\alpha]_D^{20} = -98.2$ (c 1, THF); ^{1}H NMR δ 7.82 (d, 4H, $J = 8.5$ Hz, Ar*H*), 7.47 (s, 2H, Ar*H*), 7.36 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.30 (t, 2H, $J = 7.5$ Hz, Ar*H*), 7.18 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.12 (d, 2H, $J = 8.5$ Hz, Ar*H*), 4.51 (d, 2H, $J = 11.5$ Hz, ArCH_2O), 4.42 (d, 2H, $J = 11.5$ Hz, ArCH_2O), 3.97 (m, 2H, OCH_2), 3.83 (m, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 3.45 (m, 2H, OCH_2), 3.38 (m, 4H, OCH_2), 3.28 (m, 4H, OCH_2), 3.17 (m, 2H, OCH_2); ^{13}C NMR δ 157.4, 154.9, 134.3, 134.2, 133.7, 129.8, 129.5, 128.0, 126.3, 125.7, 123.9, 121.2, 117.3, 116.5, (Ar), 70.8, 70.7, 69.9, 69.6, 68.2, (O*C*H_2), 63.8 (O*C*H_3); Anal. calcd. for $C_{37}H_{37}BrO_7$ (673.59): C 65.97, H 5.54, found C 66.12, H 5.62%.

Compound (*S*,*S*)-**9a** (98%), $[\alpha]_D^{20} = -62.0$ (c 1, THF); (*R*,*R*)-**9a** (90%), $[\alpha]_D^{20} = +62.3$ (c 1, THF); ^{1}H NMR δ 7.94 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.84 (m, 4H, Ar*H*), 7.80 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.44 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.35 (t, 2H, $J = 7.5$ Hz, Ar*H*), 7.25 (m, 6H, Ar*H*), 7.18 (d, 2H, $J = 8.5$ Hz, Ar*H*), 7.11 (t, 2H, $J = 8.0$ Hz, Ar*H*), 6.97 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.77 (d, 2H, $J = 8.0$ Hz, Ar*H*), 6.63 (t, 1H, $J = 7.5$ Hz, Ar*H*), 5.05 (d, 2H, $J = 12.5$ Hz, ArCH_2O), 4.99 (d, 2H, $J = 12.5$ Hz, ArCH_2O), 3.20 (s, 3H, OCH_3); ^{13}C NMR δ 155.56, 155.09, 151.49, 134.287, 134.04, 131.10, 130.03, 129.96, 129.30, 129.20, 128.34, 128.20, 127.49, 126.58, 125.25, 125.07, 124.66, 124.50, 123.41, 117.69, 117.04, 116.12, 115.34 (Ar), 66.22 (Ar*C*H_2O), 62.38 (O*C*H_3); Anal. calcd. for $C_{49}H_{36}O_5$ (704.81): C 83.50, H 5.15, found C 83.29, H 5.12%.

Compound (*S*,*S*)-**9b** (91%), $[\alpha]_D^{20} = -59.0$ (c 1, THF); ^{1}H NMR δ 7.97 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.86 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.83 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.78 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.45 (d, 2H,

$J = 9.0$ Hz, Ar*H*), 7.35 (t, 2H, $J = 7.0$ Hz, Ar*H*), 7.29-7.20 (m, 6H, Ar*H*), 7.16 (d, 2H, $J = 8.5$ Hz, Ar*H*), 7.1 (t, 2H, $J = 8.5$ Hz, Ar*H*), 6.98 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.31 (s, 2H, Ar*H*), 5.79 (m, 1H, = C*H*), 5.19 (dd, 1H, $J = 17.5$, 1.5 Hz, = CH_2), 5.14 (dd, 1H, $J = 10.5$, 1.0 Hz, = CH_2), 5.05 (d, 2H, $J = 12.5$ Hz, OCH_2Ar), 4.97 (d, 2H, $J = 13.0$ Hz, OCH_2Ar), 3.81 (dd, 1H, $J = 13.0$, 5.5 Hz, OCH_2CH), 3.67 (dd, 1H, $J = 12.5$, 5.0 Hz, OCH_2CH), 3.18 (s, 3H, OCH_3); ^{13}C NMR δ 155.98, 154,93, 151.54, 147.53, 134.28, 134.02, 133.73, 131.11, 129.88, 129.26, 128.34, 128.16, 127.48, 126.64, 125.20, 125.00, 124.60, 123.41, 117.76, 117.43, 116.94, 115.76, 115.36, 113.60, (Ar), 75.64 (OCH_2), 66.16 (ArCH_2O), 55.30 (OCH_3); Anal. calcd. for $C_{52}H_{40}O_6$ (760.87): C 82.08, H 5.30, found C 81.55, H 5.38%.

