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Synthesis of verbenachalcone congeners and their biological assessment against activation of the NGF-mediated neurite outgrowth of PC12D cells' activity

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Abstract—Synthesis of the verbenachalcone derivatives **3**–**5** involving littorachalcone **2** from diaryl ether **7** enabled an SAR study of enhancement activity against the NGF-mediated neurite outgrowth from PC12D cells. Littorachalcone **2** and *o*-deoxyverbenachalcone **5** showed similar activity to that of verbenachalcone **1**.

1. Introduction

In the preceding paper,[1] we described the total synthesis of verbenachalcone **1**, isolated from the aerial part of *Verbena littoralis* H. B. K. (Verbenaceae).[2] The typical dimeric structure connected with a diaryl ether linkage provides enhancement of the NGF (nerve growth factor)-mediated neurite outgrowth of PC12D cells. Our phenolic oxidation methodology[3] enabled successful construction of the core diaryl ether by dimerization of the corresponding *o*,*o*-dihalogenated phenol derivatives, followed by introduction of an alkoxy function. From the synthetic viewpoint, closely related rhuschalcone, possessing cytotoxic activity against the HT29 and HCT-116 colon tumor cell lines,[4] was synthesized by using the Ullmann coupling for its structural elucidation. Cuny et al. reported a synthesis of **1** itself by a similar coupling reaction, along with an SAR study: the pentaacetylated **1** exhibited a stronger NGF activation effect than the mother **1**, while removal of the two ketones decreased the activity.[5] They also examined the activation effect, inhibition of caspase induction, and gene expression profiles of NGF by using a tetramethyl derivative of **1**: increase of the NGF effect by masking phenols in the terminal aromatic rings suggested that these protic substituents might have no influence on the activity.[6] Against such a background, our attention was focused on the synthesis and SAR study of the verbenachalcone-class natural products. In contrast to such coupling reactions as the Ullmann coupling of phenol precursors with halogenated counterparts, the outstanding point of our synthetic approach[3b] was the economical construction of the diaryl ether core by dimerization of the Br,Cl-disubstituted phenol derivative under anodic oxidation conditions, followed by chemoselective methoxylation. Introduction of 2,4-dihydroxyphenyl moieties would be performed at the final stage to circumvent undesired side reactions during the oxidation. We describe herein synthesis and biological assessment of enhancement of the NGF activation of littorachalcone **2**,[7] isolated from the same plant as that of **1**, as well as the other congeners **3**–**5** (Fig. 1).

2. Results and discussion

As experienced in the synthesis of **1**,[1] diaryl ether **7** would be an important synthetic precursor of **2**–**5**. At the outset, **7** was synthesized from the known propyl-

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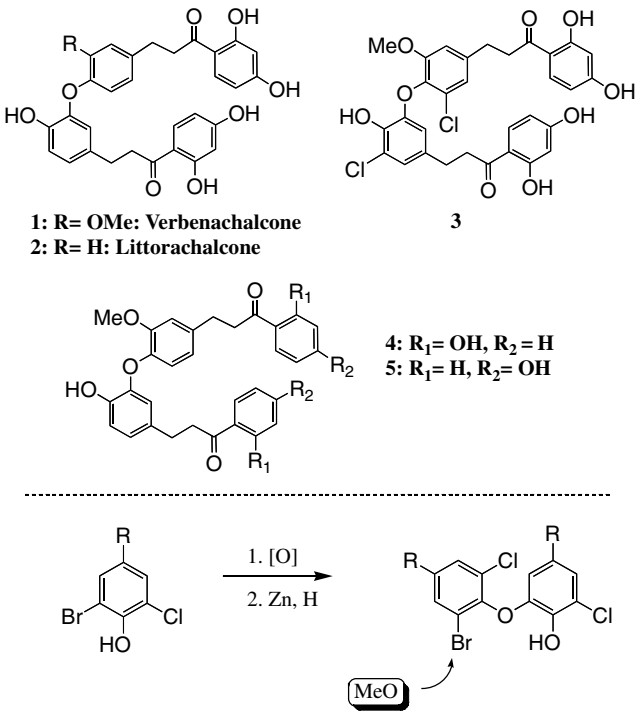


Figure 1.

benzene derivative **6**,[8] through stepwise halogenation in moderate yields (Scheme 1). Upon exposure of **7** to the standard anodic oxidation conditions [CCE (constant current electrolysis) at 20 mA ($1 \rightarrow 1.5$ V vs SCE at 10 mM concentration of the substrate **7**; undivided cell; anode: glassy carbon beaker; cathode: platinum wire; solvent: MeOH; supporting salt: $LiClO_4$)], the desired diaryl ether **8** (16%), along with a mixture (23%) of dienone **9** and benzyl ether **10**, was obtained. Among several conditions examined to improve the yield of **8**, reaction in a flow-cell apparatus provided the highest yield (62%), even using a 3 g portion of **7**, without production of undesired **9** and **10**. The flow-cell system effected decrease of the undesired side reactions leading to **9** and **10**, although polymerization of the substrates was not completely excluded.

The diaryl ether **8** in hand was submitted to Zn reduction to give **11**. After protection with an MOM group and exchange of the acetyl groups to TBS groups, a bromine group was lithiated, followed by conversion into the corresponding borate ester and oxidative treatment to give a separable mixture of **12a** and **12b** in 64% and 14% yields, respectively.

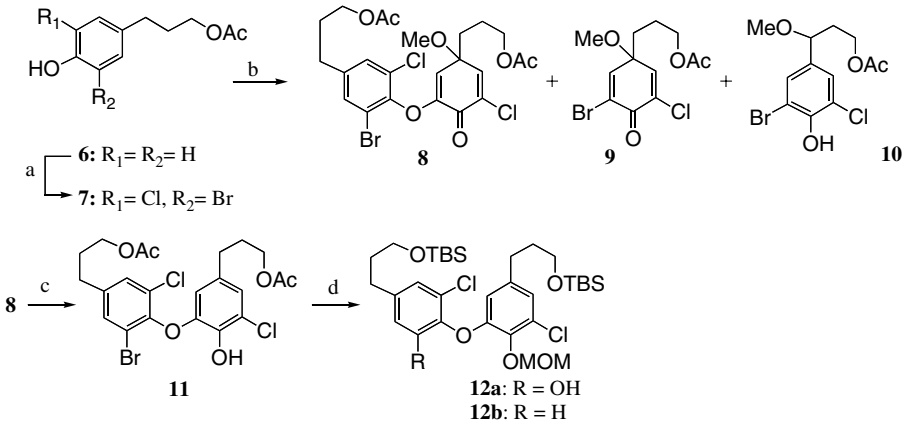
2.1. Synthesis of littorachalcone (2)

According to essentially the same procedure as that of **1**,[1] littorachalcone **2** was synthesized from **12b** (Scheme 2). Removal of chlorine atoms of **12b** under hydrogen-transfer conditions (**13**)[9] and TBS groups gave the corresponding alcohol, which was submitted to stepwise oxidation through **14** and **15**, followed by reaction with MeONHMe to afford **16**. Coupling with a lithiated **18**[10] provided the protected form **17** of **2** in good yield. Acid treatment of **17** successfully produced **2**, spectroscopic data of which were indistinguishable to the reported data.[7]

