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Synthesis of the proton-ionizable lariat crown ether and chiral recognition of primary amines

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Abstract—An optically active proton-ionizable lariat crown ether derivative **2** was prepared. Host **2** displays enantiomeric selectivity toward phenylglycinol (K_{large}/K_{small}=3.2) and phenylalaninol (K_{large}/K_{small}=1.7). The key intermediate **1** was synthesized in two steps from commercially available binaphthol in 30% yield.

1. Introduction

Optically active 1,1′-binaphthyl skeletons[1] have been widely used as highly effective catalysts in the field of asymmetric synthesis.[2] Furthermore, when substituted onto chiral crown ethers, the 1,1′-binapthyl moiety has enabled the development of receptors capable of chiral recognition.[3,4] Among these receptors, several lariat binaphthyl crown ethers have been reported,[5] most with lariat parts on the 3,3′ positions.[6] We expected that a host molecule with lariat functionality on the crown ring, especially in the opposite side of the 1,1′-binaphthyl group, could effectively discriminate chirality of guest molecules. Following this model, a novel binaphthyl crown ether **1** possessing a scaffolding hydroxy group in the opposite direction of binaphthyl, has been synthesized. One of advantages of this basic structure **1** includes capabilities to serve as a starting material to a number of tailor-made synthetic hosts by chemical transformations of the hydroxy group. In this paper, we report the synthesis of a host molecule **2** with nitrophenol as the lariat moiety,[7] and the synthesis of the intermediate binaphthyl crown alcohol **1**. The degree of chiral recognition for primary amines will additionally be discussed (Fig. 1).

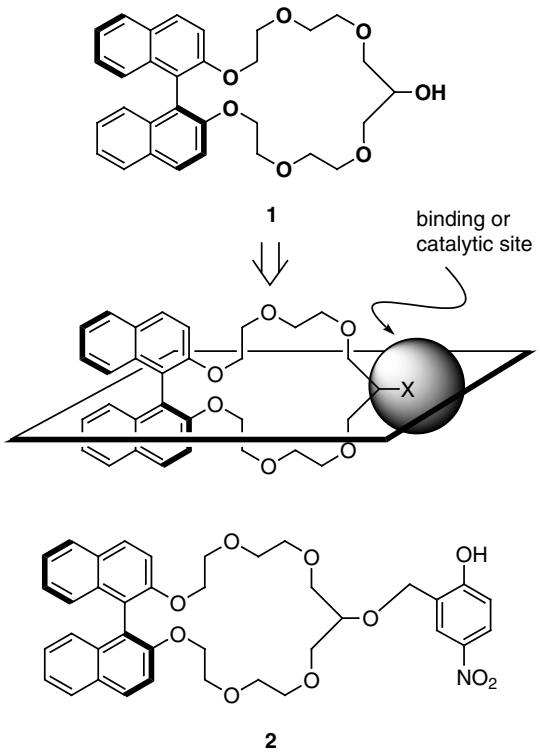

Figure 1.

2. Results and discussion

Syntheses of the intermediate **1** and host molecule **2** were carried out as outlined in Scheme 1. (*S*)-Binaphthol (>99% ee) was reacted with 2-(2-chloroethoxy)-ethanol in the presence of potassium carbonate and potassium iodide, followed by cyclization with epichlorohydrin in the presence of potassium tetrafluoroborate as a template to afford the binaphthyl crown alcohol **1** in 30% yield. As suitable conditions for determining the enantiomeric excess of **1** were not found, the binaphthyl crown alcohol was converted to its acetate **3** in 97.0% ee. The binaphthyl crown alcohol **1** (97.0% ee) was treated with TsCl to give tosylate **4**, and was then recrystallized twice from ethyl acetate in 76% yield. The tosylate **4** was converted to

