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SYNTHESES AND PHOTOPHYSICAL PROPERTIES OF AMINOBENZOPYRANOXANTHENE DYES CONTAINING VARIOUS ALKYL CHAINS AT AMINE MOIETIES

Shinichiro Kamino,[a,b]* Masaru Tanioka,[a] Daisuke Sawada,[a,b] and Shuichi Enomoto[a,b]*

[a]Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama-shi, Okayama 700-8530, Japan. [b]Next-Generation Imaging Team, RIKEN-CLST, Kobe-shi, Hyogo 650-0047, Japan; E-mail: skamino@okayama-u.ac.jp, semo@riken.jp

Dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract – Aminobenzopyranoxanthene (ABPX) dyes containing linear *n*-alkyl chains at amino groups were synthesized, and their *cis* and *trans* stereoisomers were isolated. Detailed spectrophotometric studies revealed that all the ABPX derivatives exhibited fluorescence emission in the far-red and near-infrared wavelength regions, and their fluorescence quantum efficiency increased with increasing *n*-alkyl chain length. Almost no differences in photophysical properties were observed between the *cis* and *trans* stereoisomers.

The design and syntheses of organic dye molecules that emit fluorescence in the far-red to near-infrared (NIR) region have attracted much interest because of their potential photonic and biological applications, including night vision target identification, information security, *in vivo* optical imaging, and photosensitizers for photodynamic therapy.[1,2] Rhodamines, which are among the most popular xanthene dyes, possess excellent photophysical characteristics, including high fluorescence quantum yield, high absorptivity, and photostability.[3] However, the fluorescence and absorption wavelengths of rhodamines are typically below 600 nm. By the efforts of many researchers, new rhodamines with longer fluorescence emission wavelengths have appeared over the last few decades.[1,4,5] In particular, a series of NIR-rhodamines were developed by replacing the bridged oxygen atom with other elements (Si, Ge, and Sn) and were widely used in biological imaging.[6-8] The design and synthesis of new far-red to NIR

emissive rhodamine analogues are continually required, as their development could lead to advances in chemistry, materials science, biology, and medicine.

We have developed a new class of rhodamines, named aminobenzopyranoxanthene (ABPX) dyes, by extending the π-conjugation of the rhodamine skeleton.[9,10] The prototype of ABPX, ABPX 01 (**1**), exhibits long-wavelength fluorescence with a significant bathochromic shift of approximately 50 nm relative to conventional rhodamines (Figure 1).[11] The highly emissive ABPX derivative (**2**) was designed by rigid conjugation of the xanthene moiety, and exhibits fluorescence emission over a wide wavelength region exceeding 600 nm.[12] In an effort to develop another family of far-red to NIR emissive ABPX dyes, derivatives containing linear *n*-alkyl chains at amino groups were synthesized. The *cis* and *trans* stereoisomers were also separated and their photophysical properties were characterized in detail (**3a'-d'**).

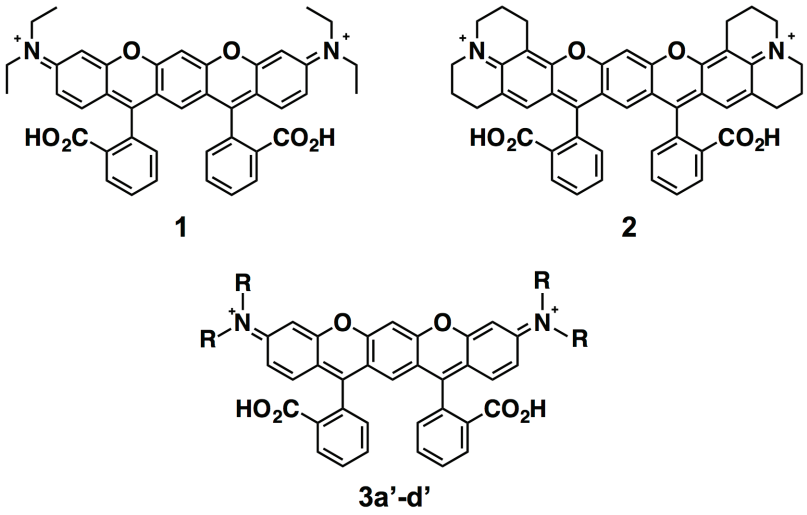
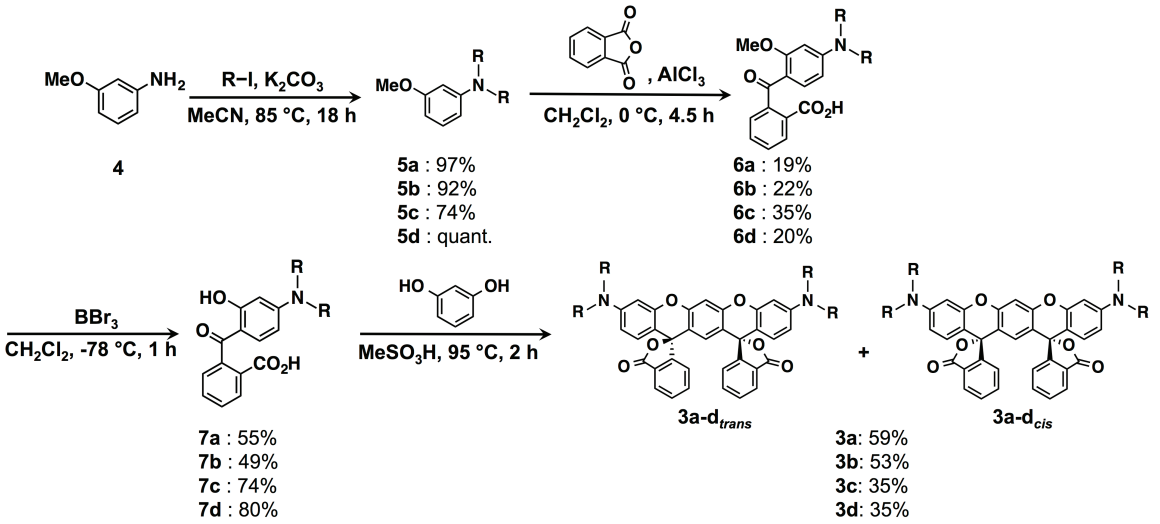


