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SYNTHESIS OF A POLY-HETEROCYCLIC TETRA-SUBSTITUTED ALKENE VIA A PALLADIUM-CATALYZED FOUR-FOLD DOMINO REACTION FOR THE DESIGN OF POLYMERIC MOLECULAR SWITCHES

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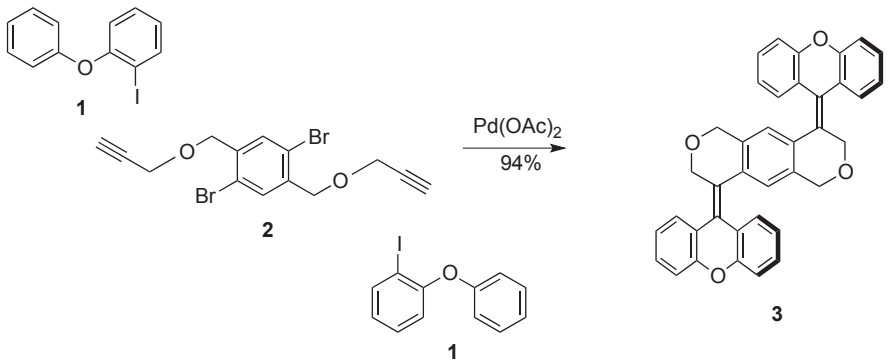
Dedicated to Professor Tohru Fukuyama

Abstract – A facile synthesis of a complex poly-heterocyclic tetrasubstituted alkene **4** with intrinsic helical chirality containing two acrylate moieties suitable for polymerization is described. Compound **4** can act as a molecular switch and was prepared via a palladium-catalyzed four-fold domino reaction including two Sonogashira reactions and two domino-carbopalladation/C–H-activation reactions.

INTRODUCTION

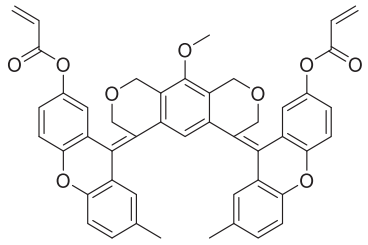
Domino reactions, as a novel methodology in synthesis, allow the highly efficient preparation of any type of compound in a green and moreover economically suitable fashion starting from simple substrates.[1] Transition metal catalysis[2] can be employed in these processes which in addition allow C–H-activation reactions[3] governed by proximity effects[4] without the need of directing groups, which have the disadvantage that they have to be removed or functionalized afterwards.[5]



Scheme 1. Three component six-fold domino-Sonogashira/carbopalladation/C–H-activation reaction

Some time ago we have shown that molecular switches[6] as **3** with two switching units can be obtained easily by a six-fold three component Pd-catalyzed domino reaction of two molecules of **1** and one molecule of **2** consisting of two Sonogashira, two carbopalladation and two C–H-activation reactions, where the latter transformations are ruled by proximity effects without directing groups (Scheme 1).[7] The yield with over 90% is astonishingly high for such a complex transformation, showing the power of the domino concept. The switching time of such molecules is very fast with about 1 pico second as shown by Femtosecond pump - supercontinuum probe (PSCP) investigations[8] in the range 260-700 nm. We have also inserted such a switch with a single acrylate moiety in a polymeric matrix using a RAFT copolymerization with *n*-butyl acrylate.[9]

Herein, we describe the efficient synthesis of the poly-heterocyclic helical tetrasubstituted overcrowded alkene **4** using a palladium-catalyzed domino approach consisting of two Sonogashira, two carbopalladation and two C–H-activation reactions containing two acrylate moieties at the two ends of the molecule (Scheme 2).