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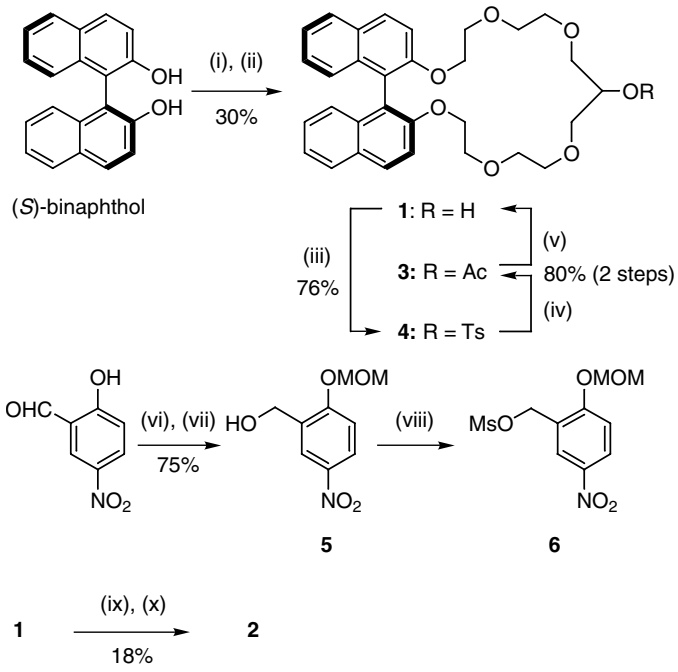


Scheme 1. *Conditions*: (i) 2-(2-Chloroethoxy)ethanol, K_2CO_3, KI; (ii) epichlorohydrin, KOH, KBF_4; (iii) TsCl, pyridine; (iv) AcOK; (v) NaOH; (vi) MOMCl; (vii) $NaBH_4$; (viii) MsCl; (ix) NaH, **6**; (x) HCl.

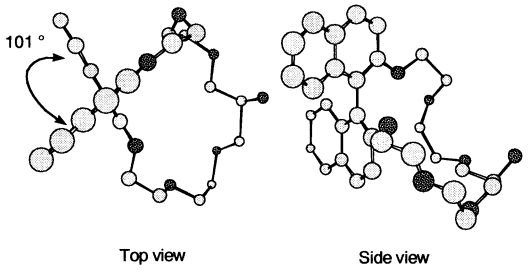


Figure 2. Crystal structure of (±)-**1**. Hydrogen atoms are excluded for clarity.

optically pure binaphthyl crown alcohol **1** by nucleophilic acetoxylation followed by hydrolysis in 80% overall yield for two steps. 5-Nitrosalicylaldehyde was protected by the MOM group and reduced with sodium borohydride to give the benzyl alcohol **5** in 75% yield. Treatment of **5** with methanesulfonyl chloride[8] gave the corresponding mesylate **6** which was reacted with binaphthyl crown alcohol **1** in the presence of sodium hydride followed by deprotection of the MOM group under acidic conditions to afford the host molecule **2** in 18% yield. An X-ray crystallographic analysis of **1** derived from (±)-binaphthol defined the structure unequivocally (Fig. 2). X-Ray analysis revealed the dihedral angle of the two naphthalene rings to be 101°.

Initially, complexation between host molecule **2** and

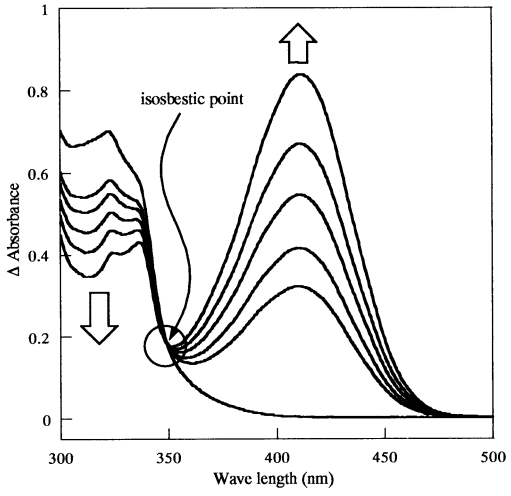


Figure 3. Absorption spectra of host **2** in the presence of *n*-butylamine in methanol/acetonitrile=1:9 at 25°C. [**2**]=5.0×10^{-5} M, [*n*-butylamine]=0–1.9×10^{-2} M.