Figure 1. Chemical structure of ABPX dyes. **3a'**: R = *n*-C_3H_7, **3b'**: R = *n*-C_4H_9, **3c'**: R = *n*-C_6H_{13}, and **3d'**: R = *n*-C_8H_{17}

Initially, *N*,*N*-dialkyl-3-methoxybenzenamines **5a-d** were obtained from the reaction of 3-methoxyaniline **4** with an iodoalkane and K_2CO_3 in MeCN at 85 °C for 18 h, affording compounds **5a-d** in 74%~ quantitative yield. Compounds **5a-d** were acylated with phthalic anhydride in the presence of $AlCl_3$ in CH_2Cl_2 at 0 °C to generate the corresponding 2-carboxy-4-(dialkylamino)-2-methoxybenzophenones **6a-d**, whose methyl groups were deprotected by BBr_3 to afford the hydroxybenzophenones **7a-d**. The ^{1}H-NMR data of compounds **5a-c**, **6a-c** and **7a-c** were consistent with those of previous reports.[9] ABPX derivatives **3a-d** were facilely prepared by heat condensation of the corresponding compounds **7a-d** with resorcinol in $MeSO_3H$. For efficient and simple purification, it was important to take into account the equilibrium species of ABPX in solution, which indicated that ABPX would exist in the ionic form and the neutral form as shown in Figure 2. Therefore, during the work-up in $MeSO_3H$, the dicationic species of ABPX **3a'-d'** were completely converted into the neutral spirolactone species with the addition of

excess alkali solution to the reaction mixture. The spirolactone species of ABPX had two stereoisomers: the *cis* form (two spirolactone rings on the same side of the xanthene moiety) and the *trans* form (two spirolactone rings on the opposite side of the xanthene moiety); these stereoisomers were isolated, and their structures were characterized.



Scheme 1. Synthetic route of ABPX dyes containing various alkyl chains at amine moieties. **a**: R = *n*-C_3H_7, **b**: R = *n*-C_4H_9, **c**: R = *n*-C_6H_{13}, **d**: R = *n*-C_8H_{17}. **3a-d** describes the yield of the mixture of *cis*- and *trans* stereoisomers.