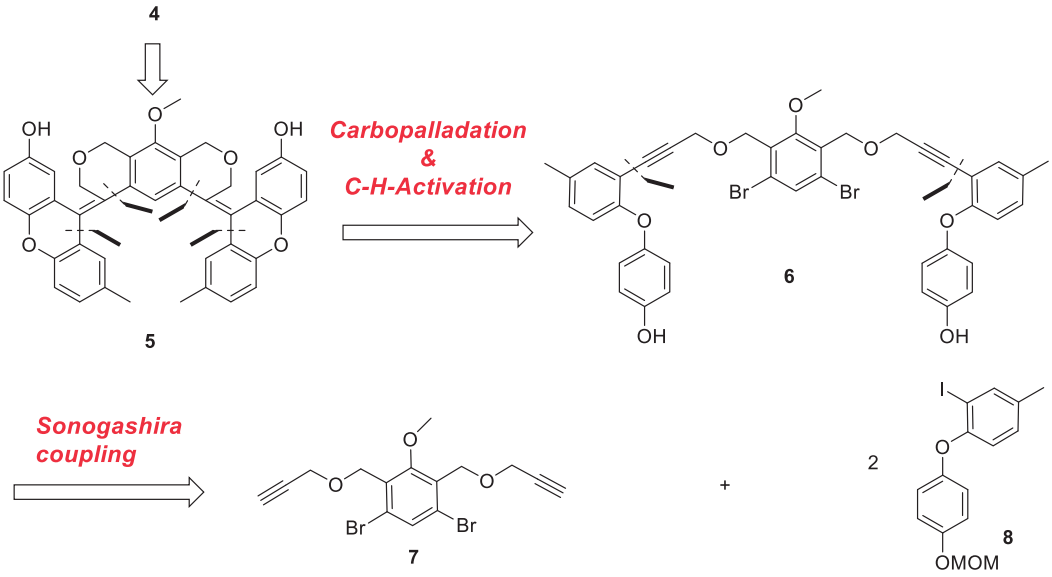
4

Scheme 2. Structure of the poly-heterocyclic helical tetrasubstituted alkene **4**

The novel structure of this poly-heterocyclic photo-switchable unit would allow the formation of photo sensitive polymers with applications ranging from optical data storage devices to biomedical super resolution imaging.[10-12] Another idea behind the synthesis of **4** is the design of novel types of fibers of which the length can be altered by irradiation with light.

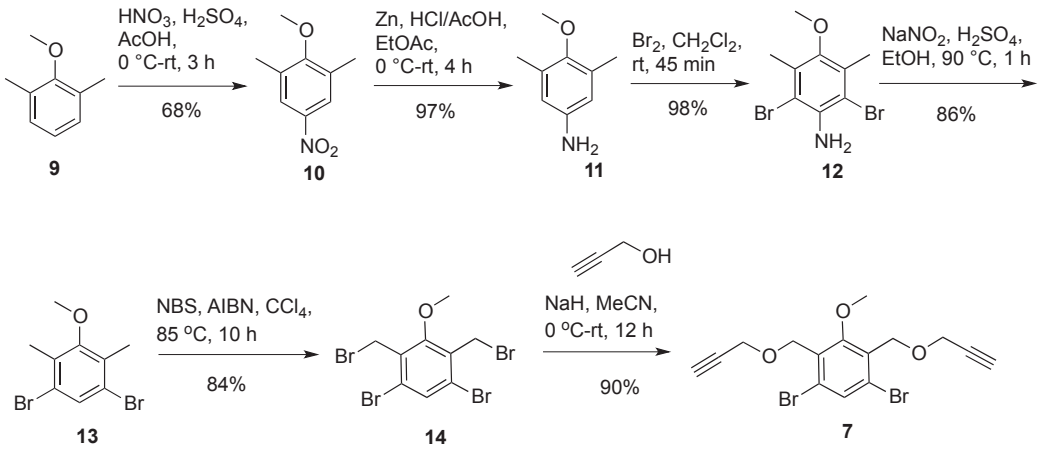
RESULTS AND DISCUSSION

According to the retrosynthesis we first had to prepare the alkene **5** with two hydroxyl groups which could later be transformed into the desired bis-acrylate **4** (Scheme 3). Compound **5** should be accessible from **6** by two carbopalladation and two C–H-activation reactions and **6** could be obtained from one molecule of **7** and two molecules of **8** by two Sonogashira reactions. For the synthesis of compound **7**, 2,6-dimethylanisol **9** was nitrated to give **10**, which was reduced with zinc in HCl/AcOH leading to **11** with 82% yield over two steps using described procedures[9] with slight modifications (Scheme 4).



