New Crown Spirobenzopyrans as Light- and Ion-Responsive Dual-Mode Signal Transducers

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Received March 10, 1997[⊗]

Abstract: A new class of crown spirobenzopyrans were designed and synthesized. The crown spirobenzopyrans showed thermally irreversible photochromism only in the presence of alkali-metal cations accompanying cation-selective coloring efficiency. Thus, the new crown spirobenzopyrans could transmit information of two different simultaneous stimuli (ion and photon) to changes in their optical properties. The dual-mode signal transducer molecules developed here can be considered to perform "AND" gate type signal transduction based on photochromism of artificial receptors. Molecular recognition abilities and photochromic properties of the new crown spirobenzopyrans were characterized by use of NMR and FAB mass spectroscopies.

Introduction

The expectation of application in molecular devices has been inspiring investigations into furnishing several functional molecules such as molecular sensors, switches, and signal transducers.[1] In all respects of these functional molecules responding to external physical and/or chemical stimuli, molecular recognition processes play a leading role.[2,3] The design of molecular devices principally demands the organization of such signal transducer molecules. The integration of molecular components and their coupled functions are also seen in many biological events.[4] For example, the common feature of all light-driven biosystems is the initial participation of respective photorecep-

tors, which induce a series of chemical and signal transformations upon light absorption.[5] For the vision process in mammals, light-induced isomerization of retinal linked to opsin triggers a conformational change of the protein, of which information is eventually transmitted to the nervous systems by use of various messenger molecules. Thus, the vision system is referred to as a highly sophisticated multimode signal transducer system, so that a mimic of such systems using simple and artificial molecules may be a worthwhile subject in its own right.

Here we present the synthesis of a new type of dual-mode signal transducer molecule based on photochromism of artificial receptors, in which only the combination of two simultaneous "chemical and physical inputs" (ion and UV light) can cause the receptors to be visible-light active.[6] We have previously reported crown ether-linked spirobenzopyrans **1**, isomerization of which to the open-chain colored merocyanines **1′·M⁺** was induced by recognition of alkali-metal cations *as well as* by UV irradiation (Scheme 1).[7] An idea that sophisticated signal transduction at the molecular level also necessitates *simultaneous-type* counterparts led us to develop the new crown spirobenzopyrans that could only be responsive to the combination of ionic and photonic stimuli. In searching for an ideal crown spirobenzopyran for this purpose, the structure **2** was developed.

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⊗ Abstract published in *Advance ACS Abstracts,* September 15, 1997.

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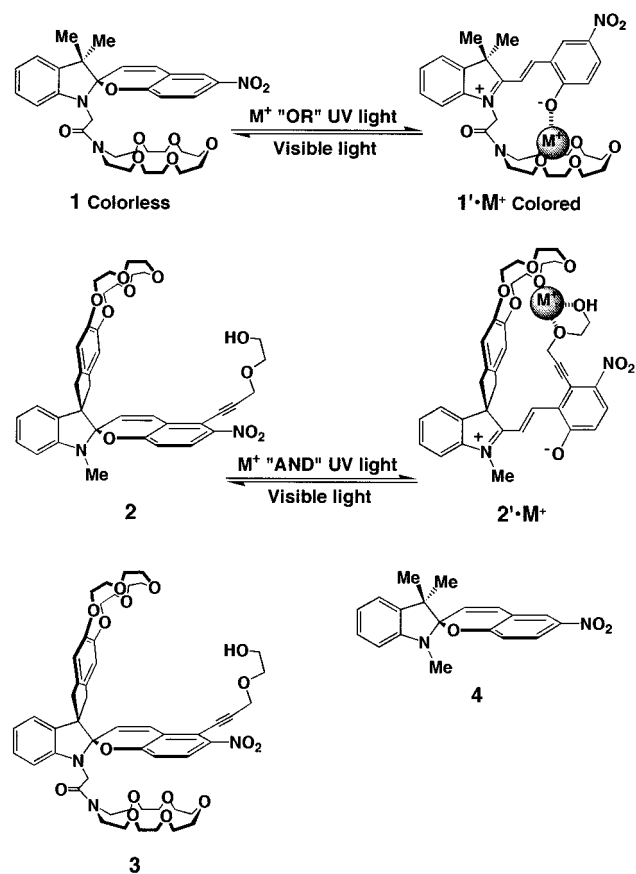
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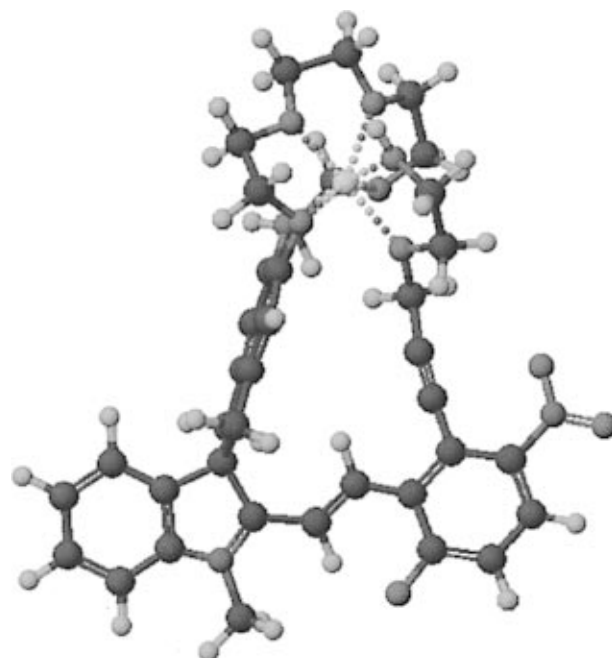
Scheme 1