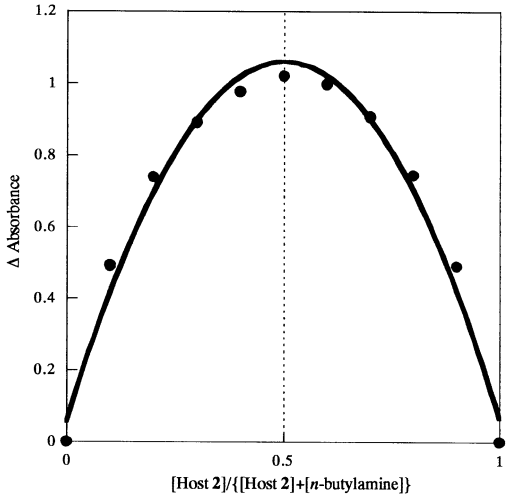


Figure 4. Job plot of host **2** and *n*-butylamine in methanol/acetonitrile=1:9 at 25°C.

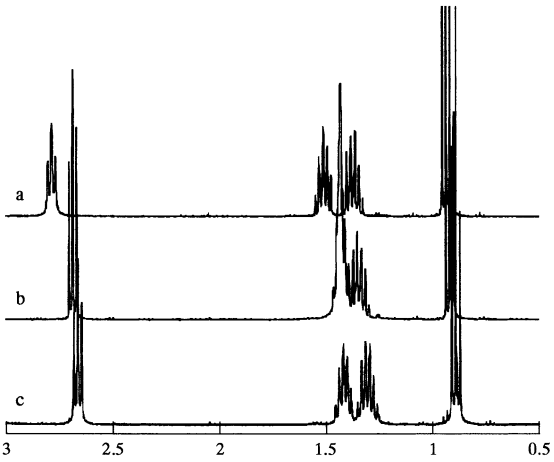


Figure 5. Partial ^{1}H NMR (400 MHz) spectra of (a) *n*-butylamine *p*-nitrophenolate, (b) *n*-butylamine and (c) 1:1 mixture of host **2** and *n*-butylamine in $CDCl_3$ at 25°C.

n-butylamine was investigated. The isosbestic point at 349 nm as well as a Job plot based on Δ absorbance at 413 nm indicated the formation of a 1:1 complex in methanol/acetonitrile=1:9 solution (Figs. 3 and 4).

To understand the mode of complexation, NMR studies of **2** and *n*-butylamine were performed (Fig. 5). Normally, the signals of *n*-butylamine *p*-nitrophenolate shift to a lower magnetic field compared to free *n*-butylamine due to a decrease in the electron density of the nitrogen atom (Fig. 5a). However, signals ascribed to *n*-butylamine in the 1:1 complex were shifted to a higher magnetic field (Fig. 5c). This indicates that *n*-butylamine is located under the shielding field of the naphthyl rings of host **2**. Furthermore, cross peaks between the crown methylene protons of **2** and α-methylene protons of *n*-butylamine, as well as the crown methylene protons and benzylic methylene protons of **2** were observed in the NOESY spectrum (Fig. 6). These findings indicate that the ammonium ion, generated from an acid–base reaction between a lariat nitrophenol of host **2** and free *n*-butylamine, is incorporated into the crown ring through cation–dipole interaction with oxygen atoms of host **2** and/or through cation–π interaction between the two naphthyl rings of host **2**.

Association constants between host molecule **2** and *n*-hexylamine in various solvents at 25°C were determined by UV–visible titration and analyzed by the Rose–Drago method.[9,10h] Solvent should play an important role in this host–guest complexation as the host, the guest, and the resulting complex will be stabilized to different degrees in solvents of various polarities. In the case of this system, acidity of the lariat nitrophenol should be affected by polarity of the solvent, thus, the trigger for the acid–base reaction between nitrophenol and *n*-hexylamine is influenced by the nature of solvent. Association constants and λ_{max} are summarized in Table 1. The association constant varies with solvent from K_a=14 (THF) to $K_a>10^5$ (DMSO). In addition, large solvatochroism was also observed with a 44 nm change to λ_{max}. With the exception of methanol, it was observed that shifts of λ_{max} roughly correlated to the $E_T(30)$ values.[11]

Since enantiomeric recognition of chiral compounds was first reported by Cram and co-workers,[3b,c] various kinds of host molecules have been synthesized. Some of them have