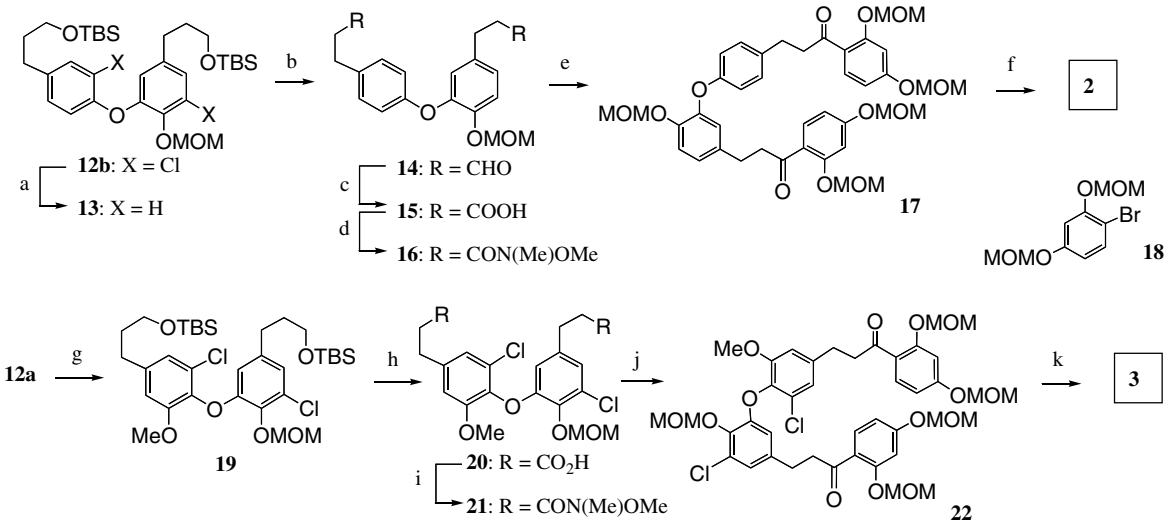
2.2. Synthesis of the verbenachalcone congeners (3–5)

Dichloroverbenachalcone **3** was synthesized from **12a**, which upon methylation gave **19** in quantitative yield (Scheme 2). The two TBS ethers were simultaneously deprotected with a fluoride ion, and primary alcohols generated were submitted to PDC oxidation to give the dicarboxylic acid **20**. After conversion to the corresponding Weinreb amide **21** as described in the case of **16**, coupling with a lithiated **18** provided **22**. The final acid hydrolysis as in the case of **2** gave the desired **3**.

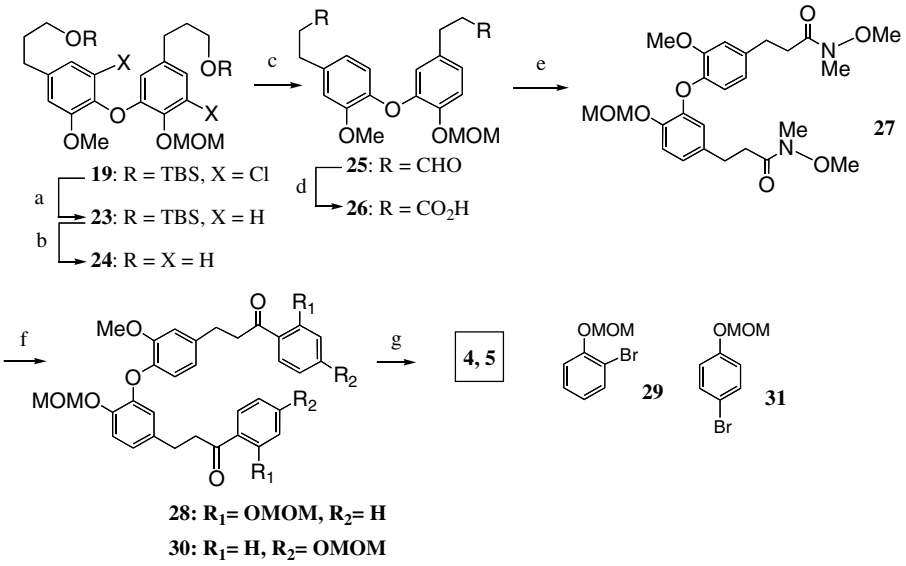
Hydrogen-transfer reaction of **19** effected dehalogenation to give **23**, two TBS ether moieties of which were manipulated by deprotection (**24**) and stepwise oxidation as mentioned above to give the dicarboxylic acid **26** through **25** (Scheme 3). After conversion to the Weinreb amide **27**, lithiated **29**[11] and **31**[12] were reacted to give the coupling products **28** and **30** in 67% and 84% yields, respectively. Their acid hydrolysis provided the deoxyverbenachalcones **4** and **5**.



Scheme 1. Reagents and conditions: (a) SO_2Cl_2 (64%), then Pyr·HBr_3/$CHCl_3$–Pyr (100%). (b) CCE at 10 mA (**8**, 50% and a mixture of **9** and **10**, 12%) or CCE at 20 mA (flow cell, **8**, 62%). (c) Zn, AcOH (70%). (d) i—MOMCl, DIPEA (100%); ii—K_2CO_3/MeOH (100%); iii—TBSCl. Imd/DMF (100%); iv—*n*-BuLi, $B(OMe)_3$, then NaOH, 30% H_2O_2 (**12a**, 64% and **12b**, 14%).



Scheme 2. Reagents: (a) Pd-C, HCO_2NH_4/EtOH (92%). (b) i—TBAF (86%); ii—Et_3N, SO_3-Pyr, DMSO (84%). (c) PDC/DMF (82%). (d) Et_3N, HOBt, WSCI, (MeO)MeNH·HCl/CH_2Cl_2 (60%). (e) *n*-BuLi, **18**/THF (64%). (f) TsOH/MeOH (88%). (g) MeI, K_2CO_3/DMF (100%). (h) i—TBAF/THF (97%); ii—PDC/DMF (71%). (i) Et_3N, HOBt, WSCI, (MeO)MeNH·HCl/CH_2Cl_2 (65%). (j) *n*-BuLi, **18**/THF (49%). (k) TsOH/MeOH (100%).



Scheme 3. Reagents: (a) Pd-C, HCO_2NH_4/EtOH (84%). (b) TBAF/THF (100%). (c) Dess–Martin periodinane/CH_2Cl_2 (81%). (d) PDC/DMF (52%). (e) Et_3N, HOBt, WSCI, (MeO)MeNH·HCl/CH_2Cl_2 (96%). (f) *n*-BuLi, **29**/THF (**28**: 67%); *n*-BuLi, **31**/THF (**30**: 84%). (g) TsOH/MeOH (**4**: 94%; **5**: 100%).

2.3. Biological activity

The effect on neurite outgrowth by the synthetic samples was evaluated by counting the number of neurite-bearing PC12D cells (Figs. 2–4). No sole effect by the samples at 10 and 30 mM concentrations on the outgrowth of neurites was observed. On the other hand, when PC12D cells were treated with NGF, the addition of the synthetic samples at 10 mM concentration exhibited enhancement activities on neurite outgrowth similar to **1**, although **4**, **22**, **28**, and **30** showed inhibition of neurite outgrowth. These inhibitory samples were submitted to the assessment as 1% DMSO solutions for their insolubility to MeOH, which was used for other samples. A possibility of the inhibition of neurite outgrowth by the solvent in these entries was excluded, since NGF-treated PC12D cells still showed normal neurite outgrowth in the presence of 1% DMSO. Further assessment in higher concentrations of active samples revealed that **2** and **5** at 30 mM dramatically enhanced the outgrowth of neurites similar to **1**. These data indicated that a MeO group adjacent to the diaryl ether linkage, as well as phenols at *ortho*-positions to the carbonyl functions in the terminal aromatic moieties, might have no positive roles to enhance the activity. Interestingly, **4**, an isomer of **5** lacking a *p*-phenol, exhibited an inhibitory activity, which might possess some reasons regarding

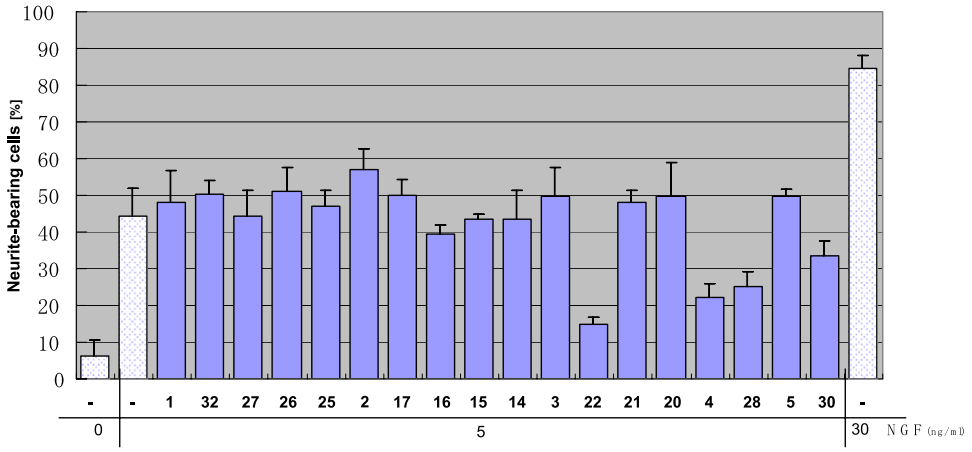


Figure 2. Enhancement of neurite growth by verbenachalcone and its derivatives in PC12D cells (concd 10 μM). White columns are controls only using NGF at 0, 5, and 30 ng/mL concentrations.