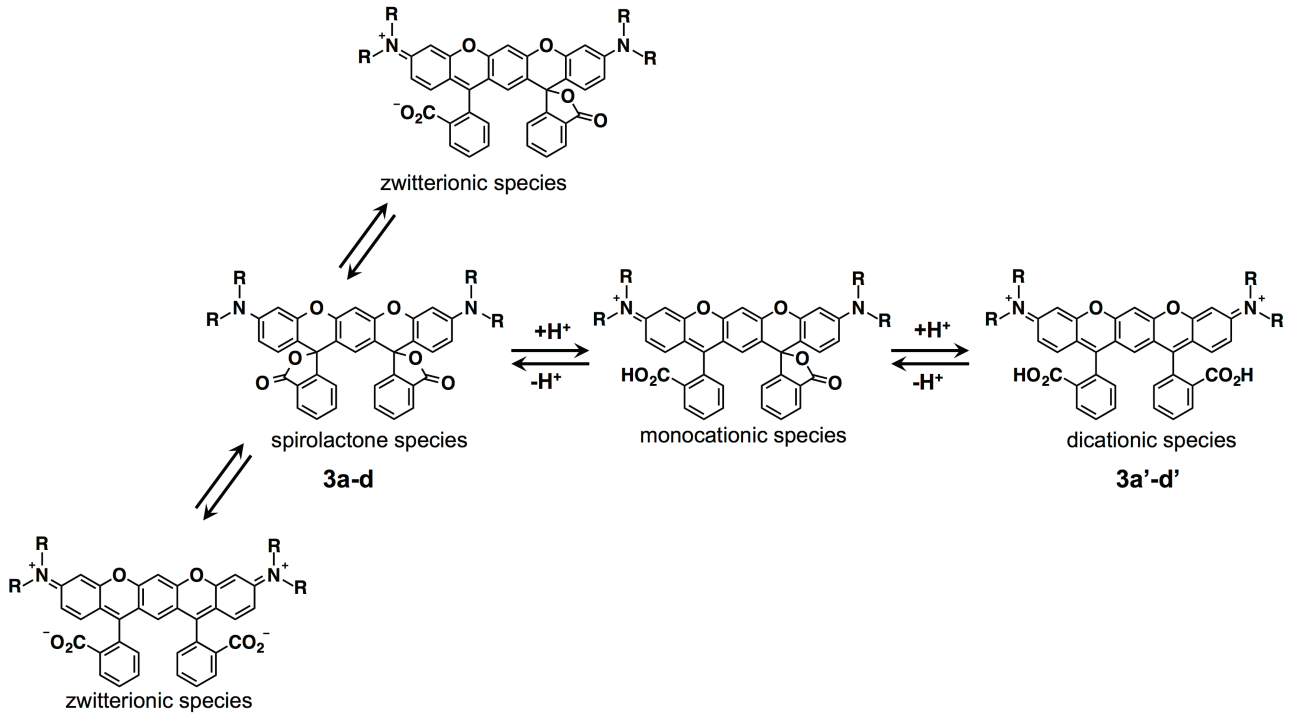


Figure 2. Chemical equilibrium species of ABPX dye in solution

To investigate the photophysical properties in solution, the spirolactone species of ABPX derivatives **3a-d** were dissolved in $CHCl_3$ containing 2.5% trifluoroacetic acid (TFA) and converted into their dicationic species **3a'-d'** (Figure 2), whose absorption and fluorescence spectra are shown in Figure 3.

The vibronic progression of the dicationic species was commonly observed in the absorption spectra, which meant that there was a coupling of the electronic and vibronic transitions. The longest wavelength band around 600 nm was attributed to the electronic 0-0 transition, and the second-longest wavelength band around 550 nm was attributed to the vibronic 0-1 transition. The molar extinction coefficients of these derivatives at $\lambda_{abs0\text{-}0}$ have a large common value of 120,000 M^{-1} cm^{-1}; all of the ABPX derivatives exhibited fluorescence over the wide far-red and NIR wavelength regions, as well as a small Stokes shift (20 nm). The relative fluorescence quantum yields (ϕ_{fl}) of these derivatives were measured by excitation at 366 nm using rhodamine B dye in ethanol (ϕ_{fl} = 0.73) as a reference. The details are summarized in Table 1, and the ϕ_{fl} of compounds **3a'-d'** were higher than those of **1**. Notably, the fluorescence quantum yields increased as the lengths of the *N*,*N*-dialkyl chains on the xanthene moiety increased, suggesting that the structural bulkiness of the alkyl chains prevented the aggregation-caused quenching. The ABPX derivatives were then dissolved in polar solvents such as MeOH, acetone, and MeCN containing 2.5% TFA, and their fluorescence spectra were measured (Figure 4). Low fluorescence quantum yields were observed in polar solvents, which were due to solvation that enhanced the nonradiative deactivation pathway in the ABPX derivatives (Table 2). However, the fluorescence wavelengths were almost unaffected by the solvent polarity changes, and the photophysical properties showed no difference between the *cis* and *trans* stereoisomers in solution for all of the ABPX derivatives.

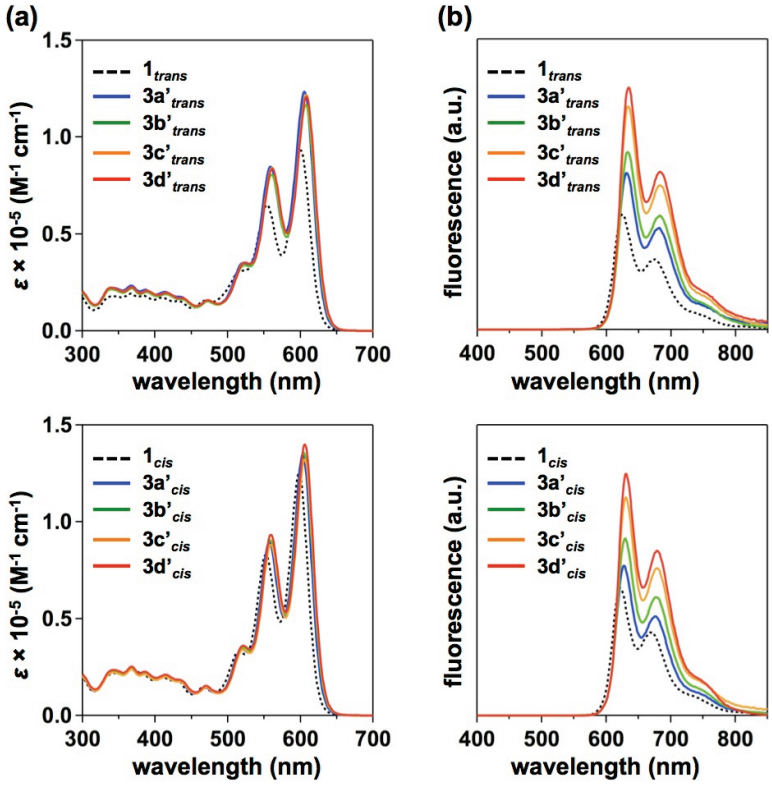


Figure 3. (a) Absorption and (b) fluorescence spectra of ABPX derivatives **3a'-d'** in $CHCl_3$ containing 2.5% TFA. Top panels: *trans* isomers; lower panels: *cis* isomers.