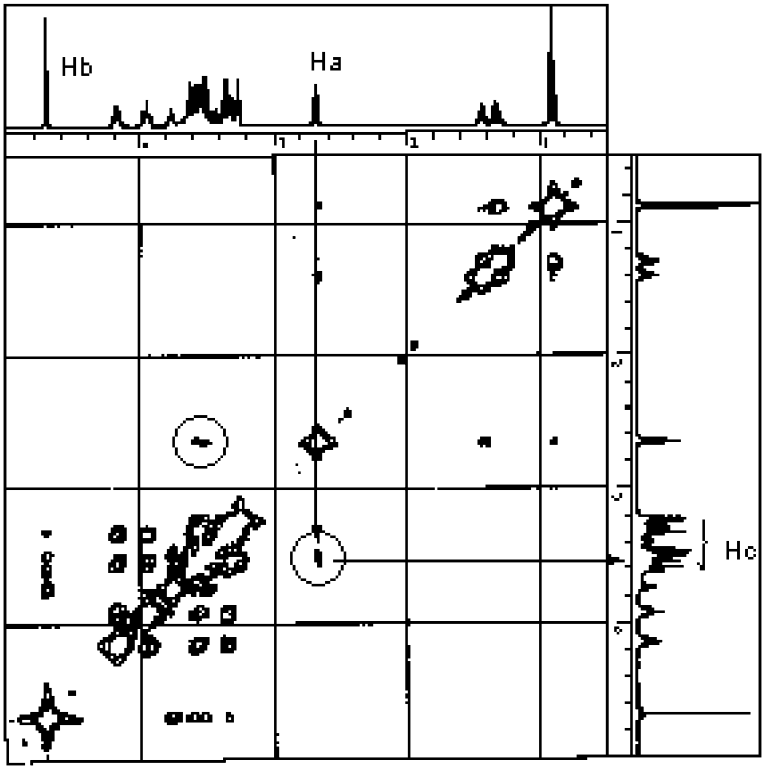


Figure 6. NOESY (400 MHz) spectrum of a 1:1 mixture of host **2** (2.2×10^{-2} M) and *n*-butylamine (2.2×10^{-2} M) in $CDCl_3$ at 21°C. Ha means the α protons of *n*-butylamine, Hb and Hc mean the benzyl protons of the lariat part and those of crown ether part of host **2**, respectively.

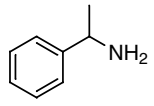
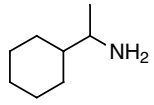
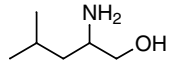
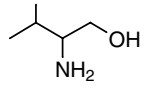
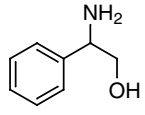
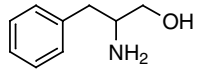
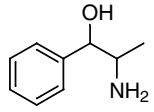
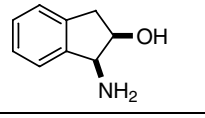
Table 1. Association constants (K_a) and λ_{max} of the complex of host **2** with *n*-hexylamine

Entry	Solvent	K_a	λ_{max} (nm)
1	THF	14±1	395
2	$CHCl_3$	46±5	407
3	CH_3CN	115±5	422
4	MeOH	5290±30	403
5	DMSO	$>10^5$	439

The association constants were determined by UV–visible titration at 25°C and analyzed by Rose–Drago method.[9,10h]

been reported to discriminate enantiomers by color change.[10] Hence, we checked the ability of the enantiomeric recognition of host molecule **2** toward various types of primary amines. The association constants (K_a) were determined by UV titration in a methanol/acetonitrile=1:9 mixed solvent system at 25°C. In each association experiment, a 1:1 binding stoichiometry has been assumed. This was generally supported by observation of the isosbestic point during titration. Table 2 shows the association constants and the enantioselectivity ratio. The association constants were generally moderate and enantioselectivity ratios were small. Unambiguous chiral discrimination was found for phenylglycinol (K_R/K_S=3.2) as shown in Fig. 7. Enantioselective recognition was also observed for phenylalaninol

Table 2. Association constants for the complexes of host **2** with various amines