Scheme 3. Retrosynthetic analysis of **5**

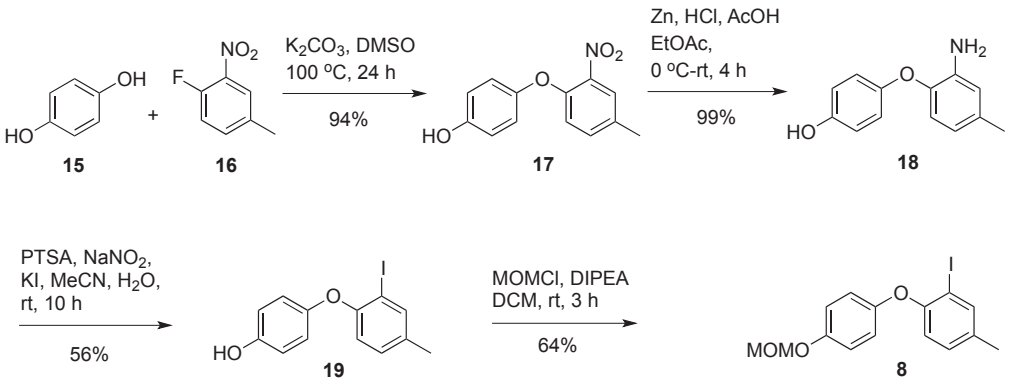
The obtained sensitive aniline was converted immediately into the dibromoaniline **12** by treatment with bromine in CH_2Cl_2 in 98% yield. The deamination of aniline **12** using standard reaction conditions afforded compound **13** in 86% yields, which was treated with NBS and AIBN to provide the tetrabromo arene **14**. Finally, substitution reaction with propargyl alcohol gave the dialkyne **7** as the first substrate for the Sonogashira reaction.



Scheme 4. Synthesis of dialkyne **7**

For the synthesis of the iodoaryl ether **8**, as the other partner of the Sonogashira reaction, nitrophenoxy ether **17** was prepared by a nucleophilic aromatic substitution of 4-fluoro-3-nitrotoluene **16** with hydroquinone **15** in 94% yield (Scheme 5). This compound was converted into amine **18** by reduction and

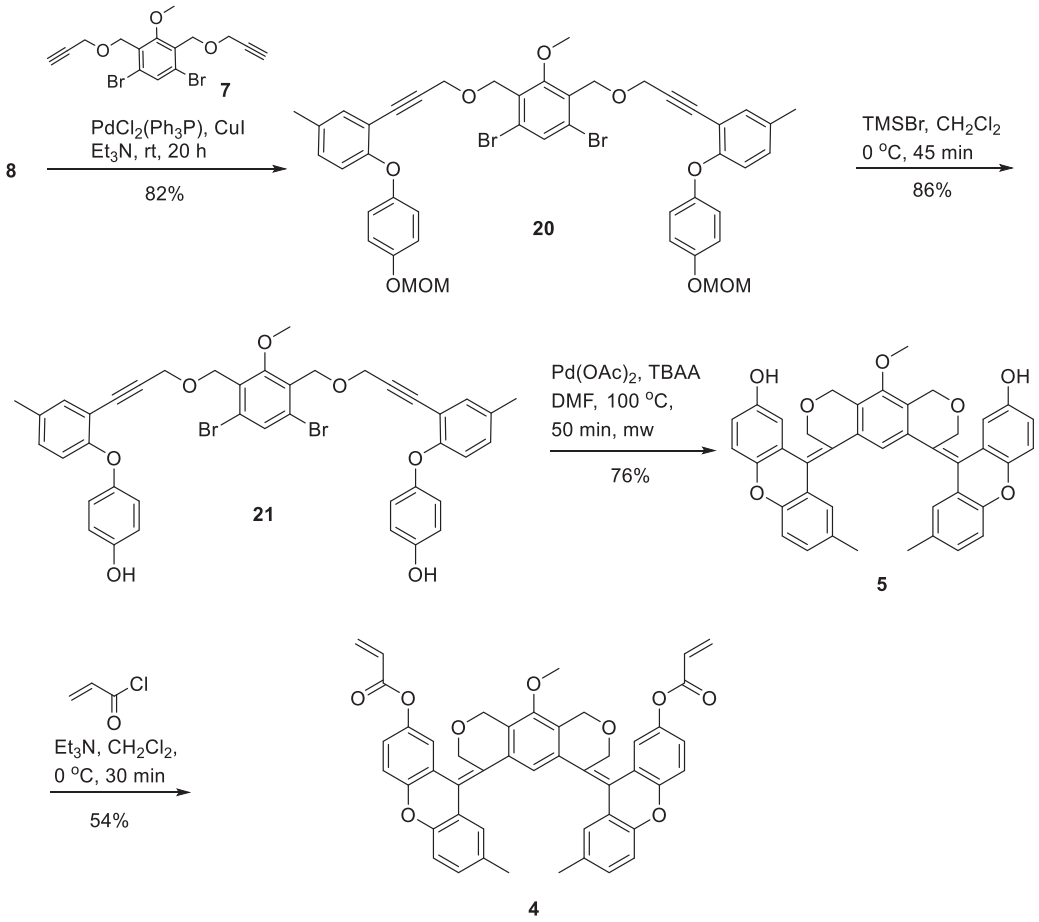
then into the iodide **19** by a Sandmayer reaction. Since **19** was not suitable for the Sonogoshira reaction the phenolic hydroxyl group was protected as MOM ether by treatment with MOMCl to give **8**.