Table 1. Photophysical properties of ABPX derivatives **3a'-d'** in $CHCl_3$ solution containing 2.5% TFA

dye	R	$\lambda_{abs0\text{-}0}$ [nm]	$\lambda_{fl0\text{-}0}$ [nm]	$\lambda_{abs0\text{-}1}$ [nm]	$\lambda_{fl0\text{-}1}$ [nm]	$\varepsilon_{0\text{-}0}$ [$M^{-1}cm^{-1}$]	Φ_{fl}*2
$\mathbf{1}_{trans}$	*n*-C_2H_5	600	620	554	675	93000	0.15
$\mathbf{1}_{cis}$		598	616	552	670	122000	0.16
$\mathbf{3a'}_{trans}$	*n*-C_3H_7	606	626	559	683	122000	0.17
$\mathbf{3a'}_{cis}$		603	621	557	675	133000	0.18
$\mathbf{3b'}_{trans}$	*n*-C_4H_9	607	628	560	684	117000	0.19
$\mathbf{3b'}_{cis}$		605	623	558	678	136000	0.21
$\mathbf{3c'}_{trans}$	*n*-C_6H_{13}	608	628	561	684	118000	0.25
$\mathbf{3c'}_{cis}$		606	624	559	678	131000	0.28
$\mathbf{3d'}_{trans}$	*n*-C_8H_{17}	608	629	561	684	120000	0.28
$\mathbf{3d'}_{cis}$		606	624	559	678	139000	0.28

*1 Dye concentration was 200 μM. *2 Relative fluorescence quantum yields (ϕ_{fl}) were calculated by using rhodamine B (ϕ_{fl} = 0.73 in ethanol) as a standard.

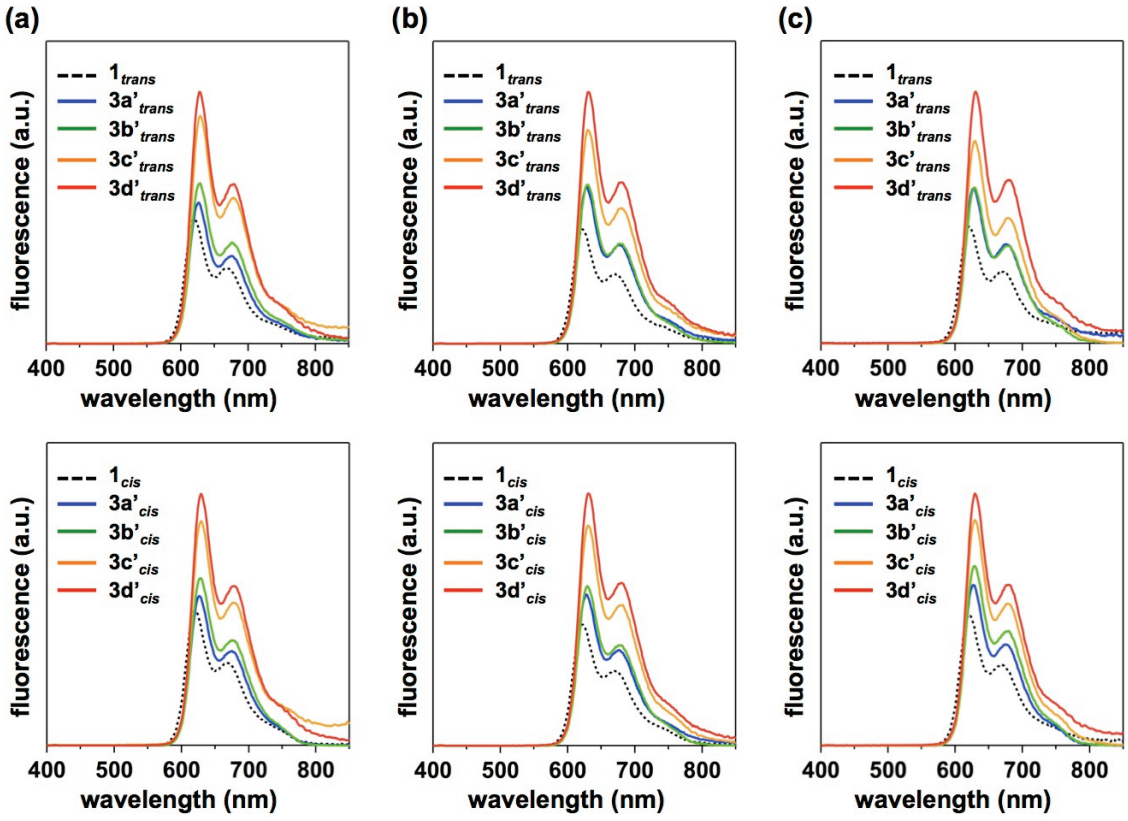


Figure 4. Fluorescence spectra of ABPX derivatives **3a'-d'** in (a) MeOH, (b) acetone, and (c) MeCN solution containing 2.5% TFA. Top panels: *trans* isomers; bottom panels: *cis* isomers.