Entry	Structure	Configuration	K_a	K_{large}/K_{small}
1		(*R*) (*S*)	66.9±2.9 62.6±2.5	1.1
2		(*R*) (*S*)	925.8±47.8 976.9±50.0	1.1
3		(*R*) (*S*)	368.3±12.8 357.3±14.0	1.0
4		(*R*) (*S*)	248.7±15.6 217.7±15.4	1.1
5		(*R*) (*S*)	30.4±1.2 9.4±0.5	3.2
6		(*R*) (*S*)	86.7±2.1 148.6±8.6	1.7
7		(1*R*,2*S*) (1*S*,2*R*)	119.7±4.0 124.3±3.4	1.0
8		(1*R*,2*S*) (1*S*,2*R*)	48.1±3.8 52.4±5.0	1.1

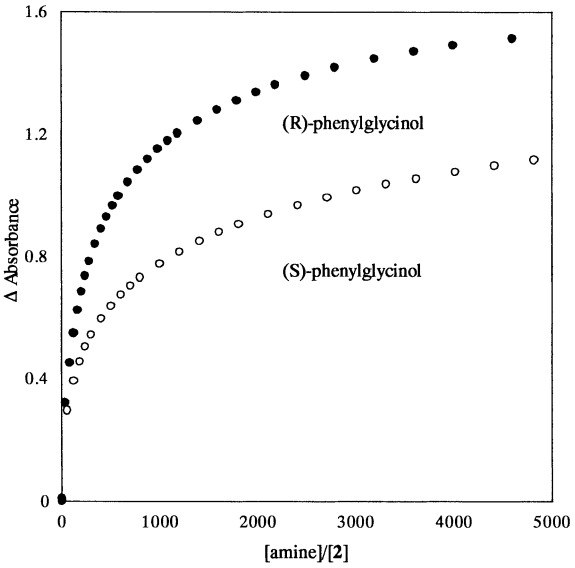


Figure 7. Δ absorbance at 413 nm vs. [amine]/[**2**] plot in methanol/acetonitrile=1:9 at 25°C.

(K_S/K_R=1.7), though the degree of selection was small. The reverse selectivity is noteworthy but as yet unexplained.

3. Conclusions

In the present study, optically active binaphthyl crown alcohol **1** was synthesized in only two steps from commercially available binaphthol in 30% yield. Introducing a nitrophenol group as a lariat moiety onto the scaffolding hydroxy group, the chromogenic host molecule **2** was easily constructed. Host **2** can discriminate enantiomers of phenylglycinol by color development. The parent crown alcohol **1** is a useful building block for chiral recognition as various lariat units, which act as binding or catalytic sites, can be introduced easily in reactions of a small number of steps.

4. Experimental

4.1. General

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 or 400 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard and couplings are expressed in Hz. FT-IR and UV spectra were obtained on a JASCO FT/IR-300 and Shimadzu-2200, respectively.

4.1.1. Binaphthyl crown alcohol (*S*)-1 (97.0% ee). A mixture of (*S*)-binaphthol (20.0 g, 70 mmol), potassium carbonate (48.0 g, 0.35 mol), potassium iodide (2.3 g, 14 mmol) and 2-(2-chloroethoxy)-ethanol (29 ml, 0.28 mol) in DMF (350 ml) was stirred at 100°C over night. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed successively with water (three times), hydrochloric acid, and brine. After drying over sodium sulfate, the solvent was evaporated in vacuo. To the solution of residue (33.6 g) in dioxane (1000 ml), potassium hydroxide

(23.0 g, 0.35 mol), potassium tetrafluoroborate (9.7 g, 77 mmol) and epichlorohydrin (6.0 ml, 77 mmol) were added and the reaction mixture was stirred at 80°C over night. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate and hydrochloric acid. The organic layer was washed successively with water (twice) and brine, dried over potassium carbonate, and evaporated. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate=1:1 to ethyl acetate) to afford **1** as colorless viscous oil (10.9 g, 30% yield). Small amount of **1** was converted to the corresponding acetate **3** to determine ee. The optical purity of **3** was determined to be 97.0% ee by HPLC (Daicel Chiralpak AD column, 1.0 ml min^{-1}, hexane/2-propanol=90:10, t_R 33.0 min for the (*S*)-isomer and 40.0 min for the (*R*)-isomer).