Figure 1. The possible dominant low-energy binding structure for **2′·** Li$^+$ obtained by MM2 followed by a PM3 level approximation on MOPAC.[14]

Results and Discussion

The design of the new crown spirobenzopyran **2** was based on the fact that the crown-bound cations could interact with the ether oxygens of the oxyethylene side arm and not the phenolate oxygen of the opened merocyanine form **2′**. Thus, we expected that the absence of the strong electrostatic interaction between crown-bound cations and the phenolate oxygen of **2′** would prevent ready thermal isomerization of **2** to **2′·M$^+$** in contrast with **1**, and that the photoisomerized, cation-accommodated merocyanine form **2′·M$^+$** would be stabilized by the additional interaction of the lariat oxyethylene side arm for the cations. In order to determine the appropriateness of the molecular design of the new crown spirobenzopyran **2**, various computer modelings (MM2, MD, MOPAC) were performed. Geometry optimization of **2′·Li$^+$** was carried out in the form that the lithium cations interacted with both the crown ring and the oxyethylene side arm of **2′**. On the basis of the comparison of the several dominant low-energy structures, a possible recognition mode is shown in Figure 1.

The new crown spirobenzopyran **2** was synthesized from two key intermediates, 3*H*-indole derivative **5**, bearing a benzo-15-crown-5, and 6-alkynyl-5-nitrosalicylaldehyde **6**, by enamine-passed aldol type cyclization in the final step. For the synthesis of the bis-crown spirobenzopyran **3**, the aldol type cyclization was followed by Mukaiyama's amide formation.[8] The crown-linked 3*H*-indole derivative **5** was prepared by Fisher-indole synthesis[9] from phenylhydrazine and an acetylindan derivative synthesized from bis(chloromethyl)benzo-15-crown-5 by the acetoacetate method. Alkynyl-substituted salicylaldehyde derivative **6** was prepared by Stille coupling[10] from the corre-

sponding iodoarene and alkynylstannane. Other compounds were commercially available or easily synthesized (Scheme 2).

The new crown spirobenzopyran **2** thus synthesized had no absorption bands above 350 nm in aprotic solvents such as CHCl₃, CH₃CN, etc., indicating a closed spiropyran form. The absorption spectra were scarcely affected upon addition of any alkali-metal iodides in CH₃CN even after several days in the dark, in contrast to the results for **1**. In the ¹H NMR spectra of **2** in CD₃CN, however, the downfield shifts and split of the signals for the crown rings in the spiropyran form (3.6–4.2 ppm) were observed after the addition of LiI (Figure 2a,b). This result suggested that the lithium cations were bound to the macrocycle of **2**, and that the colorless form was attributed to no isomerization of **2·Li$^+$** to **2′·Li$^+$**. The complexation was also corroborated on the basis of FAB mass experiments. Before addition of LiI to **2**, ion peaks for (M + H)$^+$, (M + Na)$^+$, and (M + K)$^+$ were detected; after the addition the signals decreased, while a peak for (M + Li)$^+$ appeared (Figure 3). Subsequently, irradiation (360 nm) of the alkali-metal iodide containing CH₃-CN solutions of **2** gave rise to changes in their spectra, and new absorption bands appeared. Figure 4 showed that small selective coloration for LiI was observed, and that only photoirradiation (salt free) of **2** resulted in a little change in its spectrum, suggesting the suppression of its photochromic property in the absence of the cations. The same λ_{max} (560 nm) of **2′·M$^+$** irrespective of all kinds of alkali-metal cations indicated no interaction of the crown-bound metal cations with the *p*-nitrophenolate oxygen of **2′**.[7,11]

The emerging absorption bands were presumed to be due to the merocyanine structure **2′** on the basis of the NMR spectrum (Figure 2c). The interaction of the crown-bound Li$^+$ and the incoming oxyethylene side arm but not the *p*-nitrophenolate oxygen of **2′** was confirmed by the upfield shift (0.25 ppm) of the propargyl methylene protons by comparison with those of **2** in agreement with the UV spectra. The colored solution was