Scheme 5. Synthesis of iodo-aryl ether **8**

The Pd-catalyzed reaction of two molecules of the aryl iodide **8** with dialkyne **7** using $PdCl_2$(dppf) gave **20** which was treated with TMSBr to remove the MOM group (Scheme 6). It followed the domino reaction of the obtained **21** using $Pd(OAc)_2$, PPh_3 and $(n\text{Bu})_4\text{NOAc}$ as base in DMF under microwave irradiation which proceeded in just 50 min to furnish the desired poly-heterocyclic product **5** in 76% yield. This dimeric tetrasubstituted alkene, a poly-heterocyclic structure with two free hydroxyl group, was further transformed into the diacrylate **4** as the final desired product using acryloyl chloride and triethylamine in CH_2Cl_2 with reasonable yield (Scheme 6). The polymerization of **4** using different procedures and the determination of the properties of the obtained polymers is under way.

In conclusion, we have developed a facile and efficient synthesis of a novel class of poly-heterocyclic helical dimeric tetrasubstituted alkenes using a combination of two Sonogashira, two carbopalladation and two C–H-activation reactions based on proximity effects in a four-fold domino process starting from simple precursors. This poly-heterocyclic class of compounds with photo-molecular switching properties could be useful in making photosensitive polymers and other application materials.



Scheme 6. Synthesis of **4** by two Sonogashira reactions, two carbopalladations and two C–H-activation reactions from **7** and **8** followed by the introduction of two acrylate moieties

EXPERIMENTAL

General information

All air and water sensitive reactions were carried out under Argon atmosphere in flame-dried glassware. All solvents were dried with standard procedure. Thin-layer chromatography was performed on silica gel plates from Merck (TLC Silica gel 60 F254). Column chromatography was performed with silica gel from Merck (Geduran® Si60, Ø = 32–64 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on 300, 400 and 500 MHz spectrometers. Chemical shifts δ are indicated in ppm referring to tetramethylsilane (TMS). IR spectra were recorded on a FT/IR-4100 spectrometer from JASCO. All substances were applied neat on an ATR unit. UV spectra were recorded on a V-630 spectrometer from JASCO. ESI-MS and ESI-HRMS spectra were recorded on an Apex IV spectrometer from Bruker Daltronik. EI-MS and EI-HRMS spectra were recorded on a MAT 95 spectrometer from Finnigan. Reactions in the microwave were driven in an Initiator microwave reactor from Biotage (absorption level: very high, pre-stirring: 30 sec, fixed hold time: on). Compounds **10, 11** and **12** were prepared according to reported procedures.[9]

1,5-Dibromo-3-methoxy-2,4-dimethylbenzene (13)

To a stirred solution of compound **12** (2.00 g, 5.47 mmol) in EtOH (30 mL) was slowly given at rt conc. H_2SO_4 (0.7 mL, 10.9 mmol) and stirring was continued for 5 min, then $NaNO_2$ (990 mg, 12.0 mmol) was added and the reaction mixture stirred for another 15 min at rt and then refluxed (90 °C) for 1 h. The flask was cooled to 0 °C, then water (200 mL) was added, and the mixture extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (1% EtOAc-petroleum ether) to give compound **13** as a whitish solid (1.56 g, 86%), mp 56 °C. UV (MeCN) λ_{max} (lg ε): 207 nm (2.4461). IR ῡ (cm^{-1}): 2937, 2845, 1557, 1445, 1371, 1209, 1170, 1018, 999, 939, 842, 673, 599. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (dt, *J* = 0.4 Hz, 1H), 3.67 (s, 3H), 2.28 (d, *J* = 0.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.71, 131.07, 130.82, 122.79, 60.39, 16.21. HMRS (EI) *m/z* = 291.9098 calcd for $C_9H_{10}Br_2O$ $[M]^+$, found: 291.9092.

