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# Chromophoric Binaphthyl Derivatives

**Tomáš Bříza,[†] Zdeněk Kejík,[†] Petr Vašek,[†] Jarmila Králová,[‡] Pavel Martásek,[§] Ivana Císařová,[§] and Vladimír Král*,[†]**

*Department of Analytical Chemistry Technická 5, Institute of Chemical Technology, CZ-166 28, Prague 6, Czech Republic, and Institute of Molecular Genetics, Academy of Sciences, Fleming's Square 2, CZ-166 10, Prague 6, Czech Republic, and First Faculty of Medicine, Charles University in Prague, Kateřinská 32, CZ-121 08 Prague 2, Czech Republic*

*vladimir.kral@vscht.cz*

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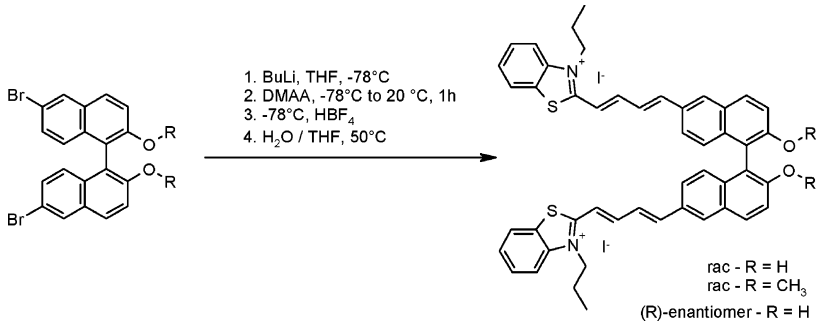
## ABSTRACT




**A short synthetic route is outlined, starting from bromo-BN derivatives, via halogen lithium exchange, subsequent Michael reaction with dimethylaminoacrolein, hydrolysis to the corresponding aldehyde, and final condensation with a benzothiazolium unit to produce a BN–pentamethinium system, which absorbs in the visible range around 450 nm. Enantiopure ligands show a decent Cotton effect in the CD spectrum. Preliminary data show potential of these compounds in the area of supramolecular chemistry (enantioselective recognition) and also for medicinal application (induction of apoptosis).**

Binaphthyl derivatives have been used in the construction of a variety of receptors, including chiral sensing systems for biologically important analytes. Examples include receptors for amino acids,[1−3] saccharides,[4−6] carboxylates.[7,8] In addition, they have been used as building blocks in syntheses of chiral dendrimers and linear polymers.[9] Despite this progress, there is a significant drawback inherent in this class of receptors. They cannot be applied in the chromophoric detection of a binding event.

This limitation may be overcome via the appendage of a chromophoric unit to the binaphthyl skeleton. There are only a few examples of chromophoric binaphthyl derivatives known to date. To the best of our knowledge, there is only one example where azobenzene photochromism is combined with the chirality of a 2,2′-dihydroxy-1,1′-binaphthyl unit.[10]

We described recently reported binaphthyl-decorated porphyrin macrocycles, where cooperativity of Binap OH groups on the macrocyclic scaffold led to selective binding of oligosaccharides in protic media.[11−13]

[†] Institute of Chemical Technology.
[‡] Academy of Sciences.
[§] Charles University in Prague.