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Scheme 2. Synthetic scheme for **2** and **3**[a]
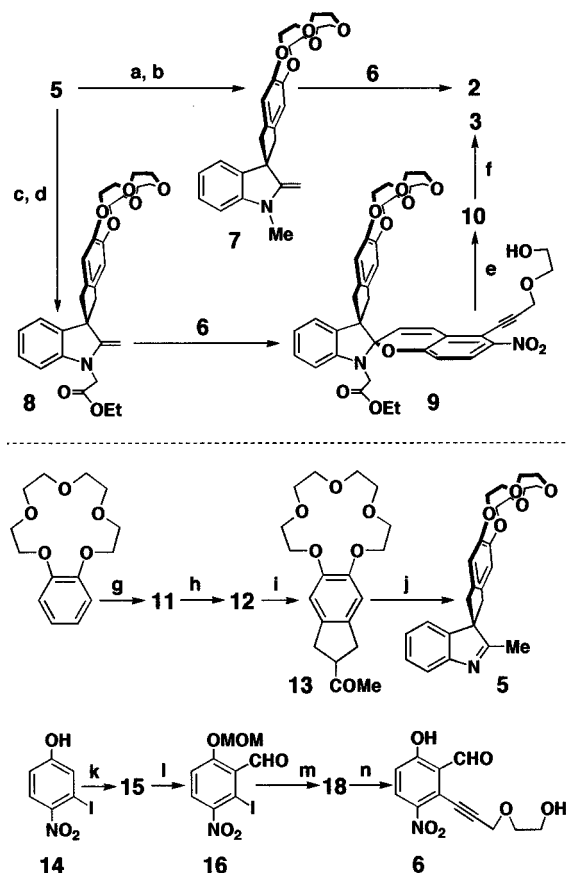
[a] Reagents: (a) MeI; (b) KOH; (c) BrCH₂CO₂Et; (d) K₂CO₃; (e) KOH; (f) monoaza-18-crown-6, 2-chloro-1-methylpyridinium iodide, *n*-Bu₃N; (g) CH₃OCH₂Cl, HCl; (h) ethyl acetoacetate, K₂CO₃; (i) KOH; (j) PhNHNH₂, ZnI₂; (k) hexamethylenetetramine, CF₃CO₂H; (l) CH₃OCH₂Cl, NaH; (m) *n*-Bu₃SnC₂CH₂O(CH₂)₂OTHP (**17**), PdCl₂(PPh₃)₂; (n) HCl.

stable and did not bleach thermally in dark conditions at room temperature even after 30 days. On the other hand, the photoisomerized colored form of the parent spirobenzopyran **4** was so labile as to disappear completely for 10 min under identical conditions. Partial isomerization of **2′·M⁺** to the colorless spiropyran form **2·M⁺** was observed upon irradiation with >480 nm light .[12]

Results obtained here show that the crown spirobenzopyran **2** is realized to operate well as dual-mode signal transducer molecules. At the present moment, although it may be difficult to determine all of the factors contributing to the thermally irreversible photochromism of **2·Li⁺** and **2′·Li⁺** in a striking contrast to the previous crown spirobenzopyrans **1** and parent spirobenzopyran **4**, we anticipate that the presence of the 3′-(benzo-15-crown-5) substituent is essential for blocking thermal isomerization in the presence of Li⁺. Bis-crown spirobenzopyran **3**, which was thought to be a "chimera" of **1** and **2**, was synthesized in order to shed light on this aspect. After addition of LiI to the CH₃CN solution of **3**, the absorption spectra of **3** were scarcely affected. Irradiation of the solution containing LiI caused **3** to isomerize to the colored merocyanine form. The colored form was identified as the merocyanine structure **3′·Li⁺** by NMR investigations. The order of the coloring efficiency of LiI, NaI, CsI, RbI, and KI, which decreased in that order, gave rough agreement for that of **2**. In this case, too, reiso-

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(12) The nitro-substituted spirobenzopyrans are so liable to fatigue that substantial decomposition was observed during a few repetitions of the photochromic cycle.[9]

merization of **3′·M⁺** to the colorless spiropyran form **3·M⁺** was observed upon irradiation with >480 nm light. These results substantiate the interpretation described above.

Conclusions

We designed and synthesized a new class of crown spirobenzopyrans **2**, in which thermally irreversible photochromism was observed only in the presence of alkali-metal cations accompanying cation-selective coloring efficiency. Thus, the new crown spirobenzopyran **2** could transmit information of two different simultaneous stimuli (ion and photon) to changes in its optical properties. The dual-mode signal transducer molecules developed here are expected to contribute to molecular-based device technologies, although significant improvements including selectivity, response, and fatigue resistance are still needed.

Experimental Section

Instrumentation. ¹H and ¹³C NMR spectra were recorded at 270 and 67.8 MHz, respectively, unless otherwise noted. EI mass spectra were measured at 70 eV. For FAB mass experiments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. The starting materials were all commercially available, and 3-iodo-4-nitrophenol (**14**) was prepared according to a literature procedure.[13]

Computational Method. Geometry optimization for the binding structures **2′·Li⁺** was carried out by using MM2 (molecular mechanics) followed by a PM3 level approximation on MOPAC by the CAChe System (CAChe Scientific, Inc.).[14] The dominant binding structure **2′·Li⁺** was obtained by varying weight point coordinates and dihedral angles for several O−Li weak bonds manually.