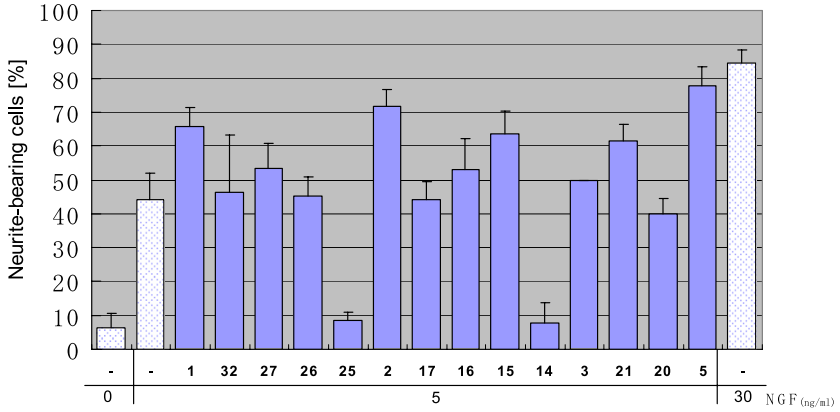


Figure 3. Enhancement of neurite growth by verbenachalcone and its derivatives in PC12D cells (concd 30 μM). White columns are controls only using NGF at 0, 5, and 30 ng/mL concentrations.

hydrogen bonding of the ketones. As Cuny also reported its crucial effect,[5] substitution of the aromatic moieties might play an important part to express the high enhancement activity. In addition, the activity appeared even in the absence of the terminal aromatics (**15**, **21**). Inhibitory activity of **14** and **25** carrying aldehydes rather than the neurite outgrowth enhancement was observed in 30 μM concentration. Remarkable difference between the Weinreb amide (**21**) and carboxylic acid (**20**) in the chlorine series was also observed: while the former provided the moderate activity, the latter disturbed it. Detailed investigation is still in progress.

3. Conclusion

Anodic oxidation of the mixed halogenated phenol derivative **7** provided the diaryl ether possessing a Br and a Cl substituents, which enabled the selective introduction of a methoxy group. Successful synthesis of littorachalcone **2** and the verbenachalcone congeners **3**–**5** was accomplished from the corresponding diaryl ethers **7**. Biological assessment of the synthesized samples revealed new information on the enhancement of NGF activation.

4. Experimental

4.1. General

IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL JNM EX-270 and JEOL JNM GX-400 spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard, unless otherwise stated. High-resolution mass spectra were obtained on a Hitachi M-80 B GC–MS spectrometer operating at an ionization energy of 70 eV. Melting points were measured on a Yanaco MP-S3 and are uncorrected. Silica-gel column chromatography was carried out using Kanto Chemical silica 60N (spherical, neutral, 63–210 μm). Preparative and analytical thin-layer chromatographies (TLC) were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merck AG, Germany). The reaction was monitored by UV (254 nm) light and/or stained with 5% phosphomolybdic acid in ethanol as a developing agent, followed in the latter case by heating on an electric plate. A flow-cell apparatus of HX-201 (Hokuto-Denko) was used. Work-up procedure: a mixture was partitioned between EtOAc or $CHCl_3$ and H_2O. The organic layer was washed with brine, dried (Na_2SO_4), and then evaporated.

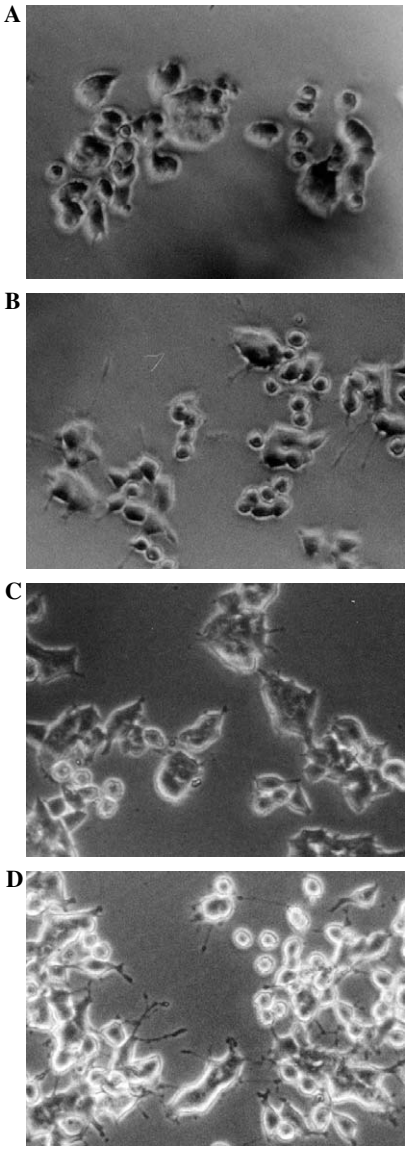


Figure 4. (A) Ordinary shape of PC12D cells in 1% MeOH solution. (B) Neurite outgrowth of the cells by NGF (5 μM). (C) Inhibition of the outgrowth by NGF (5 μM) and **22** (10 μM). (D) Enhancement of neurite outgrowth of the cells by NGF (5 μM) and **2** (30 μM).

4.2. 3-(5-Bromo-3-chloro-4-hydroxyphenyl)propyl acetate (7)

A mixture of **6**[2] (21 mg, 0.11 mmol) and SO_2Cl_2 (41 mL, 0.53 mmol) was stirred at 0 °C for 5 h under an Ar atmosphere. After the addition of satd aq $NaHCO_3$, the mixture was worked up. Purification by preparative TLC (hexane/EtOAc = 3:1) afforded a chloride (15.6 mg, 64%) as a colorless oil: IR (film) 3402, 2956, 1714 cm^{-1}; ^1H NMR δ 1.90 (tt, 2H, J = 6.4, 7.7 Hz), 2.06 (s, 3H), 2.60 (t, 2H, J = 7.7 Hz), 4.07 (t, 2H, J = 6.4 Hz), 5.73 (s, 1H), 6.92 (d, 1H, J = 8.4 Hz), 6.96 (dd, 1H, J = 8.4, 1.5 Hz), 7.13 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ 21.0, 30.2, 31.1, 63.6, 116.1, 119.6, 128.1, 128.5, 134.2, 149.5, 171.1; HRMS calcd for $C_{11}H_{13}{}^{35}ClO_3$: (M^+) 228.0552, found m/z 228.0592.

A mixture of the chloride (62 mg, 0.27 mmol) and Pyr·HBr_3 (148 mg, 0.46 mmol) in $CHCl_3$ (3 mL)–pyridine (2 mL) was stirred at 0 °C for 3 h. The mixture was worked up, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give **7** (88.1 mg, 100%) as colorless needles: mp 79.5–80 °C (Et_2O); IR (KBr) 3367, 1714 cm^{-1}; ^1H NMR δ 1.91 (tt, 2H, J = 6.4, 7.7 Hz), 2.06 (s, 3H), 2.59 (t, 2H, J = 7.7 Hz), 4.07 (t, 2H, J = 6.4 Hz), 5.76 (br, 1H), 7.12 (d, 1H, J = 1.7 Hz), 7.24 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ 21.0, 30.0, 30.9, 63.4, 110.0, 120.4, 128.6, 130.9, 135.0, 146.7, 170.9; HRMS calcd for $C_{11}H_{12}{}^{79}Br^{35}ClO_3$: ($M^+$) 305.9658, found m/z 305.9616.