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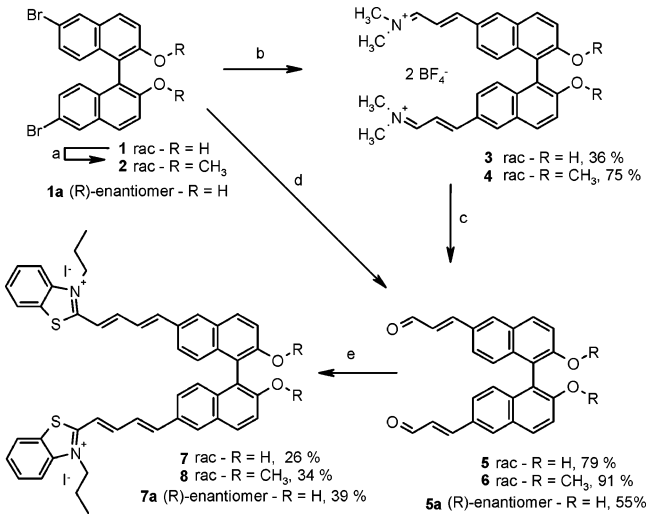
**Scheme 1.** Synthesis of Polymethinium Binaphthyl Chromophores **7** and **8**[a]




[a] Reagents and conditions: (a) $(MeO)_2SO_2$, $K_2CO_3$, $CH_3CN$. (b) (1) BuLi, THF, −78 °C, 10 min; (2) dimethylaminoacrolein, −78 °C to rt, 60 min; (3) $HBF_4$ in THF, −78 °C to rt. (c) THF/$H_2O$ (3:2), 50 °C, 2 h. (d) (1) NaH 0 °C, 15 min; (2) BuLi, THF, −78 °C, 10 min; (3) dimethylaminoacrolein, −78 °C to rt, 60 min; (4) $HBF_4$ in THF, −78 °C to rt; (5) THF/$H_2O$ (3:2), 50 °C, 2 h. (e) 2-Methyl-3-propyl benzothiazolium iodide, *n*-BuOH/benzene (7:3), $MgSO_4$, reflux 5 h.

To pursue our strategy to develop novel, inherently chromophoric 1,1′-binaphthyl systems, we selected a polymethinium salt as the chromophore. Polymethinium salts are very interesting, stable, conjugated systems with verstaile properties, allowing their use in nonlinear optical and medicinal applications.[14] They have been employed, for example, as antitumor agents.[15] Therefore, an important goal of this work is to synthesize chromophoric binaphthol−polymethine systems for use as novel photosensitizers, as potential antitumor agents for photodynamic therapy. Since the structure of this type of chromophore is very different from classical porphyrin and porphyrinoid derivatives, we envision novel properties to emanate from such compounds.

Initially, we decided to develop synthetic methods for the preparation of polymethinium binaphthyl chromophores from racemic compounds. Consequently, the method will be used for the preparation of enantiomerically pure chromophores from (*R*)-binaphthols.

As starting substrates for development of the synthetic protocol, we chose racemic 1,1′-binaphthyl-2,2′-diol **1** and racemic dimethoxyderivate **2**, prepared from commercial dibromobinaphthol **1**, according to a published procedure,[16] in 80% yield.

The key synthetic step involves selection of a proper agent for the introduction of polymethinium chains. We employed