Table 2. Fluorescence quantum yields of ABPX derivatives **3a'-d'** in various solvents

dye	R	$CHCl_3$	MeOH	acetone	MeCN
$\mathbf{1}_{trans}$	*n*-C_2H_5	0.15	0.07	0.07	0.06
$\mathbf{1}_{cis}$		0.16	0.08	0.07	0.06
$\mathbf{3a'}_{trans}$	*n*-C_3H_7	0.17	0.07	0.08	0.06
$\mathbf{3a'}_{cis}$		0.18	0.07	0.08	0.06
$\mathbf{3b'}_{trans}$	*n*-C_4H_9	0.19	0.08	0.08	0.07
$\mathbf{3b'}_{cis}$		0.21	0.08	0.08	0.07
$\mathbf{3c'}_{trans}$	*n*-C_6H_{13}	0.25	0.13	0.11	0.10
$\mathbf{3c'}_{cis}$		0.28	0.13	0.11	0.10
$\mathbf{3d'}_{trans}$	*n*-C_8H_{17}	0.28	0.14	0.13	0.12
$\mathbf{3d'}_{cis}$		0.28	0.14	0.13	0.11

[*1] Dye concentration was 200 μM. [*2] Relative fluorescence quantum yields (ϕ_{fl}) were calculated by using rhodamine B (ϕ_{fl} = 0.73 in ethanol) as a standard.

In conclusion, we synthesized aminobenzopyranoxanthene (ABPX) dyes containing various alkyl chains at amino groups and isolated their *cis* and *trans* isomers. Detailed spectrophotometric analyses revealed that these ABPX dyes exhibited fluorescence emission in the far-red and NIR wavelength regions. In addition, the fluorescence quantum yields improved with increasing alkyl chain length.

EXPERIMENTAL

Reagents and solvents were purchased from Tokyo Chemical Industries (Tokyo, Japan), Nacalai Tesque (Kyoto, Japan) and Wako Pure Chemical Industries (Osaka, Japan). All solvents were used without further purification. Flash column chromatography was conducted over silica gel (Merck Silica Gel 60 mesh 70-230). TLC plates were visualized under a UV lamp, by staining with an I_2-SiO_2 mixture, and by heating plates that were dipped in ammonium phosphomolybdate sulfate solution. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using 600 MHz (Varian UNITY INOVA) spectrometers. $CDCl_3$ were used for NMR measurements. Mass spectra were recorded by using JMX-700 (JEOL Co., Ltd.) and G6520 (Agilent Technologies, Ltd.). UV-vis spectra were collected on a JASCO V-570 spectrophotometer at room temperature using a 1 cm quartz cuvette. Fluorescence emission spectra were collected on a HITACHI F-4500 fluorescence spectrophotometer. To obtain an accurate spectrum, spectrum correction was carried out with rhodamine B concentrated solution and a secondary-standard light source. A cut filter was utilized to eliminate multiple lights, such as secondary light. All solvents for spectrophotometry were purchased from Nacalai Tesque (Kyoto, Japan).

***N*,*N*-Dioctyl-3-methoxybenzenamine (5d)**

To a stirred solution of 3-methoxyaniline **4** (4.27 g, 34.7 mmol) in MeCN (100 mL) and K_2CO_3 (10 g, 72.4 mmol), iodoalkane (25 g, 104 mmol) were added and the mixture was refluxed overnight. The reaction mixture was filtered to remove the undissolved K_2CO_3, the filtrate was evaporated, and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product. This was purified by silica gel column chromatography to obtain the pure product as oil. Yield: 12.9 g (quant.).

Compound **5d**: ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.12 (dd, 1 H, *J* = 8.4, 8.4 Hz), 6.29 (dd, 1 H, *J* = 8.4, 2.4 Hz), 6.22 (dd, 1 H, *J* = 7.8, 1.8 Hz), 6.20 (dd, 1 H, *J* = 2.4, 2.4 Hz), 3.80 (s, 3 H), 3.21-3.28 (m, 4 H), 1.54-1.63 (m, 4 H), 1.25-1.37 (m, 20 H), 0.87-0.94 (m, 6 H). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 160.98, 149.69, 129.93, 105.12, 99.77, 98.39, 55.16, 51.28, 31.98, 29.65, 29.48, 27.42, 27.34, 22.80, 14.24. HRMS (EI) calcd for $C_{23}H_{41}NO$ $[M]^+$: 347.3188, found: 347.3180.

2-[4-(Dioctylamino)-2-methoxybenzoyl]benzoic acid (6d)

To a solution of phthalic anhydride (2.13 g, 14.4 mmol) and anhydrous $AlCl_3$ (3.84 g, 28.8 mmol) in CH_2Cl_2 (100 mL), **5d** (5.00 g, 14.4 mmol) was slowly added and the mixture was stirred under nitrogen at 0 °C for 4.5 h. Then, the reaction mixture was poured into a mixture of water/6 M HCl, stirred for 10 min, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product. **6d** was purified by silica gel column chromatography to obtain the pure product as yellow viscous oil. Yield: 1.42 g (20%).