4.3. Anodic oxidation of 7

A mixture of **7** (31 mg, 0.1 mmol) and $LiClO_4$ (0.1 M) in MeOH (200 mL) was electrolyzed (CCE at 10 mA, in an undivided cell using a glassy carbon beaker or a platinum net as anodes, a platinum wire as a cathode, 3 F/mol), under an Ar atmosphere. After evaporation and work-up, the residue was separated by silica gel column chromatography using (hexane/EtOAc = 3:1) to afford 3-[3-(4-(3-acetyloxypropyl)-2-bromo-6-chlorophenoxy)-5-chloro-1-methoxy-4-oxocyclohexa-2,5-dienyl]propyl acetate **8** (14 mg, 50%) and a 3:1 mixture of 3-(5-bromo-3-chloro-4-hydroxyphenyl)-3-methoxypropyl acetate **9** and 3-(3-bromo-5-chloro-1-methoxy-4-oxocyclohexa-2,5-dienyl)propyl acetate **10** (4 mg, 12%, 1:3 = **9/10** determined by ^1H NMR).

Compound **8**: IR (film) 2939, 1738, 1693 cm^{-1}; ^1H NMR δ 1.59 (m, 2H), 1.79 (m, 2H), 2.00 (t, 2H, J = 7.8 Hz), 2.03 (s, 3H), 2.08 (s, 3H), 2.70 (t, 2H, J = 7.8 Hz), 3.22 (s, 3H), 4.00 (t, 2H, J = 6.4 Hz), 4.13 (t, 2H, J = 6.4 Hz), 5.31 (d, 1H, J = 2.9 Hz), 6.95 (d, 1H, J = 2.9 Hz), 7.28 (d, 1H, 2.0 Hz), 7.40 (d, 1H, J = 2.0 Hz); ^{13}C NMR δ 20.86, 20.89, 23.0, 29.6, 31.3, 36.7, 53.1, 63.3, 63.7, 117.3, 121.0, 128.1, 129.8, 130.1, 132.0, 133.4, 141.7, 144.5, 147.0, 148.4, 170.7, 170.8, 172.7; HRMS calcd for $C_{23}H_{25}{}^{79}Br^{35}Cl_2O_7$: (M−Cl) 527.0470, found m/z 527.0450. Compound **9**: ^1H NMR δ 1.68 (t, 2H, J = 6.4 Hz), 1.85 (t, 2H, J = 6.4 Hz), 2.06 (s, 3H), 3.27 (s, 3H), 4.06 (t, 2H, J = 6.4 Hz), 6.97 (d, 1H, J = 2.8 Hz), 7.23 (d, 1H, J = 2.8 Hz). Compound **10**: ^1H NMR δ 1.90 (m, 1H), 2.03 (m, 1H), 2.05 (s, 3H), 3.20 (s, 3H), 4.11–4.22 (complex, 3H), 5.91 (s, 1H), 7.25 (d, 1H, J = 2.0 Hz), 7.36 (d, 1H, J = 2.0 Hz).

4.4. Anodic oxidation under flow-cell conditions

A mixture of **7** (2.94 g, 9.6 mmol), pyridine (0.78 mL, 9.6 mmol), and $LiClO_4$ (51.9 g, 0.49 mol) in MeOH (960 mL) was electrolyzed (CCE at 20 mA, flow rate: 0.4 mL/min, 3.0 V, 3.0 F/mol) by using a flow-cell apparatus. After the addition of aq $NaHCO_3$ and $CHCl_3$, the mixture was evaporated to give a residue, which was worked up. A crude was separated by a silica gel column (hexane/EtOAc = 3:1) to afford **8** (1.67 g, 62%) as a colorless oil.

4.5. 3-[5-(4-(3-Acetyloxypropyl)-2-bromo-6-chlorophenoxy)-3-chloro-4-hydroxyphenyl]propyl acetate (11)

A mixture of **8** (1.91 g, 3.4 mmol) and Zn powder (8.9 g) in THF (34 mL)–AcOH (11 mL) was stirred at 0 °C overnight. The mixture was filtered through a Celite

pad, and the filtrate was evaporated. Purification by a silica gel column (hexane/EtOAc = 3:1) afforded **11** (1.26 g, 70%) and unreacted **8** (0.145 g, 8%).

Compound **11**: mp 97–98 °C (colorless needles from hexane/EtOAc): IR (KBr) 3531, 3519, 2960, 1732 cm^{-1}; ^1H NMR δ 1.80 (tt, 2H, J = 6.5, 7.7 Hz), 2.01 (tt, 2H, J = 6.3, 7.8 Hz), 2.01 (s, 3H), 2.08 (s, 3H), 2.48 (t, 2H, J = 7.7 Hz), 2.70 (t, 2H, J = 7.8 Hz), 4.00 (t, 2H, J = 6.5 Hz), 4.12 (t, 2H, J = 6.3 Hz), 6.04 (s, 1H), 6.12 (d, 1H, J = 1.4 Hz), 6.88 (d, 1H, J = 1.4 Hz), 7.28 (d, 1H, J = 1.7 Hz), 7.41 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ 21.0 (×2), 29.7, 30.0, 31.3, 31.4, 63.35, 63.42, 112.0, 118.1, 120.4, 123.4, 128.9, 129.7, 132.0, 133.1, 140.0, 141.2, 144.2, 145.7, 170.81, 170.84; HRMS calcd for $C_{22}H_{24}{}^{79}Br^{35}Cl_2O_6$: (M+H) 533.0132, found m/z 533.0164.

4.6. 3-Chloro-2-[3-chloro-2-(methoxymethoxy)-5-(3-(*tert*-butyldimethylsiloxy)propyl)phenoxy]-5-[3-(*tert*-butyldimethylsiloxy)propyl]phenol 12a and 1-chloro-3-[2-chloro-4-(3-(*tert*-butyldimethylsiloxy)propyl)phenoxy]-2-(methoxymethoxy)-5-[3-(*tert*-butyldimethylsiloxy)propyl]benzene (12b)

A mixture of **11** (29.2 mg, 0.055 mmol), MOMCl (0.01 mL, 0.11 mmol), and DIPEA (0.04 mL, 0.22 mmol) in CH_2Cl_2 (0.5 mL) under an Ar atmosphere was stirred overnight. The reaction was quenched by the addition of NH_4Cl, and the mixture was worked up. A crude was purified by a silica gel column (hexane/EtOAc = 3:1) to afford a MOM-ether (36.5 mg, 100%) as a colorless oil: IR (film) 2956, 1738 cm^{-1}; ^1H NMR δ 1.80 (tt, 2H, J = 6.5, 7.7 Hz), 2.01 (tt, 2H, J = 6.4, 7.8 Hz), 2.01 (s, 3H), 2.08 (s, 3H), 2.49 (t, 2H, J = 7.7 Hz), 2.71 (t, 2H, J = 7.8 Hz), 3.71 (s, 3H), 4.00 (t, 2H, J = 6.5 Hz), 4.12 (t, 2H, J = 6.4 Hz), 5.35 (s, 2H), 6.04 (d, 1H, J = 1.8 Hz), 6.91 (d, 1H, J = 1.7 Hz), 7.28 (d, 1H, J = 1.8 Hz), 7.41 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ 20.97, 21.00, 29.8, 29.9, 31.3, 31.6, 57.9, 63.3, 63.4, 98.9, 112.1, 118.2, 123.4, 129.0, 129.8, 132.0, 137.8, 139.9, 141.0, 145.3, 149.9, 170.8 (×2); HRMS calcd for $C_{24}H_{27}{}^{79}Br^{35}Cl_2O_7$: (M) 576.0315, found m/z 576.0296.