1,5-Dibromo-2,4-bis(bromomethyl)-3-methoxybenzene (14)

1,5-Dibromo-3-methoxy-2,4-dimethylbenzene (**13**) (500 mg, 1.7 mmol) in CCl_4 (25 mL) was treated with NBS (635 mg, 3.57 mmol) and AIBN (5 mg) at 85 °C and stirred at this temperature for 10 h. The reaction mixture was cooled to room temperature, filtered, the filter cake washed with CCl_4 and the filtrate concentrated in vacuo. The crude product was purified by column chromatography on silica gel (2% EtOAc in petroleum ether) to give compound **7** as a colorless solid (650 mg, 84%), mp 145-148 °C. UV (MeCN): λ_{max} (lg ε) = 224 nm (0.7342), 255 (0.2967), 293 (0.0800). IR: $\tilde{\upsilon}$ (cm^{-1}) = 3072, 3044, 2942, 2854, 1553, 1423, 1375, 1244, 1221, 1208, 994, 982, 880, 687, 585, 505. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 1H), 4.61 (s, 4H), 4.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.42 (-C), 133.27 (-CH), 131.68 (-C), 126.67 (C), 62.88 ($-CH_3$), 27.19 ($-CH_2$). HMRS (EI) *m/z* = 447.7309 calcd for $C_9H_8Br_4O$ $[M]^+$, found: 447.7308.

1,5-Dibromo-3-methoxy-2,4-bis((prop-2-yn-1-yloxy)methyl)benzene (7)

A mixture of propargylic alcohol (627 mg, 11.1 mmol) and NaH (60%, 885 mg, 22.1 mmol) in MeCN (40 mL) was stirred at 0 °C for 10 min. TBAI (81 mg, 221 μmol) was added, the mixture stirred at 0 °C for 10 min and compound **14** (1.00 g, 2.21 mmol) added. The mixture was stirred at rt for 12 h. Saturated aq. NH_4Cl solution (50 mL) was added and the mixture extracted with EtOAc (3 × 50 mL), then the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. Column chromatography on silica gel (5% EtOAc in petroleum ether) yielded compound **8** as a colourless solid (800 mg, 90%), mp 70-72 °C. UV (MeCN): λ_{max} (lg ε) = 210 nm (2.654), 235 (0.595), 286 (0.0865). IR: $\tilde{\upsilon}$ (cm^{-1}) = 3292, 2956, 2892, 2855, 2117, 1559, 1466, 1437, 1271, 1067,

1003, 936, 904, 848, 629, 566. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H), 4.66 (s, 4H), 4.24 (d, *J* = 2.4 Hz, 4H), 3.92 (s, 3H), 2.48 (t, *J* = 2.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.43, 132.33, 130.49, 127.16, 79.40, 74.84, 66.01, 65.09, 58.07. HMRS (ESI) *m/z* = 422.9202 calcd for $C_{15}H_{34}Br_2O_3$ $[M+Na]^+$, found: 422.9200.

4-(4-Methyl-2-nitrophenoxy)phenol (17)

A mixture of 1-fluoro-4-methyl-2-nitrobenzene (**16**) (4.00 g, 5.78 mmol), hydroquinone (**15**) (8.51 g, 77.35 mmol) and K_2CO_3 (21.37 g, 154.7 mmol) in DMSO (40 mL) in a screw capped pressure vessel was heated at 100 ºC for 24 h. After cooling to rt, water (200 mL) was added and the mixture was extracted with MTBE (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (5 to 10% EtOAc in petroleum ether to get biaryl ether **17** as a dark orange thick liquid (6.00 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.30 – 7.18 (m, 1H), 6.97 – 6.69 (m, 5H), 5.46 (brs, 1H), 2.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.33, 149.34, 149.06, 140.25, 134.76, 132.62, 125.55, 120.66, 119.33, 116.47, 20.37. Other analytical data matches with literature.[9]

4-(2-Amino-4-methylphenoxy)phenol (18)