Compound **6d**: ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 8.03 (d, 1 H, *J* = 7.8 Hz), 7.64 (d, 1 H, *J* = 8.4 Hz), 7.53 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.44 (dd, 1 H, *J* = 7.5, 7.5 Hz), 7.27-7.34 (m, 1 H), 6.21 (d, 1 H, *J* = 8.4 Hz), 5.97 (s, 1 H), 3.56 (s, 3 H), 3.27-3.34 (m, 4 H), 1.56-1.65 (m, 4 H), 1.21-1.35 (m, 20 H), 0.88 (t, 6 H, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 194.40, 169.59, 162.41, 153.77, 145.98, 134.74, 132.31, 130.84, 128.38, 127.82, 127.49, 114.27, 104.13, 93.85, 55.35, 51.33, 31.94, 29.85, 29.55, 29.41, 27.42, 27.24, 22.78, 22.26, 14.24. HRMS (EI) calcd for $C_{31}H_{45}NO_4$ $[M]^+$: 495.3349, found: 495.3355.

2-[4-(Dioctylamino)-2-hydroxybenzoyl]benzoic acid (7d)

To a stirred solution of **6d** (3.50 g, 7.06 mmol) in dry CH_2Cl_2 (100 mL) was added a solution of 1 M BBr_3 in CH_2Cl_2 (35.3 mL, 35.3 mmol) at -78 °C. After 1 h, the mixture was warmed to 0 °C. After completion of the reaction, the mixture was quenched with H_2O and evaporated to give the crude product. **7d** was purified by silica gel column chromatography to obtain the pure product as yellow viscous oil. Yield: 2.71 g (80%).

Compound **7d**: ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 12.56 (s, 1 H), 8.10 (dd, 1 H, *J* = 7.8, 1.2 Hz), 7.61 (ddd, 1 H, *J* = 7.8, 7.8, 1.2 Hz), 7.52 (ddd, 1 H, *J* = 8.1, 8.1, 0.6 Hz), 7.35 (dd, 1 H, *J* = 7.5, 0.9 Hz), 6.86 (d, 1 H, *J* = 9.6 Hz), 6.11 (d, 1 H, *J* = 2.4 Hz), 6.01 (dd, 1 H, *J* = 9.0, 2.4 Hz), 3.22-3.32 (m, 4 H), 1.53-1.65 (m, 4

H), 1.20-1.36 (m, 20 H), 0.87 (t, 6 H, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 198.32, 170.47, 165.56, 154.49, 141.37, 134.68, 132.82, 131.24, 129.25, 128.22, 127.92, 109.97, 104.06, 97.33, 51.28, 31.91, 29.53, 29.41, 27.48, 27.17, 22.75, 14.22. HRMS (EI) calcd for $C_{30}H_{43}NO_4$ $[M]^+$: 489.3192, found: 481.3189.

General procedure for the synthesis of ABPX derivatives (3)

7 (2.0 equiv.) and resorcinol (1.0 equiv.) were combined in $MeSO_3H$ in a sealed tube and heated at 95 °C for 2 h. The reaction was poured into stirred ice water, its pH was adjusted to alkaline with the saturated sodium hydroxide, and the mixture was stirred for 20 min. Then, the mixture was extracted with $CHCl_3$ three times. The organic layers were dried over $MgSO_4$ and evaporated to give the crude product. This was purified by silica gel column chromatography and further recrystallized from MeCN solution to obtain the pure product **3** *trans*-isomer was firstly eluted, followed by *cis*-isomer. The yields of *trans*- and *cis*-isomers in compound **3** were determined by using the integral of the peaks of ^{1}H-NMR.

Compound **3a**$_{trans}$: White powder. Yield: 30%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.78 (dd, 2 H, *J* = 6.9, 0.9 Hz), 7.60 (ddd, 2 H, *J* = 7.5, 7.5, 1.2 Hz), 7.50 (ddd, 2 H, *J* = 7.7, 7.7, 0.6 Hz), 7.11-7.15 (m, 2 H), 7.13 (s, 1 H), 6.47 (d, 2 H, *J* = 8.4 Hz), 6.43 (d, 2 H, *J* = 2.4 Hz), 6.29 (dd, 2 H, *J* = 9.0, 2.4 Hz), 6.03 (s, 1 H), 3.16-3.30 (m, 8 H), 1.54-1.68 (m, 8 H), 0.93 (t, 12 H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 169.30, 153.35, 152.94, 152.09, 150.25, 135.14, 129.79, 128.71, 127.89, 126.84, 124.63, 124.14, 116.40, 108.72, 105.01, 104.27, 96.85, 83.70, 52.97, 20.45, 11.53. HRMS (ESI) calcd for $C_{46}H_{45}N_2O_6$ $[M]^+$: 721.3272, found: 721.3274.