A mixture of the ether (308 mg, 0.53 mmol) and K_2CO_3 (221 mg, 1.6 mmol) in MeOH (5 mL) was stirred at room temperature overnight; the reaction mixture was filtered, and the filtrate was evaporated. The residue was worked up. Purification by silica gel column chromatography (hexane/EtOAc = 1:1) afforded a diol (270 mg, 100%) as a colorless oil: IR (film) 3375, 2939 cm^{-1}; ^1H NMR δ 1.67 (tt, 2H, J = 6.2, 7.1 Hz), 1.84 (tt, 2H, J = 6.2, 7.1 Hz), 2.30 (br, 2H), 2.44 (t, 2H, J = 7.1 Hz), 2.66 (t, 2H, J = 7.1 Hz), 3.51 (t, 2H, J = 6.2 Hz), 3.61 (t, 2H, J = 6.2 Hz), 3.67 (s, 3H), 5.30 (s, 2H), 6.03 (br, 1H), 6.87 (br, 1H), 7.25 (br, 1H), 7.36 (br, 1H); ^{13}C NMR δ 31.0, 31.4, 33.5, 33.7, 57.8, 61.3, 61.5, 98.8, 112.0, 118.0, 123.3, 128.7, 129.8, 132.0, 138.5, 139.5, 141.8, 144.9, 149.8; HRMS calcd for $C_{20}H_{23}{}^{79}Br^{35}Cl_2O_5$: (M) 492.0104, found m/z 492.0082.

A mixture of the diol (236 mg, 0.48 mmol), imidazole (487 mg, 7.2 mmol), and TBSCl (360 mg, 1.2 mmol) in DMF (5 mL, 0.1 M) under an Ar atmosphere was stirred for 6 h. After the addition of H_2O, the mixture was worked up. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1) to afford a siloxy ether (375 mg, 100%) as a colorless oil: IR (film) 2929, 2858 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.07 (s, 6H), 0.85 (s, 9H), 0.92 (s, 9H), 1.67 (tt, 2H, J = 6.1, 7.8 Hz), 1.84 (tt, 2H, J = 6.1, 7.8 Hz), 2.47 (t, 2H, J = 7.8 Hz), 2.69 (t, 2H, J = 7.8 Hz), 3.53 (t, 2H, J = 6.1 Hz), 3.64 (t, 2H, J = 6.1 Hz), 3.71 (s, 3H), 5.35 (s, 2H), 6.05 (d, 1H, J = 1.7 Hz), 6.90 (d, 1H, J = 1.3 Hz), 7.26 (d, 1H, J = 1.3 Hz), 7.39 (d, 1H, J = 1.7 Hz); ^{13}C NMR δ −5.19 (×2), 18.38, 18.40, 25.8, 26.0, 31.2, 31.5, 33.8, 34.1, 57.9, 61.7, 61.8, 98.9, 112.2, 118.1, 123.5, 128.71, 128.74, 129.9, 132.2, 138.8, 139.6, 142.0, 145.0, 149.9; HRMS calcd for $C_{32}H_{51}{}^{79}Br^{35}Cl_2O_5Si_2$: (M−Br) 641.2649, found m/z 641.2692.

To a solution of the siloxy ether (390 mg, 0.54 mmol) in dry THF (2 mL) was added n-BuLi (0.41 mL, 1.58 M solution in hexane, 0.65 mmol) under an Ar atmosphere at −78 °C. After 3 min, $B(OMe)_3$ (0.6 mL, 5.4 mmol) was added to the mixture. After being stirred for 2 h, the reaction mixture was treated with 3 M NaOH (1.0 mL, 13 mmol) and 30% H_2O_2 (1.0 mL, 35 mmol) at 0 °C, and further stirred overnight. The reaction was quenched with NH_4Cl aq and worked up. Purification by a silica gel column (hexane/EtOAc = 8:1) afforded **12a** (226 mg, 64%) as a colorless oil, along with **12b** (89 mg, 14%) as a colorless oil.

Compound **12a**: IR (film) 3336, 2929, 2858 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.06 (s, 6H), 0.86 (s, 9H), 0.91 (s, 9H), 1.68 (tt, 2H, J = 6.1, 7.7 Hz), 1.84 (tt, 2H, J = 6.1, 7.7 Hz), 2.49 (t, 2H, J = 7.7 Hz), 2.63 (t, 2H, J = 7.7 Hz), 3.54 (t, 2H, J = 6.1 Hz), 3.64 (t, 2H, J = 6.1 Hz), 3.64 (s, 3H), 5.26 (s, 2H), 6.28 (d, 1H, J = 1.7 Hz), 6.77 (d, 1H, J = 2 Hz), 6.84 (d, 1H, J = 1.7 Hz), 6.93 (d, 1H, J = 2 Hz), 7.39 (s, 1H); ^{13}C NMR δ −5.21, −5.17, 18.36, 18.40, 26.00, 26.03, 31.5, 31.7, 33.9, 34.0, 57.5, 61.8, 62.0, 98.8, 113.3, 116.2, 121.1, 123.9, 128.0, 135.8, 139.6, 141.5, 149.7, 150.4; HRMS calcd for $C_{32}H_{52}{}^{35}Cl_2O_6Si_2$: (M+H), 659.2755, found m/z 659.2772.

Compound **12b**: IR (film) 2929, 2858 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.04 (s, 6H), 0.86 (s, 9H), 0.90 (s, 9H), 1.71 (tt, 2H, J = 6.6, 7.7 Hz), 1.80 (tt, 2H, J = 6.6, 7.7 Hz), 2.52 (t, 2H, J = 7.7 Hz), 2.64 (t, 2H, J = 7.7 Hz), 3.55 (t, 2H, J = 6.6 Hz), 3.59 (s, 3H), 3.61 (t, 2H, J = 6.6 Hz), 5.19 (s, 2H), 6.5 (br, 1H), 6.77 (d, 1H, J = 8.3 Hz), 6.98 (br, 1H), 7.00 (d, 1H, J = 8.3 Hz), 7.24 (br, 1H); ^{13}C NMR δ −5.21, −5.18, 18.4 (×2), 26.00, 26.02, 31.2, 31.4, 34.0, 34.2, 57.7, 61.8, 61.9, 99.0, 117.6, 119.2, 124.3, 125.0, 128.0, 128.6, 130.4, 138.9, 139.3, 141.8, 149.8, 149.9; HRMS calcd for $C_{32}H_{52}{}^{35}Cl_2O_5Si_2$: (M−Cl), 607.3039, found m/z 607.3083.

4.7. 1-(Methoxymethoxy)-4-[3-(tert-butyldimethylsiloxy)-propyl]-2- [4-(3-(tert-butyldimethylsiloxy)propyl)phenoxy]-benzene (13)

A mixture of **12b** (267 mg, 0.42 mmol), Pd-C (100 mg), and HCO_2NH_4 (78.4 mg, 1.3 mmol) in EtOH (5 mL) was stirred at 60 °C for 5 h under an Ar atmosphere.

The reaction mixture was filtered and the filtrate was evaporated. The residue was worked up and purified by silica gel column chromatography (hexane/EtOAc = 10:1) to afford **13** (220 mg, 92%) as a colorless oil: IR (film) 2929, 2857 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.06 (s, 6H), 0.86 (s, 9H), 0.88 (s, 9H), 1.71–1.84 (complex, 4H), 2.52–2.64 (complex, 4H), 3.38 (s, 3H), 3.55–3.62 (complex, 4H), 5.11 (s, 2H), 6.78 (d, 1H, J = 1.7 Hz), 6.83 (d, 1H, J = 8.6 Hz), 6.87 (dd, 1H, J = 1.7, 8.2 Hz), 7.07 (d, 1H, J = 8.2 Hz), 7.09 (d, 1H, J = 8.6 Hz); ^{13}C NMR δ −5.21, −5.18, 18.4 (×2), 26.0 (×2), 31.27, 31.30, 34.4, 34.6, 56.1, 62.1, 62.2, 95.5, 117.0, 117.7, 121.0, 124.2, 129.2, 136.0, 137.0, 146.1, 146.5, 155.8; HRMS calcd for $C_{32}H_{54}O_5Si_2$: (M−C_4H_9), 517.2803, found m/z 517.2843.