Compound (*R*,*R*)-**2a** (85%, eluent: hexane-AcOEt = 6:4), $[\alpha]_D^{20} = +156.8$ (c 1, THF); ^{1}H NMR δ 7.92 (m, 4H, Ar*H*), 7.85 (m, 4H, Ar*H*), 7.46 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.42 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.31 (m, 4H, Ar*H*), 7.24-7.11 (m, 8H, Ar*H*), 6.90 (d, 2H, $J = 7.5$ Hz, Ar*H*), 6.76 (t, 1H, $J = 7.5$ Hz, Ar*H*), 5.04 (d, 2H, $J = 12.0$ Hz, ArCH_2O), 4.90 (d, 2H, $J = 12.5$ Hz, ArCH_2O), 4.08 (m, 2H, OCH_2), 3.84 (m, 2H, OCH_2), 3.40 (m, 2H, OCH_2), 3.15 (m, 2H, OCH_2), 3.02 (s, 3H, OCH_3), 2.85 (d, 2H, $J = 7.0$ Hz, OCH_2), 2.77 (d, 2H, $J = 7.0$ Hz, OCH_2); ^{13}C NMR δ 156.07, 154.18, 154.02, 134.25, 134.17, 130.37, 129.62, 129.50, 129.31, 129.22, 129.16, 129.08, 127.79, 126.30, 125.44, 123.86, 123.78, 123.63, 121.02, 120.29, 116.25, 115.71, (*Ar*), 70.21, 69.73, 68.72 (OCH_2), 66.65 (ArCH_2O), 61.92, (OCH_3); Anal. calcd. for $C_{55}H_{46}O_7$ (818.95): C 80.66, H 5.66, found C 80.48, H 5.60%.

Compound (*R*,*R*)-**2b** (35%, eluent: hexane-AcOEt = 4:6), $[\alpha]_D^{20} = +143.6$ (c 1, THF); ^{1}H NMR δ 7.94 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.86 (m, 6H, Ar*H*), 7.44 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.33 (m, 6H, Ar*H*), 7.24-7.12 (m, 8H, Ar*H*), 6.99 (d, 2H, $J = 7.5$ Hz, Ar*H*), 6.81 (t, 1H, $J = 7.5$ Hz, Ar*H*), 5.07 (d, 2H, $J = 13.0$ Hz, ArCH_2O), 4.94 (d, 2H, $J = 12.5$ Hz, ArCH_2O), 4.12 (m, 2H, OCH_2), 3.95 (m, 2H, OCH_2), 3.50 (m, 2H, OCH_2), 3.31 (m, 2H, OCH_2), 3.18 (s, 3H, OCH_3), 3.10 (m, 8H, OCH_2); ^{13}C NMR δ 155.74, 154.56, 154.34, 134.43, 130.68, 129.69, 129.60, 129.49, 129.38, 129.25, 128.04, 126.57, 126.48, 125.70, 125.66, 124.25, 123.95, 123.89, 121.11, 120.58, 116.62, 115.85 (Ar), 70.66, 70.45, 69.97, 69.51 (OCH_2), 66.86 (ArCH_2O), 61.99 (OCH_3); Anal. calcd. for $C_{57}H_{50}O_8$ (863.00): C 79.33, H 5.84, found C 79.02, H 5.88%.

Compound (*S*,*S*)-**2c** (32%, eluent: hexane-AcOEt = 7:3), $[\alpha]_D^{20} = -96.1$ (c 1, THF); ^{1}H NMR δ 7.93 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.90 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.84 (t, 4H, $J = 7.5$ Hz, Ar*H*), 7.47 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.41 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.31 (t, 4H, $J = 6.5$ Hz, Ar*H*), 7.23-7.14 (m, 6H, Ar*H*), 7.09 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.45 (s, 2H, Ar*H*), 5.46 (m, 1H, = C*H*), 5.01-4.92 (m, 4 + 2H, OCH_2Ar, = CH_2), 4.2-4.09 (m, 2H, OCH_2CH), 4.04 (m, 2H, OCH_2), 3.81 (m, 2H, OCH_2), 3.39 (m, 2H, OCH_2), 3.21 (s, 3H, OCH_3), 3.13 (m, 2H, OCH_2), 2.88 (m, 2H, OCH_2), 2.82 (m, 2H, OCH_2); ^{13}C NMR δ 155.52, 154.38, 154.01, 148.62, 134.37, 133.98, 131.77, 130.03, 129.64, 129.59, 129.54, 129.34,128.06, 128.01, 126.62, 126.57, 125.68, 125.60, 123.97, 123.94, 120.82, 120.69, 116.63, 116.13, 115.87, 114.32, (Ar), 75.54 (OCH_2CH), 70.49, 69.86 69.17 (OCH_2), 66.59 (ArCH_2O), 55.31 (OCH_3); Anal. calcd. for $C_{58}H_{50}O_8$ (875.01): C 79.61, H 5.76, found C 79.32, H 5.80%.