Compound **3a**$_{cis}$: White powder. Yield: 29%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.79-7.83 (m, 2 H), 7.40-7.45 (m, 4 H), 7.14 (s, 1 H), 6.89-6.94 (m, 2 H), 6.46 (d, 2 H, *J* = 9.0 Hz), 6.44 (d, 2 H, *J* = 3.0 Hz), 6.29 (dd, 2 H, *J* = 9.0, 3.0 Hz), 5.97 (s, 1 H), 3.10-3.30 (m, 8 H), 1.52-1.68 (m, 8 H), 0.92 (t, 12 H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 168.93, 153.39, 153.17, 152.16, 150.25, 134.18, 129.35, 128.65, 128.62, 127.40, 124.97, 123.53, 116.40, 108.68, 105.15, 104.37, 97.89, 83.37, 52.95, 20.43, 11.51. HRMS (ESI) calcd for $C_{46}H_{45}N_2O_6$ $[M]^+$: 721.3272, found: 721.3274.

Compound **3b**$_{trans}$: White powder. Yield: 27%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.77-7.80 (m, 2 H), 7.61 (ddd, 2 H, *J* = 7.2, 7.2, 1.0 Hz), 7.51 (ddd, 2 H, *J* = 7.5, 7.5, 0.6 Hz), 7.14 (s, 1 H), 7.12-7.15 (m, 2 H), 6.48 (d, 2 H, *J* = 9.0 Hz), 6.44 (d, 2 H, *J* = 2.4 Hz), 6.30 (dd, 2 H, *J* = 9.0, 3.0 Hz), 6.04 (s, 1 H), 3.23-3.30 (m, 8 H), 1.53-1.62 (m, 8 H), 1.30-1.39 (m, 8 H), 0.95 (t, 12 H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 169.25, 153.31, 152.91, 152.06, 150.18, 135.09, 129.75, 128.68, 127.83, 126.81, 124.58, 124.10, 116.37, 108.66, 104.92, 104.25, 97.76, 83.68, 50.89, 29.37, 20.39, 14.08. HRMS (ESI) calcd for $C_{50}H_{53}N_2O_6$ $[M]^+$: 777.3898, found: 777.3917.

Compound **3b*cis***: White powder. Yield: 26%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.79-7.82 (m, 2 H), 7.40-7.45 (m, 4 H), 7.15 (s, 1 H), 6.90-6.94 (m, 2 H), 6.48 (d, 2 H, *J* = 8.4 Hz), 6.44 (d, 2 H, *J* = 3.0 Hz), 6.29 (dd, 2 H, *J* = 9.3, 2.4 Hz), 5.97 (s, 1 H), 3.22-3.30 (m, 8 H), 1.52-1.60 (m, 8 H), 1.30-1.38 (m, 8 H), 0.95 (t, 12 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 168.92, 153.40, 153.17, 152.15, 150.21, 134.18, 129.34, 128.65, 128.61, 127.42, 124.96, 123.53, 116.40, 108.66, 105.10, 104.40, 97.86, 83.40, 50.92, 29.39, 20.40, 14.10. HRMS (ESI) calcd for $C_{50}H_{53}N_2O_6$ $[M]^+$: 777.3898, found: 777.3904.

Compound **3c*trans***: White powder. Yield: 18%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.77-7.80 (m, 2 H), 7.61 (ddd, 2 H, *J* = 7.5, 7.5, 1.4 Hz), 7.51 (ddd, 2 H, *J* = 7.5, 7.5, 0.6 Hz), 7.15 (s, 1 H), 7.12-7.16 (m, 2 H), 6.48 (d, 2 H, *J* = 9.0 Hz), 6.43 (d, 2 H, *J* = 2.4 Hz), 6.30 (dd, 2 H, *J* = 9.0, 2.4 Hz), 6.04 (s, 1 H), 3.21-3.30 (m, 8 H), 1.52-1.63 (m, 8 H), 1.27-1.37 (m, 24 H), 0.86-0.94 (m, 12 H). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 169.25, 153.32, 152.91, 152.06, 150.17, 135.09, 129.74, 128.68, 127.83, 126.83, 124.59, 124.11, 116.38, 108.65, 104.91, 104.26, 97.76, 83.68, 51.18, 31.78, 27.20, 26.86, 22.77, 14.15. HRMS (ESI) calcd for $C_{58}H_{69}N_2O_6$ $[M]^+$: 889.5150, found: 889.5178.

Compound **3c*cis***: White powder. Yield: 17%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.78-7.83 (m, 2 H), 7.40-7.46 (m, 4 H), 7.15 (s, 1 H), 6.90-6.95 (m, 2 H), 6.47 (d, 2 H, *J* = 9.6 Hz), 6.43 (d, 2 H, *J* = 2.4 Hz), 6.29 (dd, 2 H, *J* = 9.3, 2.1 Hz), 5.98 (s, 1H), 3.20-3.30 (m, 8 H), 1.52-1.62 (m, 8 H), 1.26-1.37 (m, 24 H), 0.86-0.92 (m, 12 H). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 168.91, 153.38, 153.17, 152.12, 150.17, 134.18, 129.34, 128.65, 128.60, 127.40, 124.93, 123.53, 116.39, 108.62, 105.06, 104.38, 97.82, 83.39, 51.18, 31.78, 27.19, 26.86, 22.77, 14.15. HRMS (ESI) calcd for $C_{58}H_{69}N_2O_6$ $[M]^+$: 889.5150, found: 889.5166.