4.8. 3-[4-(2-(Methoxymethoxy)-5-(3-oxopropyl)phenoxy)-phenyl]propanal (14)

A mixture of **13** (219 mg, 0.63 mmol) and TBAF (1 M in THF, 1.9 mL, 1.9 mmol) in THF (5 mL) was stirred at 0 °C for 3 h under an Ar atmosphere. After evaporation and work-up, a crude product was purified by a silica gel column ($CHCl_3$/MeOH = 15:1) to afford a diol (113 mg, 86%) as a colorless oil: IR (film) 3348, 2935 cm^{-1}; ^1H NMR δ 1.53 (br, 2H), 1.76–1.92 (complex, 4H), 2.60 (t, 2H, J = 7.8 Hz), 2.67 (t, 2H, J = 7.8 Hz), 3.42 (s, 3H), 3.63 (t, 2H, J = 6.5 Hz), 3.66 (t, 2H, J = 6.5 Hz), 5.13 (s, 2H), 6.80 (d, 1H, J = 1.8 Hz), 6.86 (d, 1H, J = 8.6 Hz), 6.90 (dd, 1H, J = 1.8, 8.4 Hz), 7.11 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 8.6 Hz); ^{13}C NMR δ 31.3 (×2), 34.2, 34.3, 56.2, 62.1, 62.2, 95.5, 117.2, 117.8, 120.9, 124.2, 129.3, 135.8, 136.7, 146.1, 146.6, 155.9; HRMS calcd for $C_{20}H_{26}O_5$: (M), 346.1777, found m/z 346.1737.

A mixture of the diol (22.1 mg, 0.064 mmol), Et_3N (0.29 mL), and SO_3-Pyr (162 mg, 1 mmol) in a 1:1 mixture of DMSO and CH_2Cl_2 (1 mL) was stirred at room temperature for 2 h. After the addition of H_2O, the mixture was worked up. The residue was separated by a silica gel column (hexane/EtOAc = 3:1) to afford **14** (18.4 mg, 84%) as a colorless oil: IR (film) 2924, 1721 cm^{-1}; ^1H NMR: δ 2.69–2.79 (complex, 4H), 2.83–2.95 (complex, 4H), 3.41 (s, 3H), 5.13 (s, 2H), 6.80 (br, 1H), 6.86 (d, 1H, J = 8.2 Hz), 6.91 (d, 1H, J = 8.6 Hz), 7.11 (d, 1H, J = 8.6 Hz), 7.14 (d, 1H, J = 8.2 Hz), 9.78 (s, 1H), 9.81 (s, 1H); ^{13}C NMR δ 27.4 (×2), 45.2, 45.4, 56.2, 95.4, 117.3, 117.8, 120.9, 124.3, 129.2, 134.3, 135.1, 146.0, 147.0, 156.1, 201.1, 201.4; HRMS calcd for $C_{20}H_{22}O_5$: (M), 342.1465, found m/z 342.1422.

4.9. 3-[4-(5-(2-Carboxyethyl)-2-(methoxymethoxy)phenoxy)phenyl]propionic acid (15)

A mixture of **14** (54.1 mg, 0.16 mmol) and PDC (476 mg, 1.3 mmol) in DMF (2 mL, 0.1 M) was stirred at room temperature overnight. After the addition of H_2O, the mixture was worked up. Purification by a silica gel column ($CHCl_3$/MeOH = 15:1) to afford **15** (48.2 mg, 82%) as a colorless oil: IR (film) 3300–3000 (br), 2925, 2854, 1711 cm^{-1}; ^1H NMR δ 2.60–2.65 (complex, 4H), 2.82–3.00 (complex, 4H), 3.41 (s, 3H), 5.14 (s, 2H), 6.79 (br, 1H), 6.86 (d, 1H, J = 8.2 Hz), 6.90 (br, 1H), 7.12 (d, 1H, J = 7.9 Hz), 10.1 (br, 2H); ^{13}C NMR δ 29.8, 30.0, 35.7, 35.9, 56.2, 95.4, 117.5, 117.7, 120.7, 124.1, 129.3, 134.2, 135.0, 146.3, 146.9, 156.1, 178.7, 178.8; HRMS calcd for $C_{20}H_{22}O_7$: (M), 374.1363, found m/z 374.1342.

4.10. *N*-Methoxy-3-[4-[2-(methoxymethoxy)-5-(2-(*N*-methoxy-*N*-methylcarbamoyl)ethyl)phenoxy]phenyl]-*N*-methylpropanamide (16)

Compound **16** (48.2 mg, 0.13 mmol) was treated at room temperature with Et_3N (0.22 mL), HOBt (214 mg, 1.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCI) (121 mg, 0.52 mmol), and (MeO)-MeNH·HCl (61.7 mg, 0.52 mmol) in CH_2Cl_2 (2 mL). After the addition of 0.5M HCl, the mixture was worked up. The residue was purified by a silica gel column (EtOAc) to give **16** (35.7 mg, 60%) as a colorless oil: IR (film) 2937, 2825, 1662 cm^{-1}; ^1H NMR δ 2.67 (t, 2H, J = 7.6 Hz), 2.72 (t, 2H, J = 7.6 Hz), 2.86 (t, 2H, J = 7.8 Hz), 2.92 (t, 2H, J = 7.8 Hz), 3.16 (s, 3H), 3.18 (s, 3H), 3.42 (s, 3H), 3.61 (s, 3H), 3.63 (s, 3H), 5.13 (s, 2H), 6.83 (d, 1H, J = 2.0 Hz), 6.87 (d, 1H, J = 8.8 Hz), 6.95 (dd, 1H, J = 2.0, 8.3 Hz), 7.14 (d, 1H, J = 8.3 Hz), 7.15 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 29.7, 29.9, 32.2 (×2), 33.7, 33.8, 56.1 (×2), 61.2, 95.5, 117.2, 117.8, 120.9, 124.3, 129.3, 135.3, 136.1, 146.0, 146.8, 156.0, 173.5 (×2); HRMS, calcd for $C_{24}H_{32}N_2O_7$: (M), 460.2207, found m/z 460.2160.

4.11. MOM-protected 2-demethoxylittorachalcone (17)

To a stirring solution of **18** (138 mg, 0.5 mmol) in dry THF (2 mL) was added n-BuLi (1.58 M solution in hexane, 0.3 mL, 0.48 mmol) under an Ar atmosphere at −78 °C. A solution of **16** (21.7 mg, 0.047 mmol) in dry THF was added (1 mL), and the mixture was stirred for further 30 min. After the addition of aq NH_4Cl, the mixture was worked up and purified by a silica gel column (hexane/EtOAc = 5:1) to afford **17** (22.2 mg, 64%) as a colorless oil: IR (film) 2929, 1666 cm^{-1}; ^1H NMR δ 2.92 (t, 2H, J = 7.4 Hz), 2.99 (t, 2H, J = 7.4 Hz), 3.22 (t, 2H, J = 7.8 Hz), 3.27 (t, 2H, J = 7.8 Hz), 3.42 (s, 3H), 3.43 (s, 3H), 3.47 (s, 3H), 3.47 (s, 3H), 3.48 (s, 3H), 5.13 (s, 2H), 5.19 (s, 2H), 5.20 (complex, 4H), 5.24 (s, 2H), 6.70 (dd, 1H, J = 2.0, 8.8 Hz), 6.73 (dd, 1H, J = 2.0, 8.8 Hz), 6.80 (d, 1H, J = 2.0 Hz), 6.82 (d, 1H, J = 2.0 Hz), 6.84 (d, 1H, J = 2.0 Hz), 6.86 (d, 1H, J = 8.8 Hz), 6.95 (dd, 1H, J = 2.0, 7.6 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.70 (d, 1H, J = 8.8 Hz), 7.74 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 29.76, 29.85, 45.1, 45.3, 56.0, 56.2, 56.3, 56.47, 56.52, 94.1, 94.4, 94.46, 94.50, 95.53, 102.7, 102.8, 108.9, 117.2, 117.8, 120.9, 122.4, 122.5, 124.3, 129.3, 132.12, 132.14, 135.8, 136.6, 146.1, 146.7, 155.9, 157.8, 157.9, 161.47, 161.49, 199.3, 199.5; HRMS calcd for $C_{40}H_{46}O_{13}$: (M), 734.2938. found m/z 734.2931.