4,5-Bis(chloromethyl)benzo-15-crown-5 Ether (11). To a CH₂Cl₂ (70 mL) solution of benzo-15-crown-5 ether (13.4 g, 50.0 mmol) were added a concentrated HCl aqueous solution (10 mL) and chloromethyl methyl ether (32.2 g, 400 mmol) at room temperature. The reaction mixture was stirred at that temperature for 12 h. The reaction mixture was dissolved in water and extracted with CH₂Cl₂. The CH₂Cl₂ extract was evaporated and subjected to column chromatography (silica gel; eluent, AcOEt) to give **11**: yield = 28% (5.11 g, 14.0 mmol); mp 151−153 °C; IR (KBr) 2945, 2883, 1606, 1527, 1367, 1281, 1234, 1157, 1136, 1080, 866, 677 cm⁻¹; ¹H NMR (CDCl₃) δ 3.73−3.76 (s, 8H), 3.89−3.92 (m, 4H), 4.14−4.17 (m, 4H), 4.67 (s, 4H), 6.87 (s, 2H); ¹³C NMR (CDCl₃) δ 43.41, 69.10, 69.13, 69.45, 70.48, 116.00, 129.14, 149.46; MS *m/e* (rel intensity) 364 (M⁺, 2).
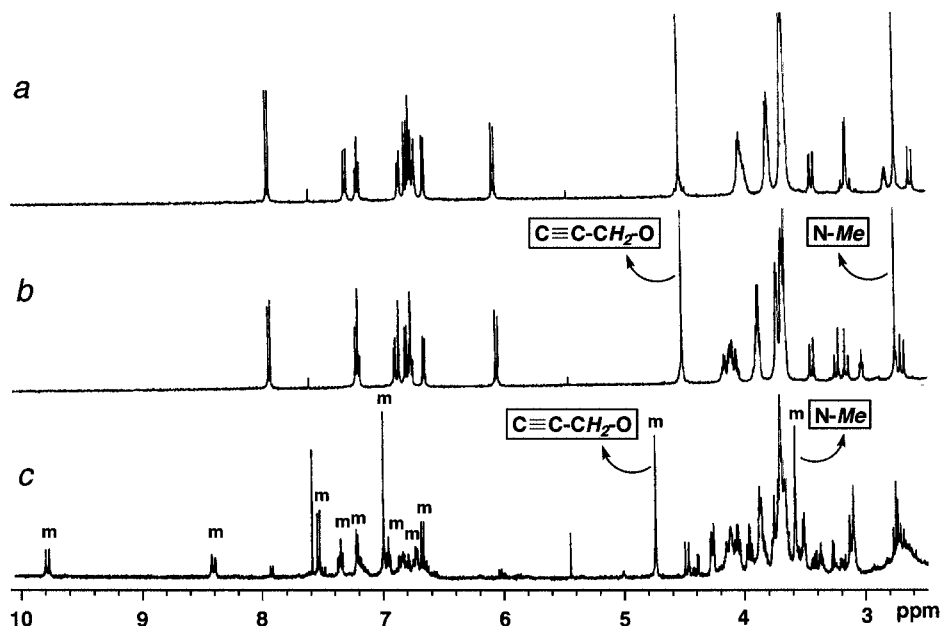
2-Acetyl-2-(ethoxycarbonyl)-5,6-(1,4,7,10,13-pentaoxatridecylene)indan (12). To an acetone (70 mL) suspension of finely ground K₂CO₃ (6.63 g, 48.0 mmol) was added ethyl acetoacetate (3.12 g, 24.0 mmol) dropwise at room temperature. After stirring at the same temperature for 30 min, to the suspension was added a DMF (70 mL) solution of **11** (4.38 g, 12.0 mmol) dropwise. The reaction mixture was stirred at 50 °C for 5 h. After removal of the solvent, the residue was dissolved in water and extracted with CH₂Cl₂. The CH₂Cl₂ extract was evaporated and chromatographed (silica gel; eluent, AcOEt) to give **12**: yield = 70% (3.55 g, 8.40 mmol); oil; IR (KBr) 2929, 2870, 1738, 1713, 1608, 1508, 1454, 1234, 1134, 939, 731 cm⁻¹; ¹H NMR (CDCl₃) δ 1.27 (t, *J* = 7.3 Hz, 3H), 2.21 (s, 3H), 3.42 (d, *J* = 16.2 Hz, 2H), 3.45 (d, *J* = 16.2 Hz, 2H), 3.75 (s, 8H), 3.87−3.91 (m, 4H), 4.07−4.09 (m, 4H), 4.22 (q, *J* = 7.3 Hz, 2H), 6.70 (s, 2H); ¹³C NMR (CDCl₃) δ 13.88, 25.87, 38.76, 61.59, 67.21, 69.17, 69.45, 70.40, 70.80, 110.20, 132.07, 148.57, 172.24, 202.62; MS *m/e* (rel intensity) 422 (M⁺, 53).

2-Acetyl-5,6-(1,4,7,10,13-pentaoxatridecylene)indan (13). To a THF (30 mL) solution of **12** (3.55 g, 8.40 mmol) was added 1 N KOH aqueous solution (15 mL). The reaction mixture was stirred at room temperature for 12 h. After removal of the solvent, the residue was dissolved in water and extracted with CH₂Cl₂. The CH₂Cl₂ extract was evaporated and chromatographed (silica gel; eluent, AcOEt) to give **13**: yield = 60% (1.77 g, 5.05 mmol); mp 62−65 °C; IR (KBr) 2927,