Compound (*S*,*S*)-**2d** (67%), $[\alpha]_D^{20} = -111$ (c 1, THF); ^{1}H NMR δ 7.97 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.92 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.86 (d, 2H, $J = 8.0$ Hz, Ar*H*), 7.84 (d, 2H, $J = 9.5$ Hz, Ar*H*), 7.47 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.43 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.32 (m, 4H, Ar*H*), 7.19 (m, 6H, Ar*H*), 7.10 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.31 (s, 2H, Ar*H*), 5.07 (q, 4H, OCH_2Ar), 4.11 (m, 2H, OCH_2), 3.89 (m, 2H, OCH_2), 3.44 (m, 2H, OCH_2), 3.20 (m, 2H, OCH_2), 3.13 (s, 3H, OCH_3), 2.80 (s, 4H, OCH_2); ^{13}C NMR δ 154.10, 153.43, 152.81, 146.09, 134.13, 134.11, 129.91, 129.57, 129.47, 129.43, 128.02, 127.95, 126.56, 126.49, 125.53, 125.41, 125.08, 123.91, 123.83, 120.26, 120.09, 115.75, 114.79, 112.58, (*Ar*), 70.76, 70.38, 69.54, 69.45, 69.26, 68.82 (OCH_2), 68.01 (ArCH_2O), 55.25 (OCH_3); Anal. calcd. for $C_{55}H_{46}O_8$ (834.95): C 79.12, H 5.55, found C 78.87, 5.52%.

Compound (*S*)-**14** (52%, eluent: hexane-AcOEt = 1:1); ^{1}H NMR δ 7.92 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.84 (d, 2H, $J = 8.5$ Hz, Ar*H*), 7.39 (d, 2H, $J = 9.0$ Hz, Ar*H*), 7.31 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.2 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.15 (d, 2H, $J = 8.0$ Hz, Ar*H*), 6.73 (s, 2H, Ar*H*), 4.39 (d, 2H, $J = 15.5$ Hz, ArCH_2O), 4.21 (d, 2H, $J = 15.5$ Hz, ArCH_2O), 4.02 (m, 2H, ArOCH_2), 3.88 (m, 2H, ArOCH_2), 3.46 (m, 4H, OCH_2), 3.29 (m, 2H, OCH_2), 3.21 (m, 4H, OCH_2), 3.05 (m 2H, OCH_2); ^{13}C NMR δ 188.1, 186.9, 154.8, 146.0, 134.2, 132.3, 129.8, 129.7, 128.0, 126.4, 125.8, 124.0, 121.1, 117.0, (Ar), 71.2, 71.1, 70.8, 70.3, 67.1, (OCH_2); Anal. calcd. for $C_{36}H_{34}O_8$ (594.65): C 72.71, H 5.76, found C 72.56, H 5.71%.

Compound (*S*,*S*)-**15** (94%); ^{1}H NMR δ 7.95 (t, 4H, $J = 10.0$ Hz, Ar*H*), 7.86 (d, 4H, $J = 7.5$ Hz, Ar*H*), 7.40 (dd, 4H, $J = 9.0$, 3.5 Hz, Ar*H*), 7.33 (m, 4H, Ar*H*), 7.21 (t, 4H, $J = 8.0$ Hz, Ar*H*), 7.15 (d, 2H, $J = 8.5$ Hz, Ar*H*), 7.09 (d, 2H, $J = 8.5$ Hz, Ar*H*), 6.27 (s, 2H, Ar*H*), 4.82 (d, 2H, $J = 16.5$ Hz, ArCH_2O), 4.66 (d, 2H, $J = 16.5$ Hz, ArCH_2O), 4.10 (m, 2H, OCH_2), 3.93 (m, 2H, OCH_2), 3.48 (m, 2H, OCH_2), 3.32 (m, 2H, OCH_2), 3.18 (s, 4H, OCH_2); ^{13}C NMR δ 186.94, 185.66, 153.92, 153.89, 153.84, 134.07, 133.94, 132.97, 131.76, 130.01, 129.81, 129.75, 129.46, 129.30, 127.92, 127.88, 126.60, 126.38, 125.52, 125.17, 124.24, 123.84, 121.86, 119.67, 117.61, 115.17 (Ar), 70.66, 70.46, 69.93, 69.17, 68.93, 68.72 66.26 (OCH_2); Anal. calcd. for $C_{52}H_{42}O_8$ (818.91): C 79.20, H 5.17, found C 79.04, H 5.25%.