4.1.2. Tosylate (*S*)-4. *p*-Toluenesulfonyl chloride (1.80 g, 9.54 mmol) was added portionwise to a solution of **1** (97% ee, 3.3 g, 6.36 mmol) in pyridine (30 ml) at 0°C and the reaction mixture was stirred over night. Additional toluenesulfonyl chloride (0.36 g, 1.91 mmol) was added to the solution and stirred for further 8 h. The reaction mixture was poured into the mixed solvent of ethyl acetate and hydrochloric acid. The organic layer was separated, washed successively with water (twice), aqueous sodium hydrogen carbonate, water, and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was recrystallized from ethyl acetate (twice) to afford **4** as pale yellow crystals (3.27 g, 76% yield), mp 121–123°C; $[\alpha]_D^{20}=-106.1$ (c=1.01, $CHCl_3$); IR (KBr) 3055, 1620, 1508 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.1–3.6 (16H), 3.9–4.2 (4H), 4.61 (m, 1H), 7.1–7.5 (10H), 7.7–8.0 (6H); HRMS Calcd for $C_{38}H_{40}O_9S$: 672.2393. Found: 672.2364; Anal. Calcd for $C_{38}H_{40}O_9S$: C, 67.84; H, 5.99. Found: C, 67.66; H, 6.05. Small amount of **4** was converted to the acetate **3** to determine its ee (>99% ee).

4.1.3. Binaphthyl crown alcohol (*S*)-1 (>99% ee). A mixture of **4** (3.0 g, 4.46 mmol) and potassium acetate (4.4 g, 44.6 mmol) in DMF (50 ml) was stirred at 100°C for 8 h. The reaction mixture was poured into the mixed solvent of ethyl acetate and hydrochloric acid. The organic layer was separated and washed with water (twice), brine and then dried over sodium sulfate. Evaporation to dryness in vacuo gave (*S*)-**3** (3.0 g), which was directly used for the next step without further purification. A small amount of (*S*)-**3** was subjected to further purification by PTLC to give analytical sample as colorless viscous oil (>99% ee). $[\alpha]_D^{20}=-115.4$ (c=0.51, $CHCl_3$); IR (KBr) 2890, 1734, 1591 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.2–3.7 (16H), 3.9–4.3 (4H), 5.03 (m, 1H), 7.1–7.5 (8H), 7.8–8.0 (4H); HRMS Calcd for $C_{33}H_{36}O_8$: 560.2411. Found: 560.2407; Anal. Calcd for $C_{33}H_{36}O_8$: C, 70.70; H, 6.47. Found: C, 70.44; H, 6.74. The solution of crude (*S*)-**3** (3.0 g) in THF (50 ml), methanol (25 ml) and 0.2 M sodium hydroxide (20 ml) was stirred over night at room temperature. The reaction mixture was poured into the mixed solvent of ethyl acetate and hydrochloric acid. The organic layer was separated, washed successively with water (twice) and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate=1:1 to ethyl acetate) to afford **1** as colorless viscous oil (1.86 g, 80% yield). $[\alpha]_D^{20}=-135.1$ (c=1.00, $CHCl_3$); IR (KBr) 3435, 3055, 1610 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.64 (brs, 1H), 3.0–3.7 (16H), 3.82 (m, 1H), 3.9–4.3 (4H), 7.1–7.5 (8H), 7.8–8.0 (4H); HRMS Calcd for $C_{31}H_{34}O_7$: 518.2305. Found: 518.2291. Anal. Calcd for $C_{31}H_{34}O_7$: C, 70.57; H, 6.69. Found: C, 70.71; H, 6.65.

4.1.4. Benzyl alcohol 5. To a mixture of 5-nitrosalicylaldehyde (10.0 g, 60 mmol) and potassium carbonate (125 g, 0.9 mol) in DMF (200 ml), methoxymethyl chloride (70 g, 0.9 mol) was added dropwise under water-bath cooling. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed with brine (three times), dried over magnesium sulfate, and evaporated in vacuo to give a residue (21.5 g). Sodium borohydride (11.0 g, 0.9 mol) was added portionwise to the residue (21.5 g) in methanol (200 ml) at 0°C for 1.5 h. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed successively with hydrochloric acid and brine (three times), dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate=1:1) to afford **5** as a pale yellow solid (9.56 g, 75% yield), mp 77–78°C; IR (KBr) 3365, 1612, 1512 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.51 (s, 3H), 4.78 (s, 2H), 5.33 (s, 2H), 7.19 (d, J=9.0 Hz, 1H), 8.16 (dd, J=9.0 2.2 Hz, 1H), 8.31 (d, J=2.2 Hz, 1H); HRMS Calcd for $C_9H_{11}NO_5$: 213.0637. Found: 213.0639. Anal. Calcd for $C_9H_{11}NO_5$: C, 50.57; H, 5.20; N, 6.57. Found: C, 50.74; H, 5.24; N, 6.42.