To a solution of compound **17** (1.45 g, 5.91 mmol) in EtOAc (14 mL) were added slowly conc. HCl (38 mL) and conc AcOH (38 mL) at 0 ºC. Zinc powder (20 g, 0.402 mol) was added in portions and the reaction mixture was stirred at rt for 4 h. The reaction was quenched by dropwise addition of 33% aq. NH_3 solution (600 mL) at 0 ºC. The mixture was filtered and the filter cake washed with EtOAc. The filtrate was extracted with EtOAc (3 × 100 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield amine **12** as a grey solid (1.068 g, 99%). ^{1}H NMR (301 MHz, DMSO-d_6): δ 9.08 (s, 1H), 6.85 – 6.66 (m, 4H), 6.63 – 6.52 (m, 2H), 6.31 (dd, *J* = 8.0, 2.2 Hz, 1H), 4.71 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (76 MHz, DMSO-d_6): δ 152.58, 149.78, 141.24, 139.48, 132.79, 118.73, 118.26, 116.89, 116.06, 115.83, 20.57. Other analytical data matches with literature.[9]

4-(2-Iodo-4-methylphenoxy)phenol (19)

A solution of $NaNO_2$ (3.27 g, 47.4 mmol) and KI (7.86 g, 47.4 mmol) in water (20 mL) was added dropwise to a stirred mixture of compound **18** (5.1 g, 23.7 mmol) and *p*-TsOH•H_2O (13.52 g, 71.1 mmol) in MeCN (250 mL) at rt and stirring was continued for 10 h. After adding water (300 mL) the mixture was extracted with MTBE (3 × 200 mL) and the combined organic layers were washed with sat. aq.

$Na_2S_2O_3$ solution, brine, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The crude product was purified by column chromatography on silica gel (5 to 10% EtOAc in petroleum ether) to give compound **19** as a brown solid (4.36 g, 56%), mp 101 ºC. UV (MeCN): λ_{max} (lg ε) = 200 nm (2.2985), 225 (1.0599), 282 (0.2374). IR: $\tilde{\upsilon}$ (cm^{-1}) = 3389, 3029, 2956, 2916, 1501, 1475, 1444, 1358, 1196, 1096, 1035, 884, 818, 782, 587. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.90 – 6.73 (m, 4H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.14 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.88, 151.28, 150.56, 139.80, 134.55, 130.06, 119.81, 118.09, 116.24, 87.98, 20.17. HMRS (EI) *m/z* = 325.9804 calcd for $C_{13}H_{11}IO_2$ $[M]^+$, found: 325.9798.

2-Iodo-1-(4-(methoxymethoxy)phenoxy)-4-methylbenzene (8)

MOMCl (0.7 mL g, 9.2 mmol) was added slowly to a stirred mixture of compound **19** (2.0 g, 6.13 mmol) and DIPEA (4.27 mL, 24.52 mmol) in CH_2Cl_2 (70 mL) at rt. Stirring was continued at rt for 3 h (TLC), and the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (1% EtOAc in petroleum ether) to yield compound **14** as a colorless oil (1.45 g, 64%). UV (MeCN): λ_{max} (lg ε): = 224 nm (0.7970), 282 (0.1565). IR: $\tilde{\upsilon}$ (cm^{-1}) = 2950, 2921, 2892, 1500, 1223, 11187, 1148, 1076, 994, 920, 885, 829, 777, 660, 584. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 2.1, 0.9 Hz, 1H), 7.11 – 6.80 (m, 5H), 6.71 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 3.47 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.77, 153.14, 151.58, 139.85, 134.69, 130.09, 119.39, 118.42, 117.48, 94.99, 88.21, 55.96, 20.21. HMRS (EI) *m/z* = 370.0066 calcd for C15H15IO3 $[M]^+$, found: 370.0069.