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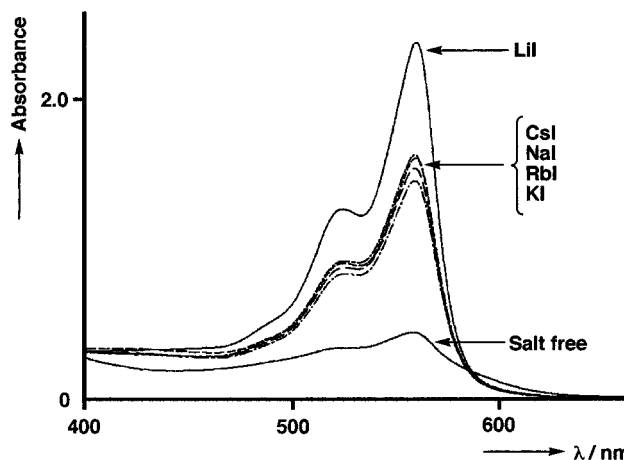
Figure 2. ^{1}H NMR spectra (500 MHz) of **2** (0.5 mM) in CD$_3$CN (a) before the addition of LiI (2.5 mM), (b) after the addition, and (c) after irradiation (360 nm) of (b). The signals marked with "m" are for the merocyanine structure **2′**.
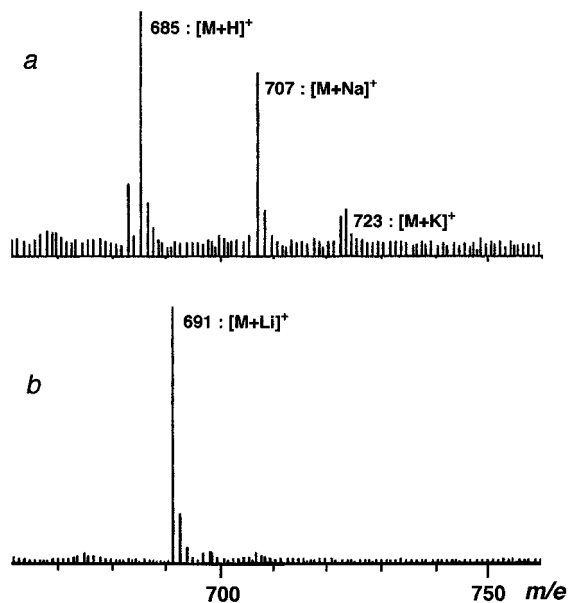
Figure 3. FAB mass spectra of **2** with 3-nitrobenzyl alcohol matrix (a) before the addition of LiI and (b) after the addition.

Figure 4. Electronic absorption spectra of **2** (0.1 mM) in CH$_3$CN in the presence of alkali-metal iodides (0.5 mM) after 1 h of irradiation (360 nm).

2872, 1701, 1508, 1458, 1244, 1128, 1045, 939 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.22 (s, 3H), 3.08−3.11 (m, 4H), 3.38−3.53 (m, 1H), 3.76 (s, 8H), 3.92−3.94 (m, 4H), 4.10−4.11 (m, 4H), 6.79 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 28.41, 34.90, 52.35, 69.45, 69.73, 70.62, 71.03, 110.63, 133.83, 148.53, 209.44; MS *m/e* (rel intensity) 350 (M$^+$, 24).

Benzo-15-crown-5-Substituted 3*H*-Indole 5. To a *p*-xylene (40 mL) suspension of **13** (1.75 g, 5.00 mmol) and ZnI$_2$ (1.69 g, 5.00 mmol) was added phenylhydrazine (1.35 g, 12.5 mmol) dropwise at room temperature. The reaction mixture was stirred at 110 °C for 7 h. After removal of the solvent, the residue was dissolved in 1 N HCl aqueous solution and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extract was evaporated and chromatographed (silica gel; eluent, CH$_2$Cl$_2$:EtOH = 30:1) to give **5**: yield = 60% (1.27 g, 3.00 mmol); mp 133−135 °C; IR (KBr) 3433, 3390, 2910, 2872, 1576, 1504, 1456, 1311, 1207, 1120, 1105, 1053, 939, 758 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.16 (s, 3H), 3.13 (s, 4H), 3.67− 3.80 (m, 8H), 3.92−3.94 (m, 4H), 4.10−4.11 (m, 4H), 6.79 (s, 2H), 7.11 (d, *J* = 3.7 Hz, 1H), 7.27−7.32 (m, 2H), 7.53 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 16.18, 40.78, 63.67, 68.20, 68.62, 69.37, 69.85, 110.12, 119.76, 120.94, 125.48, 127.91, 134.20, 144.83, 147.58,

153.99, 185.70; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 446 (M$^+$ + Na, 57).

6-Iodo-5-nitrosalicylaldehyde (15). A CF$_3$CO$_2$H (20 mL) suspension of 3-iodo-4-nitrophenol (**14**)^{13} (6.63 g, 25.0 mmol) and hexamethylenetetramine (3.15 g, 22.5 mmol) was stirred at 80 °C for 4 h. After addition of water (5 mL), the mixture was stirred at room temperature for 30 min. The reaction mixture was dissolved in water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extract was evaporated and subjected to column chromatography (silica gel; eluent, CHCl$_3$) to give **15**: yield = 34% (2.49 g, 8.45 mmol); mp 110−112 °C; IR (KBr) 1653, 1568, 1525, 1443, 1329, 1277, 1263, 1176 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.08 (d, *J* = 9.2 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 10.29 (s, 1H), 12.72 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 96.50, 119.00, 119.64, 132.18, 165.89, 203.47; MS *m/e* (rel intensity) 293 (M$^+$, 100).