4.1.5. Host (*S*)-2. To a solution of **5** (3.49 g, 16.4 mmol) and triethylamine (22.9 ml, 164 mmol) in dichloromethane (85 ml) was added dropwise methanesulfonyl chloride (3.8 ml, 49.2 mmol) at 0°C. After stirring for 1 h, the mixture was poured into the mixed solvent of diethyl ester and water. The organic layer was separated, washed successively with water, hydrochloric acid, aqueous sodium hydrogen carbonate, water (three times), and brine, dried over magnesium sulfate, and evaporated in vacuo to give crude mesylate **6**,[8] which was directly used for the next step without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 3.10 (s, 3H), 3.52 (s, 3H), 3.3 (m, 4H), 7.26 (d, J=9.2 Hz, 1H), 8.26 (dd, J=9.2, 2.6 Hz, 1H), 8.32 (d, J=2.6 Hz, 1H); HRMS Calcd for $C_{10}H_{13}NO_7S$: 291.0413. Found: 291.0423. In another vessel, sodium hydride (60% in mineral oil, 0.27 g, 6.56 mmol) was added portionwise to a solution of **1** (1.70 g, 3.28 mmol) in DMF (30 ml) at 0°C and the mixture was stirred for 30 min. Crude mesylate **6** in DMF (30 ml) was added dropwise to the mixture at 0°C and the mixture was stirred over night at room temperature followed by warming to 50°C for 1 h. The mixture was poured into the mixed solvent of ethyl acetate and aqueous hydrochloric acid. The organic layer was separated, washed successively with water (three times) and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was dissolved in 4 M hydrogen chloride in ethyl acetate (3.0 ml) and the solution was stirred for 8 h. The reaction mixture was evaporated in vacuo and the residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate=1:1) to afford **2** as pale yellow foam (0.394 g, 18% yield). For

determination of binding constants, **2** was further purified by preparative recycling HPLC (chloroform). $[\alpha]_D^{19}=-178.2$ ($c=1.00$, $CHCl_3$); IR (KBr): 3272 (br), 1621, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.20–3.64 (16H), 3.76–3.80 (1H), 3.92–4.21 (4H), 4.38 (s, 2H), 6.92 (d, $J=9.0$ Hz, 1H), 7.17–7.26 (4H), 7.30–7.35 (2H), 7.46 (dd, $J=12.1$, 9.0 Hz, 2H), 7.85 (dd, $J=8.0$, 4.6 Hz, 2H), 7.91 (t, $J=9.0$ Hz, 2H), 7.99 (d, $J=2.9$ Hz, 1H), 8.11 (dd, $J=9.4$, 3.0 Hz, 1H); HRMS Calcd for $C_{38}H_{39}NO_{10}$: 669.2574. Found: 669.2556. Anal. Calcd for C_{38} $H_{39}NO_{10}\cdot H_2O$: C, 66.36; H, 6.01; N, 2.04. Found: C, 66.34; H, 5.70; N, 2.03.

4.1.6. X-Ray crystallographic analysis of (±)-1. $C_{31}H_{34}O_7$, $M=518.61$, triclinic, $a=11.719(1)$, $b=12.8204(8)$, and $c=10.0773(7)$ Å, $\alpha=92.135(6)$, $\beta=103.795(6)$, and $\gamma=66.940(5)°$, $V=1350.2(2)$ $Å^3$, space group P-1 (#2), $Z=2$, $D_{calcd}=1.276$ g cm^{-3}, μ(Cu Kα)=7.33 cm^{-1}, λ(Cu Kα)=1.54178 Å, $T=296$ K, 4822 reflections measured, 4594 unique ($R_{int}=0.023$) which were used in all calculations. $R_1=0.093$, $Rw=0.075$. Further details of the crystal structural investigation are available on request from the Director of the Cambridge Crystallographic Data Centre.

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