Compound **3d*trans***: White powder. Yield: 18%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.76-7.80 (m, 2 H), 7.61 (ddd, 2 H, *J* = 7.5, 7.5, 0.6 Hz), 7.51 (ddd, 2 H, *J* = 7.5, 7.5, 0.6 Hz), 7.15 (s, 1 H), 7.12-7.16 (m, 2 H), 6.49 (d, 2 H, *J* = 9.0 Hz), 6.44 (d, 2 H, *J* = 2.4 Hz), 6.30 (dd, 2 H, *J* = 9.0, 2.4 Hz), 6.06 (s, 1 H), 3.21-3.32 (m, 8 H), 1.53-1.64 (m, 8 H), 1.20-1.40 (m, 40 H), 0.89 (t, 12 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 169.15, 153.25, 152.86, 152.01, 150.10, 135.02, 129.68, 128.62, 127.77, 126.78, 124.52, 124.03, 116.34, 108.60, 104.87, 104.17, 97.70, 83.59, 51.11, 31.85, 29.49, 29.34, 27.18, 27.13, 22.69, 14.15. HRMS (FAB) calcd for $C_{66}H_{85}N_2O_6$ $[M]^+$: 1001.6402, found: 1001.6432.

Compound **3d*cis***: White powder. Yield: 17%. ^{1}H-NMR ($CDCl_3$, 600 MHz): δ 7.78-7.84 (m, 2 H), 7.40-7.46 (m, 4 H), 7.15 (s, 1 H), 6.90-6.95 (m, 2 H), 6.47 (d, 2 H, *J* = 9.0 Hz), 6.43 (d, 2 H, *J* = 2.4 Hz), 6.29 (dd, 2 H, *J* = 9.3, 2.7 Hz), 5.98 (s, 1 H), 3.20-3.30 (m, 8 H), 1.52-1.62 (m, 8 H), 1.21-1.36 (m, 40 H), 0.89 (t, 12 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ 168.90, 153.38, 153.17, 152.15, 150.18, 134.16, 129.34, 128.65, 128.60, 127.41, 124.93, 123.52, 116.39, 108.63, 105.06, 104.36, 97.83, 83.38, 51.18, 31.92, 29.55, 29.41, 27.23, 27.20, 22.75, 14.22. HRMS (FAB) calcd for $C_{66}H_{85}N_2O_6$ $[M]^+$: 1001.6402, found: 1001.6414.

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REFERENCES

1. K. Umezawa, D. Citterio, and K. Suzuki, *Anal. Sci.*, 2014, **30**, 327.
2. L. Yuan, W. Y. Lin, K. B. Zheng, L. W. He, and W. M. Huang, *Chem. Soc. Rev.*, 2013, **42**, 622.
3. M. Beija, C. A. M. Afonso, and J. M. G. Martinho, *Chem. Soc. Rev.*, 2009, **38**, 2410.
4. G. L. Niu, W. M. Liu, J. S. Wu, B. J. Zhou, J. H. Chen, H. Y. Zhang, J. C. Ge, Y. Wang, H. T. Xu, and P. F. Wang, *J. Org. Chem.*, 2015, **80**, 3170.
5. T. Pastierik, P. Sebej, J. Medalova, P. Stacko, and P. Klan, *J. Org. Chem.*, 2014, **79**, 3374.
6. M. Y. Fu, Y. Xiao, X. H. Qian, D. F. Zhao, and Y. F. Fu, *Chem. Commun.*, 2008, 1780.
7. W. Piao, S. Tsuda, Y. Tanaka, S. Maeda, F. Y. Liu, S. Takahashi, Y. Kushida, T. Komatsu, T. Ueno, T. Terai, T. Nakazawa, M. Uchiyama, K. Morokuma, T. Nagano, and K. Hanaoka, *Angew. Chem. Int. Ed.*, 2013, **52**, 13028.
8. Y. Koide, Y. Urano, K. Hanaoka, T. Terai, and T. Nagano, *ACS Chem. Biol.*, 2011, **6**, 600.
9. S. Kamino, Y. Horio, S. Komeda, K. Minoura, H. Ichikawa, J. Horigome, A. Tatsumi, S. Kaji, T. Yamaguchi, Y. Usami, S. Hirota, S. Enomoto, and Y. Fujita, *Chem. Commun.*, 2010, **46**, 9013.
10. M. Tanioka, S. Kamino, A. Muranaka, Y. Ooyama, H. Ota, Y. Shirasaki, J. Horigome, M. Ueda, M. Uchiyama, D. Sawada, and S. Enomoto, *J. Am. Chem. Soc.*, 2015, **137**, 6436.
11. S. Kamino, A. Muranaka, M. Murakami, A. Tatsumi, N. Nagaoka, Y. Shirasaki, K. Watanabe, K. Yoshida, J. Horigome, S. Komeda, M. Uchiyama, and S. Enomoto, *Phys. Chem. Chem. Phys.*, 2013, **15**, 2131.
12. S. Kamino, M. Murakami, M. Tanioka, Y. Shirasaki, K. Watanabe, J. Horigome, Y. Ooyama, and S. Enomoto, *Org. Lett.*, 2014, **16**, 258.