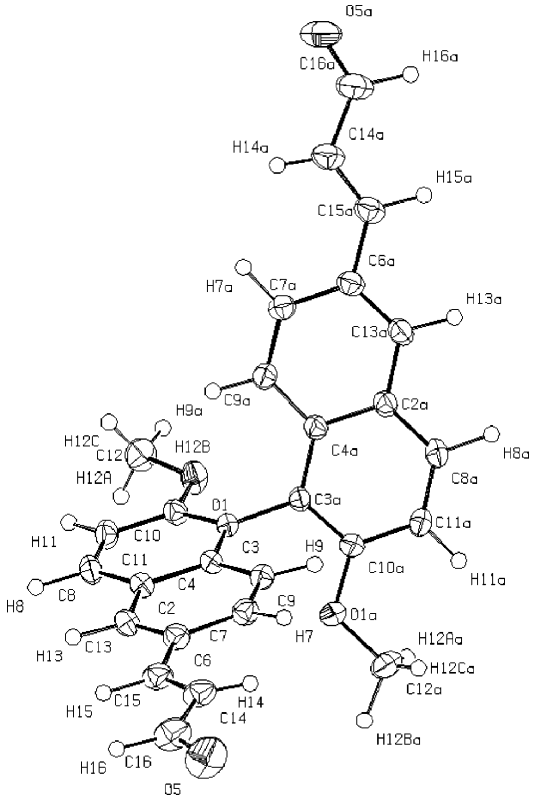



**Figure 1.** Single-crystal X-ray structure of dialdehyde **6**.

*N*,*N*-dimethylaminoacroleine (DMAA). Binaphthyl derivatives **1** and **2**, after transmetalation with BuLi at −78 °C, were transformed to the corresponding lithium salts. In the case of binaphthyl **1**, we used 4 equiv of BuLi due to the two −OH groups. The lithium salts were treated with DMAA over a temperature range from −78 to 20 °C. The reaction was quenched with an ethereal solution of tetrafluoroboric acid to furnish the binaphthyl trimethinium salts **3** and **4**. These salts are sensitive to air and solvent moisture. Therefore, they were used without further purification.

Trimethinium salts **3** and **4** do not fulfill the requirement for photosensitizers, since their maxima in the UV−vis region are at 220 nm. Therefore, we extended the conjugation of the trimethinium chromophore to pentamethinium, according to the strategy summarized in (Scheme 1). The trimethinium salts **3** and **4** were converted to corresponding aldehydes **5** and **6** (Figure 1) via hydrolysis in a THF−$H_2O$ medium at 50 °C.

Aldehydes **5** and **6** were used as building blocks toward the synthesis of desired polymethinium binaphthyl salts **7** and **8**. We used a general method for transforming polymethine aldehydes to polymethinium salts.[17] We reacted 2-methyl-3-propyl-benzothiazolium iodide with **5** or **6**[18] in a mixture of *n*-BuOH/PhH (7:3) in the presence of anhydrous $MgSO_4$. This afforded the desired binaphthyl salts **7** and **8**.[19]

In the second-generation synthesis, involving optically pure materials, we decided to prepare the chromophore from (*R*)-

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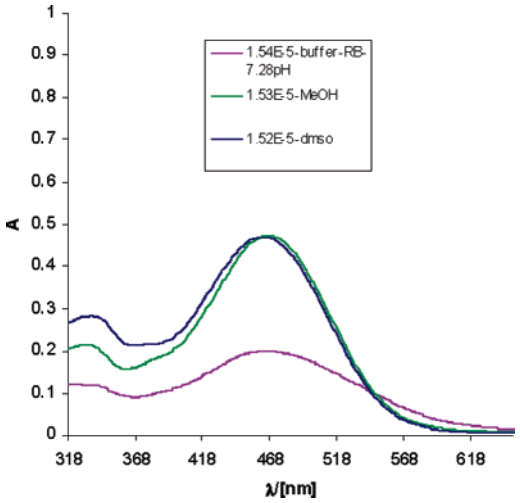


**Figure 2.** UV−vis spectra of receptor **8** in various solvents.

6,6′-dibromo-1,1′-binaphthyl-2,2′-diol **1a**. We have slightly modified the aforementioned method. First, **1a** was transformed to the sodium salt with NaH followed by lithiation. After addition of DMAA, the reaction was quenched with tetrafluoroboric acid. The salt was not isolated, and a solution of THF and $H_2O$ (3:2) was added. After the mixture was heated at 50 °C, the corresponding bisaldehyde **5a** was obtained. The final step involving connection of the benzothiazolium unit was accomplished under the same conditions as described above, resulting in the desired (*R*)-polymethinium binaphthyl chromophore **7a** (Scheme 1).

UV−vis spectra of binaphthyl derivative **8** were measured in buffer-RB-7.28 pH, methanol, and dimethyl sulfoxide (Figure 2).

For chiral binaphthyl derivate **7a**, the ECD spectra were measured in dimethyl sulfoxide (Figure 3).