2,2'-((((4,6-Dibromo-2-methoxy-1,3-phenylene)bis(methylene))bis(oxy))bis(prop-1-yne-3,1-diyl))bis-(1-(4-(methoxymethoxy)phenoxy)-4-methylbenzene) (20)

Compound **8** (827 mg, 2.23 mmol) was dissolved in NEt_3 (20 mL) and degassed thoroughly. $Pd(PPh_3)_2Cl_2$ (44.5 mg, 0.05 mmol), CuI (24 mg, 0.11 mmol) and dialkyne **7** (510 mg, 1.11 mmol) were added and the reaction mixture was stirred at rt for 20 h. The mixture was concentrated in vacuo and the residue purified by column chromatography on silica gel (5% EtOAc in petroleum ether) to give compound **20** as a pale yellow thick liquid (920 mg, 82%). UV **(**MeCN) λ_{max} (lg ε) = 210 nm (2.6455), 253 (0.8226), 287 (0.2370), 307 (0.1834). IR: $\tilde{\upsilon}$ (cm^{-1}) = 2944, 2888, 2845, 2228, 1559, 1504, 1487, 1350, 1261, 1218, 1189, 1149, 1072, 998, 920, 839, 823. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.30 – 7.26 (m, 1H), 7.02 (ddd, *J* = 8.4, 2.1, 0.8 Hz, 2H), 6.99 – 6.84 (m, 9H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.09 (s, 4H), 4.65 (s, 4H), 4.43 (s, 4H), 3.88 (s, 3H), 3.45 (s, 6H), 2.28 (d, *J* = 0.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.53, 156.15, 153.03, 151.76, 133.97, 132.26, 130.76, 130.40, 127.07, 119.63, 118.02, 117.39, 114.20, 94.96, 89.11, 82.73, 65.84, 64.96, 58.92, 55.91, 26.96, 20.50. HMRS (ESI) *m/z* = 907.1088 calcd for $C_{45}H_{42}O_9Br_2$ $[M+Na]^+$, found: 907.1095.

4,4'-((((((4,6-Dibromo-2-methoxy-1,3-phenylene)bis(methylene))bis(oxy))bis(prop-1-yne-3,1-diyl))-bis(4-methyl-2,1-phenylene))bis(oxy))diphenol (21)

A solution of TMSBr (407 mg, 2.66 mmol) in CH_2Cl_2 (2 mL) was added slowly to a stirred solution of compound **20** (590 mg, 0.665 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After stirring for 45 min at 0 °C, the reaction was quenched with aq $NaHCO_3$ solution and the mixture extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography on silica gel (20% EtOAc in petroleum ether) yielded compound **21** as a brown solid (458 mg, 86%), mp 73-75 °C. UV (MeCN): λ_{max} (lg ε) = 210 nm (1.7012), 254 (0.4777), 287 (0.1964). IR: $\tilde{\upsilon}$ (cm^{-1}) = 3336, 2943, 2882, 2857, 2220, 2190, 1560, 1506, 1486, 1445, 1375, 1350, 1212, 1194, 1168, 1007, 839, 805. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.27 (d, *J* = 2.2 Hz, 2H), 7.03 (ddd, *J* = 8.3, 2.1, 0.8 Hz, 2H), 6.87 – 6.79 (m, 4H), 6.76 – 6.68 (m, 6H), 4.91 (brs, 2H), 4.60 (s, 4H), 4.41 (s, 4H), 3.81 (s, 3H), 2.27 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.61, 156.31, 151.40, 150.89, 134.07, 132.49, 132.27, 130.68, 130.58, 127.20, 119.80, 118.16, 116.23, 114.16, 89.13, 82.83, 65.88, 64.88, 58.93, 20.44. HMRS (ESI) *m/z* = 819.0563 calcd for $C_{41}H_{34}O_7Br_2$ $[M+Na]^+$, found: 819.0575.

9,9'-(10-Methoxy-1*H*,3*H*-pyrano[4,3-*g*]isochromene-4,6(7*H*,9*H*)-diylidene)bis(7-methyl-9*H*-xanthen-2-ol) (5)