4.12. Littorachalcone (2)

A solution of **17** (11.1 mg, 0.0015 mmol) in MeOH (1 mL) in the presence of TsOH (20 mg) was stirred at room temperature overnight. After evaporation, the

mixture was worked up and purified by preparative TLC (hexane/EtOAc = 3:2) to afford **2** (6.8 mg, 88%) as a colorless oil: IR (film) 3348, 2925, 1707 cm^{-1}; ^1H NMR δ 2.82 (t, 2H, J = 7.6 Hz), 2.85 (t, 2H, J = 7.6 Hz), 3.13 (t, 2H, J = 7.6 Hz), 3.18 (t, 2H, J = 7.6 Hz), 6.20 (s, 2H), 6.28 (dd, 1H, J = 2.0, 8.8 Hz), 6.30 (dd, 1H, J = 2.0, 8.8 Hz), 6.65 (d, 1H, J = 2.0 Hz), 6.67 (d, 1H, J = 2.0 Hz), 6.76 (d, 1H, J = 2.0 Hz), 6.79 (d, 1H, J = 8.8 Hz), 6.86 (dd, 1H, J = 2.0, 7.6 Hz), 7.11 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, J = 8.8 Hz), 7.67 (d, 1H, J = 8.8 Hz), 7.72 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 40.03, 40.05, 60.5 (×2), 103.4, 108.57, 108.62, 113.7, 113.8, 117.3, 117.7, 121.8, 125.8, 130.2, 133.48, 133.54, 133.8, 135.8, 143.6, 148.0, 157.1, 165.2, 165.3, 166.00, 166.02, 204.6, 204.7; HRMS calcd for $C_{30}H_{26}O_8$: (M), 514.1625, found m/z 514.1625.

4.13. 1-[5-Chloro-4-(3-chloro-2-(methoxymethoxy)-5-(3-(*tert*-butyldimethylsiloxy)propyl)-3-methoxyphenyl)]-3-(*tert*-butyldimethylsiloxy)propane (19)

A mixture of **12a** (10.4 mg, 0.016 mmol), K_2CO_3 (21.8 mg, 0.16 mmol), and MeI (0.01 mL, 0.16 mmol) in DMF (05 mL) was stirred overnight under an Ar atmosphere. After work-up, the residue was separated by a silica gel column (hexane/EtOAc = 40:1) to afford **19** (10.7 mg, 100%) as a colorless oil: IR (film) 2928, 2857 cm^{-1}; ^1H NMR δ 0.00 (s, 6H), 0.07 (s, 6H), 0.86 (s, 9H), 0.92 (s, 9H), 1.66 (tt, 2H, J = 6.2, 7.6 Hz), 1.86 (tt, 2H, J = 6.2, 7.6 Hz), 2.45 (t, 2H, J = 7.6 Hz), 2.68 (t, 2H, J = 7.6 Hz), 3.53 (t, 2H, J = 6.2 Hz), 3.66 (t, 2H, J = 6.2 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 5.35 (s, 2H), 6.11 (d, 1H, J = 1.6 Hz), 6.72 (d, 1H, J = 1.5 Hz), 6.85 (d, 1H, J = 1.6 Hz), 6.90 (d, 1H, J = 1.5 Hz); ^{13}C NMR δ −5.28, −5.24, 18.26, 18.30, 25.9, 26.0, 31.4, 31.9, 33.99, 34.04, 56.0, 57.7, 61.7, 61.8, 98.8, 111.5, 112.2, 121.6, 122.8, 128.16, 128.19, 136.8, 138.5, 139.6, 140.7, 150.8, 152.8; HRMS calcd for $C_{33}H_{54}{}^{35}Cl_2O_6Si_2$: (M−OMe), 641.2648, found m/z 641.2623.

4.14. 3-[4-[5-(2-Carboxyethyl)-3-chloro-2-(methoxymethoxy)phenoxy]-5-chloro-3-methoxyphenyl]propanoic acid (20)

A mixture of **19** (99.2 mg, 0.15 mmol) and TBAF (1 M in THF solution, 0.44 mL, 0.45 mmol) in THF (3 mL) was stirred for 2 h and then evaporated. The residue was worked up and purified by a silica gel column (EtOAc) to afford a diol (63.6 mg, 97%) as a colorless oil: IR (film) 3365, 2937 cm^{-1}; ^1H NMR δ 1.71 (tt, 2H, J = 6.3, 7.4 Hz), 1.91 (tt, 2H, J = 6.3, 7.4 Hz), 2.07 (br, 2H), 2.47 (t, 2H, J = 7.4 Hz), 2.71 (t, 2H, J = 7.4 Hz), 3.56 (t, 2H, J = 6.3 Hz), 3.70 (t, 2H, J = 6.3 Hz), 3.70 (s, 3H), 3.72 (s, 3H), 5.35 (s, 2H), 6.13 (br, 1H), 6.74 (br, 1H), 6.86 (br, 1H), 6.91 (br, 1H); ^{13}C NMR δ 31.4, 31.9, 33.77, 33.81, 56.1, 57.8, 61.7 (×2), 98.8, 111.4, 112.2, 121.6, 122.7, 128.26, 128.31, 136.8, 138.2, 139.7, 140.5, 150.8, 152.9; HRMS calcd for $C_{21}H_{26}{}^{35}Cl_2O_6$: (M), 444.1104, found m/z 444.1101.

The diol (9 mg, 0.02 mmol) was treated with PDC (76 mg, 0.2 mmol) in DMF (0.5 mL) for 3.5 h. After the addition of H_2O, the mixture was worked up and purified by silica gel column chromatography (EtOAc) to afford **20** (6.8 mg, 71%) as a colorless oil: IR (film) 3300–3000 (br), 2929, 1709 cm^{-1}; ^1H NMR δ 2.50 (t, 2H, J = 6.6 Hz), 2.75 (complex, 4H), 2.97 (t, 2H, J = 7.1 Hz), 3.70 (s, 3H), 3.71 (s, 3H), 5.35 (s, 2H), 6.11 (br, 1H), 6.74 (br, 1H), 6.85 (br, 1H), 6.93 (s, 1H); ^{13}C NMR δ 29.7, 30.6, 35.2, 35.3, 56.1, 57.9, 98.9, 111.7, 111.9, 121.7, 123.1, 128.49, 128.51, 136.9, 137.5, 138.4, 140.3, 151.2, 152.8, 178.6, 178.8; HRMS calcd for $C_{21}H_{22}{}^{35}Cl_2O_8$: (M), 472.0689, found m/z 472.0687.

4.15. *N*-Methoxy-3-[2-chloro-5-methoxy-4-[3-chloro-2-(methoxymethoxy)-5-(2-(*N*-methoxy-*N*-methylcarbamoyl)-ethyl)phenoxy]phenyl]-*N*-methylpropanamide (21)

Compound **20** (29.8 mg, 0.063 mmol) was treated with Et_3N (0.4 mL), HOBt (94 mg, 0.69 mmol), WSCI (132 mg, 0.25 mmol), and MeONHMe·HCl (67.6 mg, 0.25 mmol) in CH_2Cl_2 (3 mL), as described in the case of **16** to afford **21** (23 mg, 65%) as a colorless oil: IR (film) 2937, 1731 cm^{-1}; ^1H NMR δ 2.61 (t, 2H, J = 7.8 Hz), 2.73 (t, 2H, J = 7.8 Hz), 2.79 (t, 2H, J = 7.6 Hz), 2.99 (t,. 2H, J = 7.6 Hz), 3.14 (s, 3H), 3.21 (s, 3H), 3.59 (s, 3H), 3.68 (s, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 5.35 (s, 2H), 6.17 (d, 1H, J = 2.0 Hz), 6.79 (d, 1H, J = 1.2 Hz), 6.89 (d, 1H, J = 2.0 Hz), 6.94 (d, 1H, J = 1.2 Hz); ^{13}C NMR δ 30.1, 30.4, 32.2 (×2), 33.3, 33.4, 56.1, 57.8, 61.2, 61.3, 98.8, 111.6, 112.3, 121.5, 122.8, 128.38, 128.44, 137.0, 137.7, 140.0, 140.1, 150.9, 153.0, 173.0 (×2); HRMS calcd for $C_{25}H_{32}{}^{35}Cl_2N_2O_8$: (M), 558.1633, found m/z 558.1531.