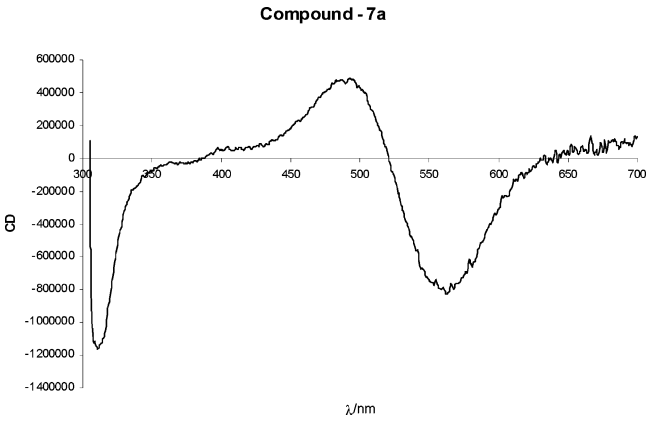


**Figure 3.** ECD spectrum of receptor **7a** in DMSO.

Initial studies of enantioselective complexation involved selected amino acids in buffered media (pH 7.2). Phe ($c = 1.16 \times 10^{-4}$) was used in 11.6 equiv for 1 equiv of binaphthyl **7a** ($c = 1.00 \times 10^{-5}$). The complexation of D- and L-phenylalanine by receptor **7a** was carried out at pH 7.2 (Figure 4).

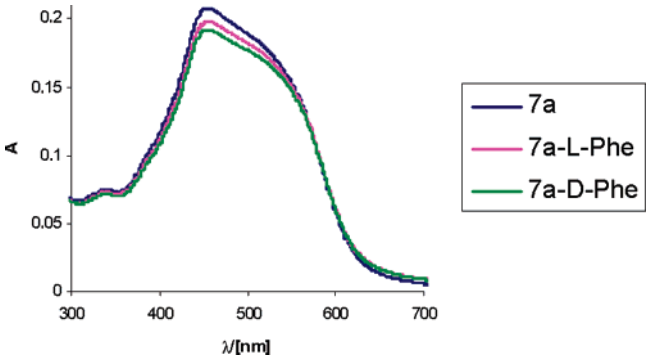


**Figure 4.** UV−vis spectrum of **7a**: interaction with D- and L-phenylalanine pH 7.2, 67 mM phosphate buffer.

We have developed the synthesis of chromophores **7**, **7a**, and **8**, trimethinium and pentamethinium binaphthyl systems, in rameric **7**, **8**, and enantioselective **7a** form as well. Although the major focus of the present work is on synthetic methodology, we would like to present also potential for

(18) **Compound 6: Description of Synthesis.** A flask equipped with a magnetic stirbar and a septum was charged with polymethinium salt **4** (90 mg, 0.14 mmol), $H_2O$ (2 mL), and THF (3 mL). The reaction mixture was heated in an oil bath to 55 °C for 2 h. After the reaction mixture was cooled to laboratory temperature, $H_2O$ (5 mL) was added. The reaction mixture was extracted with $CH_2Cl_2$ (2 × 5 mL). The organic portion was dried with anhydrous $MgSO_4$. Solvents were removed in vacuo. After column chromatography on silica (3 × 27 cm, eluent = $Et_2O$), product bis-aldehyde **6** (53 mg, 91%) was obtained. $^1$H NMR (300 MHz, $CDCl_3$, 20 °C, TMS): $\delta$ = 9.76 (d, $^3J$ (H,H) = 7.7 Hz, 2H), 8.05 (d, $^3J$ (H,H) = 9.6 Hz, 2H), 8.03 (d, $^3J$ (H,H) = 2.47 Hz, 2H), 7.60 (d, $^3J$ (H,H) = 15.7 Hz, 2H), 7.50 (d, $^3J$ (H,H) = 9.1 Hz, 2H), 7.42 (dd, $^4J$ (H,H) = 1.9 Hz, $^3J$ (H,H) = 9.1 Hz, 2H), 7.10 (d, $^3J$ (H,H) = 9.1 Hz, 2H), 6.72 (dd, $^3J$ (H,H) = 7.7 Hz, $^3J$ (H,H) = 15.7 Hz, 2H), 3.81 (s, 6H). $^{13}$C NMR (100.6 MHz, $CDCl_3$, 20 °C, TMS): $\delta$ = 193.7, 156.6, 153.0, 135.2, 131.2, 130.8, 129.4, 128.7, 127.8, 126.0, 124.2, 119.0, 114.4, 56.6. IR ($CDCl_3$) $\nu$ = 3024, 1674, 1618 (C=O). LRMS: calcd for $C_{28}H_{22}O_4$ (MH), 422.5; found, 422.7.