2-Iodo-6-(methoxymethoxy)-3-nitrobenzaldehyde (16). To a THF (20 mL) suspension of NaH (480 mg, 12.0 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added a THF (15 mL) solution of **15** (2.34 g, 7.99 mmol) dropwise at 0 °C. After stirring at that temperature for 30 min, to the solution was added chloromethyl methyl ether (3.22 g, 40.0 mmol) dropwise at the same temperature. After stirring for an additional 2 h at room temperature, the reaction mixture was neutralized to pH 7 with 1 N NaOH aqueous solution and evaporated. The residue was dissolved in water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extract was evaporated and

subjected to column chromatography (silica gel; eluent, CH$_2$Cl$_2$:AcOEt = 5:1) to give **16**: yield = 70% (1.89 g, 5.61 mmol); mp 92−94 °C; IR (KBr) 2962, 1701, 1653, 1578, 1527, 1523, 1450, 1331, 1261, 1161, 1107, 1091, 964, 935, 800 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.51 (s, 3H), 5.32 (s, 2H), 7.33 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 9.2 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 56.98, 87.95, 95.14, 115.30, 129.01, 159.71, 191.48; MS m/e (rel intensity) 337 (M$^+$, 75).

2-[1,4-Dioxa-7-(tri-*n*-butylstannyl)hept-6-ynyl]tetrahydropyran (17). To an Et$_2$O (100 mL) solution of ethylene glycol (9.31 g, 150 mmol) containing a small amount of concentrated HCl aqueous solution (several drops) was added 3,4-dihydro-2*H*-pyran (DHP) (13.44 g, 160 mmol) at room temperature. The reaction mixture was stirred at this temperature for 2 h. After addition of finely ground K$_2$CO$_3$ (2.0 g), the reaction mixture was stirred for an additional 10 min and filtered. The filtrate was evaporated, and the residue was subjected to column chromatography (silica gel; eluent, AcOEt) to give 2-(2-hydroxy-ethoxy)tetrahydropyran: yield = 41% (9.00 g, 61.6 mmol); oil; IR (KBr) 3435, 2943, 2871, 1456, 1351, 1201, 1161, 1124, 1072, 1033, 985, 870 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.51−1.86 (m, 6H), 2.81 (br s, 1H), 3.51−3.59 (m, 1H), 3.69−3.81 (m, 4H), 3.89−3.98 (m, 1H), 4.56−4.59 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 20.04, 25.24, 30.82, 62.33, 63.32, 70.82, 100.22; MS m/e (rel intensity) 146 (M$^+$, 8). To a THF (50 mL) suspension of NaH (2.00 g, 50 mmol; commercial 60% dispersion was washed thoroughly with hexane prior to use) was added 2-(2-hydroxyethoxy)tetrahydropyran (9.00 g, 61.6 mmol) dropwise at 0 °C, and the reaction mixture was stirred for 30 min at the same temperature. Propargyl bromide (7.14 g, 60.0 mmol) was added dropwise to the solution at the same temperature. The reaction mixture was stirred at room temperature for an additional 15 h. After removal of the solvent, the residue was dissolved in water and extracted with CHCl$_3$. The CHCl$_3$ extract was evaporated and distilled under reduced pressure to give 2-(1,4-dioxahept-6-ynyl)tetrahydropyran: yield = 57% (6.45 g, 35.0 mmol); bp 90−95 °C (4 mmHg); oil; IR (KBr) 3290, 3255, 2943, 2872, 1442, 1354, 1201, 1124, 1076, 1036, 985, 930, 872, 814, 673 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.49−1.99 (m, 6H), 2.43 (t, J = 2.4 Hz, 1H), 3.47−3.55 (m, 1H), 3.59−3.69 (m, 1H), 3.73 (t, J = 4.1 Hz, 2H), 3.84−3.94 (m, 2H), 4.23 (d, J = 2.4 Hz, 2H), 4.64 (t, J = 4.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 19.50, 25.46, 30.58, 58.45, 62.31, 66.50, 69.15, 74.44, 79.80, 98.98; MS m/e (rel intensity) 184 (M$^+$, 2). To a THF (60 mL) solution of 2-(1,4-dioxahept-6-ynyl)tetrahydropyran (2.76 g, 15.0 mmol) was added an *n*-hexane solution of *n*-BuLi (13.5 mmol) dropwise at 0 °C. After stirring at that temperature for 30 min, to the solution was added tri-*n*-butyltin chloride (3.91 g, 12.0 mmol) at the same temperature. The reaction mixture was stirred at room temperature for an additional 15 h. After removal of the solvent, the residue was dissolved in brine and extracted with CHCl$_3$. The CHCl$_3$ extract was evaporated and distilled under reduced pressure to give **17**: yield = 80% (5.68 g, 12.0 mmol); bp 210−215 °C (4 mmHg); IR (KBr) 2927, 2852, 1524, 1464, 1342, 1201, 1124, 1076, 1036, 962, 874, 816, 671 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.90 (t, J = 6.8 Hz, 9H), 0.99 (t, J = 7.3 Hz, 6H), 1.26−1.40 (m, 6H), 1.47−1.77 (m, 12H), 3.47−3.54 (m, 1H), 3.60−3.69 (m, 1H), 3.70−3.78 (m, 2H), 3.83−3.93 (m, 2H), 4.24 (d, J = 1.1 Hz, 2H), 4.64 (t, J = 3.2 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 11.07, 13.64, 19.48, 25.50, 26.98, 28.88, 30.58, 59.38, 62.21, 66.52, 68.68, 89.78, 98.90, 105.92.