A solution of compound **21** (150 mg, 0.187 mmol) in DMF (3 mL) was charged with $Pd(OAc)_2$ (4.2 mg, 0.0187 mmol), PPh_3 (24.6, 0.093 mmol) and (nBu)$_4$NOAc (338 mg, 1.12 mmol) under an argon atmosphere and the mixture was irradiated in a microwave reactor for 50 min at 100 °C. After addition of an aqueous saturated NH_4Cl solution the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. Column chromatography on silica gel (5 to 30% EtOAc in petroleum ether) yielded the desired compound **5** as a light brown solid (91 mg, 76%) (mixture of 3 diastereomers according to analytical HPLC on chiral support), mp 145-150 °C (decomposition). UV (MeCN): λ_{max} (lg ε) = 222 nm (3.9763), 299 (1.5448), 347 (1.4263). IR: $\tilde{\upsilon}$ (cm^{-1}) = 3318, 2960, 2925, 2855, 1702, 1615, 1593, 1453, 1285, 1252, 1195, 1084, 1035, 857, 813, 767, 725. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.21 (m, 1H), 7.12 – 6.86 (m, 7H), 6.86 – 6.76 (m, 2H), 6.72 (ddd, *J* = 8.7, 4.8, 2.8 Hz, 1H), 6.60 (ddd, *J* = 8.7, 5.6, 2.9 Hz, 1H), 6.41 (t, *J* = 2.7 Hz, 1H), 5.71, 5.32, 5.29 (3 x brs, -OH), 4.90, 4.88, 4.85, 4.84 (4 × s, 3'-H, 5'-H), 4.71, 4.66 (2 × brs, 2'-H, 7'-H), 3.78, 3.76, 3.74 (3 × s, -OCH_3), 2.33 (s, 2H), 2.32, 1.85, 1.83 (4 × s, -CH3). HMRS (ESI) *m/z* = 635.2075 calcd for $C_{41}H_{32}O_7$ $[M-H]^+$, found: 635.2031.

(10-Methoxy-1*H*,3*H*-pyrano[4,3-*g*]isochromene-4,6(7*H*,9*H*)-diylidene)bis(7-methyl-9*H*-xanthen-2-yl-9-ylidene) diacrylate (4)

A solution of acryloyl chloride (62 mg, 0.69 mmol) in CH_2Cl_2 (2 mL) was added slowly to a solution of compound **5** (110 mg, 0.17 mmol) and triethylamine (0.191 mL, 1.37 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After stirring for 30 min at 0 °C, the reaction was quenched with water and the mixture extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and after filtration concentrated under reduced pressure. Column chromatography on silica gel (5 to 20% EtOAc in petroleum ether) yielded the target compound **4** as a pale yellow solid (70 mg, 54%), mp 121-124 °C (decomposed). UV (MeCN): λ_{max} (lg ε) = 230 nm (4.0184), 289 (2.0632), 342 (1.8682). IR: $\tilde{\upsilon}$ (cm^{-1}) = 2950, 2920, 2852, 1734, 1655, 1615, 1465, 1400, 1364, 1288, 1237, 1144, 1022, 973, 908, 859, 802. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.15 (m, 3H), 7.15 – 6.75 (m, 10H), 6.60 (dd, *J* = 17.5, 1.0 Hz, 1H), 6.38 – 6.19 (m, 2H), 6.11 – 5.96 (m, 3H), 5.77 (ddd, *J* = 18.3, 10.4, 1.4 Hz, 1H), 4.92, 4.91, 4.89 (3 × s, 3'-H, 5'-H), 4.69, 4.66, 4.63 (3 × brs, 2'-H, 7'-H), 3.79, 3.79, 3.79 (3 × s, -OCH_3), 2.35, 1.88, 1.85 (3 × s, -CH3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.78, 164.74, 164.18, 164.11, 152.50, 152.44, 152.28, 152.24, 151.78, 151.76, 151.63, 151.54, 151.48, 145.29, 145.23, 145.20, 132.80, 132.75, 132.33, 132.27, 132.17, 132.00, 131.96, 131.88, 131.74, 131.71, 131.22, 130.80, 129.29, 129.18, 128.92, 128.87, 128.84, 128.75, 128.68, 128.59, 128.56, 128.46, 127.78, 127.76, 127.71, 126.96, 126.90, 126.84, 126.57, 126.46, 126.22, 126.20, 126.05, 125.01, 124.96, 124.93, 124.75, 123.96, 123.74, 123.53, 122.88, 122.83, 122.01, 121.92, 121.86, 121.84, 121.38, 121.32, 121.02, 121.01, 120.86, 120.79, 119.74, 119.65, 118.09, 117.86, 117.14, 117.08, 116.87, 116.26, 116.24, 68.01, 67.82, 67.72, 67.61, 64.97, 64.75, 64.69, 61.27, 61.22, 61.19, 21.02, 20.38, 20.33. HMRS (ESI) *m/z* = 767.2252 calcd for $C_{47}H_{36}O_9$ $[M+Na]^+$, found: 767.2237.

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