(19) **Compound 8: Description of Synthesis.** A flask equipped with a magnetic stirbar and an azeotropic head with a reflux condenser was charged with dialdehyde **6** (88 mg, 0.21 mmol), 2-methyl-3-propyl-benzothiazolium iodide (133 mg, 0.42 mmol), dry PhH (4.5 mL), and dry butan-1-ol (10.5 mL). Dry $MgSO_4$ (1 g) was added to the azeotropic head. The mixture was heated at reflux for 6 h and 25 min. After this time, starting bis-aldehyde was consumed (monitored by TLC). The reaction mixture was evaporated to dryness, and $CH_2Cl_2$ (5 mL) was added. The solid was material was filtered. The solution after filtration was shaken with $Et_2O$ (2 mL), and the solid was filtered off and washed with MeOH (2 mL). Both solid fractions were mixed and dried in vacuo. The salt **8** was obtained as a black-red solid (72 mg, 34%). $^1$H NMR (300 MHz, DMSO-$d_6$, 20 °C, TMS): $\delta$ = 8.42 (d, $^3J$ (H,H) = 8.0 Hz, 2H), 8.30 (d, $^3J$ (H,H) = 8.3 Hz, 2H), 8.24−8.08 (m, 6H), 7.86 (t, $^3J$ (H,H) = 7.4 Hz, 2H), 7.76 (t, $^3J$ (H,H) = 7.7 Hz, 2H), 7.72−7.58 (m, 8H), 7.46 (dd, $^3J$ (H,H) = 14.9 Hz, $^3J$ (H,H) = 15.1 Hz, 2H), 7.00 (d, $^3J$ (H,H) = 8.8 Hz, 2H), 4.72 (t, $^3J$ (H,H) = 7.2 Hz, 4H), 3.77 (s, 6H), 1.86 (q, $^3J$ (H,H) = 7.2 Hz, 4H), 1.00 (t, $^3J$ (H,H) = 7.2 Hz, 6H). $^{13}$C NMR (100.6 MHz, DMSO-$d_6$, 20 °C, TMS): $\delta$ = 171.0, 156.2, 150.0, 145.7, 141.3, 134.2, 130.9, 130.8, 130.6, 129.5, 128.6, 128.3, 128.1, 126.8, 125.3, 124.4, 124.1, 118.2, 116.7, 115.8, 114.9, 56.2, 49.9, 22.1, 10.7. UV/vis (MeOH): $\lambda_{max}$ ($\epsilon$) = 468 (29779), 331 (13830), 220 (53195). LRMS: for $C_{50}H_{46}N_2O_2S_2$. **2I** (MH-2I): calcd, 771.1; found, 771.6.

application of this class of compounds, namely, in two areas: First, even reported systems showed enantioselective complexation of selected amino acids under physiological conditions (See Supporting Information). The synthesis of more advanced receptors and enantioselective complexation is currently being explored in our laboratory. The vision for the second potential application came from recently reported interesting behavior of polymethine salts, which can function as inducers of apoptosis.[20]

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**Supporting Information Available:** Experimental details for various compounds mentioned herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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