6-(Methoxymethoxy)-3-nitro-2-[4-oxa-6-(tetrahydropyranyloxy)-hex-1-ynyl]benzaldehyde (18). To a toluene (3.0 mL) suspension of **16** (505 mg, 1.50 mmol) and (PPh$_3$)$_2$PdCl$_2$ (42 mg, 0.06 mmol) was added **17** (1065 mg, 2.25 mmol) dropwise at room temperature. The reaction mixture was stirred at 80 °C for 3 h. The reaction mixture was chromatographed (silica gel; eluent, CH$_2$Cl$_2$:AcOEt = 5:1) to give **18**: yield = 83% (490 mg, 1.25 mmol); oil; IR (KBr) 2870, 1709, 1574, 1462, 1352, 1279, 1201, 1097, 1036, 1020, 949, 926, 908, 872, 810, 731 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.48−1.88 (m, 6H), 3.53 (s, 3H), 3.50−3.54 (m, 1H), 3.65−3.72 (m, 1H), 3.84−3.99 (m, 4H), 4.56 (d, J = 1.6 Hz, 2H), 4.67 (t, J = 3.8 Hz, 1H), 5.37 (s, 2H), 7.31 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 10.57 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 19.44, 25.42, 30.50, 56.94, 59.08, 62.23, 66.46, 69.45, 94.94, 98.86, 101.39, 114.89, 120.59, 127.06, 130.11, 145.07, 160.84, 188.66; MS m/e (rel intensity) 393 (M$^+$, 9).

6-(6-Hydroxy-4-oxahex-1-ynyl)-5-nitrosalicylaldehyde (6). A MeOH (30 mL) solution of **18** (490 mg, 1.25 mmol) containing a small

amount of concentrated HCl aqueous solution (several drops) was refluxed for 1 h. The reaction mixture was neutralized to pH 7 with 1 N NaOH aqueous solution and evaporated. The residue was dissolved in water and extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ extract was evaporated to give **6**: yield = 75% (249 mg, 0.94 mmol); mp 52−54 °C; IR (KBr) 2926, 2873, 1655, 1606, 1570, 1522, 1456, 1336, 1300, 1221, 1178, 1107, 1076, 1022, 928, 770 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.50−3.83 (m, 4H), 4.58 (s, 2H), 7.06 (d, J = 9.2 Hz, 1H), 8.27 (d, J = 9.2 Hz, 1H), 10.56 (s, 1H), 12.38 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 59.20, 61.85, 71.87, 102.36, 118.95, 132.74, 166.01, 196.70; MS m/e (rel intensity) 265 (M$^+$, 20).

Benzo-15-crown-5-Substituted *exo*-Methyleneindoline 7. To a CH$_3$CN (5 mL) solution of **5** (169 mg, 0.40 mmol) was added methyl iodide (284 mg, 2.0 mmol) dropwise at room temperature. The reaction mixture was stirred at 50 °C for 7 h. After removal of the solvent, the residue was dissolved in water. The aqueous solution was washed with ether in order to remove the unreacted starting materials and basified to pH 9−10 by the addition of 1 N KOH aqueous solution. The aqueous solution was extracted with CH$_2$Cl$_2$, and the CH$_2$Cl$_2$ extract was evaporated. The residue was chromatographed (silica gel; eluent, CHCl$_3$:hexane:Et$_3$N = 20:30:1) to give **7**: yield = 45% (79 mg, 0.18 mmol); oil; ^{1}H NMR (CDCl$_3$) δ 3.05 (s, 3H), 3.20 (s, 4H), 3.79−3.86 (m, 9H), 3,87 (s, 1H), 3.91−3.94 (m, 4H), 4.12−4.15 (m, 4H), 6.55 (d, J = 7.9 Hz, 1H), 6.64 (t, J = 6.7, 1H), 6.76 (s, 2H), 6.84 (d, J = 6.7 Hz, 1H), 7.13 (t, J = 7.9 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 28.84, 49.96, 54.93, 69.31, 69.71, 70.52, 71.01, 73.65, 104.91, 110.63, 118.59, 121.42, 127.85, 134.42, 137.35, 146.51, 148.47, 162.07; MS m/e (rel intensity) 437 (M$^+$, 94).

Crown Spirobenzopyran 2. To an EtOH (1.5 mL) solution of **6** (48 mg, 0.18 mmol) was added an EtOH (1.5 mL) solution of **7** (79 mg, 0.18 mmol) dropwise at room temperature. The reaction mixture was refluxed for 3 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CHCl$_3$:EtOH = 15:1) to give **2**: yield = 43% (53 mg, 0.077 mmol); mp 117−120 °C; IR (KBr) 3359, 2870, 1564, 1506, 1454, 1327, 1288, 941, 748 cm^{-1}; ^{1}H NMR (500 MHz, CD$_3$CN) δ 2.60 (d, J = 15.5 Hz, 1H), 2.73 (s, 3H), 2.81 (br s, 1H), 3.13 (d, J = 15.5 Hz, 1H), 3.15 (d, J = 15.5 Hz, 1H), 3.42 (d, J = 15.5 Hz, 1H), 3.60−3.70 (m, 12H), 3.71−3.83 (m, 4H), 3.92−4.08 (m, 4H), 4.51 (s, 2H), 6.06 (d, J = 10.6 Hz, 1H), 6.64 (d, J = 7.3 Hz, 1H), 6.71 (s, 1H), 6.74 (t, J = 7.3 Hz, 1H), 6.76 (s, 1H), 6.78 (d, J = 9.2 Hz, 1H), 6.84 (d, J = 7.3 Hz, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 10.6 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 28.98, 29.71, 38.36, 42.00, 59.26, 61.81, 64.58, 69.06, 69.19, 69.49, 70.32, 70.80, 71.55, 79.25, 98.62, 105.11, 107.29, 110.20, 115.36, 115.86, 119.88, 121.34, 122.80, 125.66, 126,76, 128.23, 133.31, 134.08, 135.43, 143.01, 147.82, 148.41, 158.51; FABMS (in 3-nitrobenzyl alcohol) m/e (rel intensity) 685 (MH$^+$, 100).