Synthesis of Crowned Azophenols (*S*)-3a and (*S*,*S*)-3b

Quinone (*S*)-**14** or (*S*,*S*)-**15** (0.2 mmol) and 2,4-DNPH (0.042 g, 0.21 mmol) were dissolved in

EtOH-$CHCl_3$ = 1:1 mixture (5 ml), one drop of 37% HCl was added and stirred overnight at ambient temperature. The solution was then diluted with $CHCl_3$ (10 ml), washed with dilute aq. HCl and dried. After removal of the solvent, the residue was chromatographed on silica to give **3a**,**b** as orange solids.

Compound (*S*)-**3a** (59%, eluent: hexane-AcOEt = 6:4); ^{1}H NMR δ 8.76 (d, 1H, J = 2.0 Hz, Ar*H*), 8.48 (dd, 1H, J = 9.0, 2.5 Hz, Ar*H*), 7.84 (m, 7H, Ar*H*), 7.41 (d, 2H, J = 9.0 Hz, Ar*H*), 7.32 (t, 2H, J = 6.5 Hz, Ar*H*), 7.21 (t, 2H, J = 8.0 Hz, Ar*H*), 7.17 (d, 2H, J = 8.0 Hz, Ar*H*), 4.60 (d, 2H, J = 12.0 Hz, ArCH_2O), 4.56 (d, 2H, J = 11.5 Hz, ArCH_2O), 4.10 (m, 2H, ArOCH_2), 4.03 (m, 2H, ArOCH_2), 3.55 (m, 4H, OCH_2), 3.44 (m, 2H, OCH_2), 3.37 (m, 2H, OCH_2), 3.28 (m, 4H, OCH_2); ^{13}C NMR δ 160.95, 154.71, 149.21, 147.19, 146.74, 146.13, 134.25, 129.77, 129.49, 128.03, 127.82, 126.43, 126.22, 125.84, 125.74, 123.99, 121.11, 120.32, 120.27, 116.80, (*Ar*), 70.40, 70.09, 70.03, 70.00, 69.86, (OC H_2); Anal. calcd. for $C_{42}H_{38}N_4O_{11}$ (774.77): C 65.11, H 4.94, N 7.23, found C 64.89, H 5.01, N 7.12%.

Compound (*S*,*S*)-**3b** (40%, eluent: hexane-AcOEt = 7:3); ^{1}H NMR δ 8.77 (d, 1H, J = 2.0 Hz, Ar*H*), 8.50 (dd, 1H, J = 8.5, 2.0 Hz, Ar*H*), 7.98 (d, 2H, J = 9.0 Hz, Ar*H*), 7.88 (m, 5H, Ar*H*), 7.82 (d, 2H, J = 8.0 Hz, Ar*H*), 7.64 (m, 2H, Ar*H*), 7.51 (d, 2H, J = 9.0 Hz, Ar*H*), 7.37-7.29 (m, 6H, Ar*H*), 7.24-7.19 (m, 4H, Ar*H*), 7.12 (m, 4H, Ar*H*), 5.18 (d, 2H, J = 12.5 Hz, ArCH_2O), 5.07 (d, 2H, J = 12.0 Hz, ArCH_2O), 4.06 (m, 2H, OCH_2), 3.87 (m, 2H, OCH_2), 3.44 (m, 2H, OCH_2), 3.26 (m, 2H, OCH_2), 2.99 (q, 4H, OCH_2); ^{13}C NMR δ 158.44, 154.22, 153.75, 149.23, 147.19, 146.50, 146.04, 134.26, 134.22, 129.99, 129.79, 129.62, 128.13, 128.10, 127.73, 126.79, 126.71, 125.80, 125.64, 125.11, 124.85, 124.32, 124.03, 121.17, 120.58, 120.32, 119.79, 115.94, 115.50, (Ar), 70.63, 69.87, 69.34 (OC H_2), 68.70 (Ar*C* H_2O); Anal. calcd. for $C_{60}H_{46}N_4O_{11}$ (999.03): C 72.13, H 4.64, N 5.60, found C 71.97, H 4.62, N 5.50%.

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