Benzo-15-crown-5-Substituted *exo*-Methyleneindoline 8. To a CH$_3$CN (10 mL) solution of **5** (318 mg, 0.75 mmol) was added ethyl bromoacetate (626 mg, 3.75 mmol) dropwise at room temperature. The reaction mixture was stirred at 50 °C for 12 h. After removal of the solvent, the residue was dissolved in water. The aqueous solution was washed with ether in order to remove the unreacted starting materials and basified to pH 9−10 by the addition of K$_2$CO$_3$ aqueous solution. The aqueous solution was extracted with CH$_2$Cl$_2$, and the CH$_2$Cl$_2$ extract was evaporated. The residue was chromatographed (silica gel; eluent, AcOEt:Et$_3$N = 30:1) to give **8**: yield = 45% (171 mg, 0.34 mmol); oil; ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J = 3.1 Hz, 3H), 3.22 (s, 4H), 3.75−3.80 (m, 9H), 3.87−3.99 (m, 4H), 4.06−4.24 (m, 7H), 6.53 (d, J = 6.7 Hz, 1H), 6.64 (t, J = 6.7 Hz, 1H), 6.76 (s, 2H), 6.84 (d, J = 6.7 Hz, 1H), 7.12 (t, J = 6.7 Hz, 1H); MS m/e (rel intensity) 509 (M$^+$, 26).

Ester-Substituted Crown Spirobenzopyran 9. To an EtOH (4 mL) solution of **6** (80 mg, 0.30 mmol) was added a CH$_2$Cl$_2$ (4 mL) solution of **8** (152 mg, 0.30 mmol) dropwise at room temperature. The reaction mixture was stirred at 50 °C for 4 h. After removal of the solvent, the residue was chromatographed (silica gel; eluent, CH$_2$Cl$_2$:MeOH = 15:1) to give **9**: yield = 46% (104 mg, 0.14 mmol). This compound was used for the next reaction without further purification and identification.

Carboxylic Acid-Substituted Crown Spirobenzopyran 10. To a THF (10 mL) solution of **9** (104 mg, 0.14 mmol) was added 1 N KOH aqueous solution (3 mL). The reaction mixture was stirred at room

temperature for 10 h. The reaction mixture was neutralized to pH 7 with 1 N HCl aqueous solution and evaporated. The residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated to give **10**: yield = 100% (100 mg, 0.14 mmol). This compound was used for the next reaction without further purification and identification.

Bis-Crown Spirobenzopyran 3. To a CH_3CN (4 mL) solution of monoaza-18-crown-6 ether (53 mg, 0.20 mmol), 2-chloro-1-methylpyridinium iodide (52 mg, 0.20 mmol), and *n*-Bu_3N (70 mg, 0.69 mmol) was added a CH_2Cl_2 (4 mL) solution of **10** (100 mg, 0.14 mmol) dropwise at room temperature. The reaction mixture was stirred at 50 °C for 4 h. After removal of the solvent, the residue was dissolved in water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was evaporated and chromatographed (silica gel; eluent, CH_2Cl_2:MeOH = 20:1; then ODS reversed-phase silica gel; eluent, MeOH:H_2O = 4:1) to give **3**: yield = 29% (39 mg, 0.040 mmol); mp 77−80 °C; IR (KBr) 3340, 1635, 1506, 1456, 1261, 1097, 802 cm^{-1}; ^{1}H NMR (500 MHz, CD_3CN) δ 2.79 (d, J = 15.5 Hz, 1H), 3.00 (br s, 1H), 3.25 (d J = 15.5 Hz, 1H), 3.31 (d, J = 15.5 Hz, 1H), 3.42−3.82 (m, 33H), 3.83−3.94 (m, 6H), 4.01−4.17 (m, 6H), 4.25 (s, 2H), 4.59 (s, 2H), 6.14 (d, J = 10.6 Hz, 1H), 6.58 (d, J = 6.7 Hz, 1H), 6.76 (s, 1H), 6.81 (t, J = 6.7 Hz, 1H), 6.88 (s, 1H), 6.90 (d, J = 9.1 Hz, 1H), 6.98 (d, J = 6.7 Hz, 1H), 7.21 (t, J = 6.7 Hz, 1H), 7.26 (d, J = 10.6 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 38.22, 42.50, 45.15, 47.03, 48.91, 59.28, 61.61, 65.51, 68.59, 69.13, 69.17, 69.83−71.67, 79.07, 98.80, 105.17, 107.01, 109.76, 110.67, 115.50, 115.78, 119.66, 121.34, 121.38, 123.50, 126.23, 126.58, 128.27, 133.81, 134.16, 134.36, 142.95, 147.01, 147.80, 158.27, 169.32; FABMS (in 3-nitrobenzyl alcohol) *m/e* (rel intensity) 974 (MH$^+$, 93), 996 (M$^+$ + Na, 100).