4.16. MOM-protected 2,2′-dichloroverbenachalcone (22)

Compound **21** (23.9 mg, 0.043 mmol) was reacted with a lithiated **18** (190 mg, 0.69 mmol) in dry THF (2 mL), essentially the same procedure as in the case of **17** to afford **22** (17.6 mg, 49%) as a colorless oil: IR (film) 2954, 1666 cm^{-1}; ^1H NMR δ 2.79 (t, 2H, J = 7.8 Hz), 3.03 (t, 2H, J = 7.3 Hz), 3.13 (t, 2H, J = 7.8 Hz), 3.33 (t, 2H, J = 7.3 Hz), 3.45 (s, 3H), 3.48 (s, 3H), 3.48 (s, 3H), 3.50 (s, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 5.16 (s, 2H), 5.19 (s, 2H), 5.21 (s, 2H), 5.27 (s, 2H), 5.35 (s, 2H), 6.18 (br, 1H), 6.71 (dd, 1H, J = 2.0, 8.8 Hz), 6.74 (dd, 1H, J = 2.0, 8.8 Hz), 6.90 (br, 1H), 6.94 (br, 1H), 7.69 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 30.1, 30.2, 44.7, 44.9, 56.0, 56.1, 56.3, 56.5, 56.6, 57.9, 94.1, 94.3, 94.5, 94.6, 98.9, 102.7, 102.8, 108.7, 108.86, 108.94, 111.7, 112.3, 121.5, 122.1, 122.2, 122.8, 128.30, 128.33, 128.4, 129.7, 132.2, 138.2, 139.9, 140.6, 150.9, 153.0, 157.9, 161.6, 161.7, 198.8, 198.9; HRMS calcd for $C_{41}H_{46}O_{14}{}^{35}Cl_2Na$: (M+Na), 855.2162, found m/z 855.2187.

4.17. 2,2′-Dichloroverbenachalcone (3)

A mixture of **22** (8 mg, 0.01 mmol) and TsOH (30 mg) in MeOH (0.4 mL) was stirred at room temperature overnight to afford **3** (6.2 mg, 100%) as a yellow oil: IR (film) 3355, 2927, 1699 cm^{-1}; ^1H NMR δ 2.69 (t, 2H, J = 7.3 Hz), 2.77 (br, 2H), 2.93 (t, 2H, J = 7.6 Hz), 3.06 (t, 2H, J = 7.3 Hz), 3.29 (t, 2H, J = 7.6 Hz), 3.62

(s, 3H), 6.19 (d, 1H, $J = 2.4$ Hz), 6.20 (d, 1H, $J = 2.0$ Hz), 6.21 (d, 1H, $J = 2.4$ Hz), 6.28 (dd, 2H, $J = 2.4$, 8.8 Hz), 6.32 (dd, 2H, $J = 2.4$, 8.8 Hz), 6.84 (d, 1H, $J = 2.0$ Hz), 6.96 (br, 1H), 6.97 (br, 1H), 7.64 (d, 1H, $J = 8.8$ Hz), 7.75 (d, 1H, $J = 8.8$ Hz), 12.57 (s, 1H), 12.62 (s, 1H); ^{13}C NMR δ 29.4, 29.6, 38.9, 39.2, 56.1, 103.27, 103.33, 108.05, 108.10, 111.5, 112.8, 113.0, 114.7, 120.0, 121.5, 123.0, 128.2, 131.89, 131.93, 132.6, 139.8, 140.5, 145.4, 152.9, 164.00, 164.05, 165.1, 202.6, 202.9; HRMS, calcd for $C_{31}H_{26}O_9{}^{35}Cl_2$: (M), 612.0954, found *m/z* 612.0955.

4.18. 1-[4-(2-(Methoxymethoxy)-5-(3-(*tert*-butyldimethylsiloxy)propyl)-3-methoxyphenyl)]-3-(*tert*-butyldimethylsiloxy)propane (23)

A mixture of **19** (232 mg, 0.34 mmol), Pd-C (100 mg), and HCO_2NH_4 (200 mg, 3.4 mmol) in EtOH (50 mL) was heated 60 °C for 3 h under an Ar atmosphere. The reaction mixture was treated with essentially the same procedure as in the case of **13** to afford **23** (174 mg, 84%) as a colorless oil: IR (film) 2929, 2856 cm^{-1}; ^{1}H NMR δ 0.00 (s, 6H), 0.04 (s, 6H), 0.86 (s, 9H), 0.90 (s, 9H), 1.71 (tt, 2H, $J = 6.3$, 7.7 Hz), 1.82 (tt, 2H, $J = 6.3$, 7.7 Hz), 2.52 (t, 2H, $J = 7.7$ Hz), 2.64 (t, 2H, $J = 7.7$ Hz), 3.44 (s, 3H), 3.56 (t, 2H, $J = 6.3$ Hz), 3.63 (t, 2H, $J = 6.3$ Hz), 3.82 (s, 3H), 5.16 (s, 2H), 6.63 (d, 1H, $J = 2.0$ Hz), 6.66 (dd, 1H, $J = 1.7$, 7.9 Hz), 6.72 (d, 1H, $J = 7.9$ Hz), 6.79 (d, 1H, $J = 1.7$ Hz), 6.81 (dd, 1H, $J = 2.0$, 8.3 Hz), 7.08 (d, 1H, $J = 8.3$ Hz); ^{13}C NMR δ −5.15, −5.14, 18.40, 18.44, 26.0 (×2), 31.4, 31.9, 34.46, 34.50, 55.9, 56.1, 62.3 (×2), 95.7, 112.8, 117.6, 118.7, 118.9, 120.4, 123.2, 136.9, 137.9, 143.8, 145.6, 147.0, 150.1; HRMS calcd for $C_{33}H_{56}O_6Si_2$: (M−OMe), 537.3429, found *m/z* 573.3438.

4.19. 3-[4-(5-(3-Hydroxypropyl)-2-(methoxymethoxy)phenoxy)-3-methoxyphenyl]propan-1-ol (24)

Compound **23** (65.6 mg, 0.11 mmol) was treated with TBAF (1 M in THF, 0.33 mL, 0.33 mmol) in THF (1 mL) to afford **24** (48.4 mg, 100%) as a colorless oil: IR (film) 3367, 2937 cm^{-1}; ^{1}H NMR δ 1.59 (br, 2H), 1.79 (tt, 2H, $J = 6.4$, 7.7 Hz), 1.90 (tt, 2H, $J = 6.4$, 7.7 Hz), 2.56 (t, 2H, $J = 7.7$ Hz), 2.69 (t, 2H, $J = 7.7$ Hz), 3.46 (s, 3H), 3.60 (t, 2H, $J = 6.4$ Hz), 3.68 (t, 2H, $J = 6.4$ Hz), 3.83 (s, 3H), 5.18 (s, 2H), 6.64 (d, 1H, $J = 2.0$ Hz), 6.68 (dd, 1H, $J = 1.7$, 8.1 Hz), 6.75 (d, 1H, $J = 8.1$ Hz), 6.81 (d, 1H, $J = 1.7$ Hz), 6.83 (dd, 1H, $J = 2.0$, 8.2 Hz), 7.11 (d, 1H, $J = 8.2$ Hz); ^{13}C NMR δ 31.4, 31.9, 34.2, 34.3, 56.0, 56.2, 62.1, 62.2, 95.6, 112.8, 117.7, 118.7, 118.9, 120.4, 123.2, 136.4, 137.6, 143.8, 145.7, 147.0 150.2; HRMS calcd for $C_{21}H_{28}O_6$: (M−OMe), 345.1711, found *m/z* 345.1726.

4.20. 3-[3-Methoxy-4-(2-(methoxymethoxy)-5-(3-oxopropyl)phenoxy)phenyl]propanal (25)

To a solution of **24** (11.3 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) were added pyridine (0.01 mL, 0.09 mmol) and the Dess–Martin periodinane (76 mg, 0.09 mmol) at room temperature under an Ar atmosphere. After being stirred for 2 h, the reaction was quenched with H_2O and worked up. Purification by a silica gel column (hexane/EtOAc = 1:1) afforded **25** (9.1 mg, 81%) as a colorless oil: IR (film) 3423, 2927, 1722 cm^{-1}; ^{1}H NMR δ 2.68 (t, 2H, $J = 6.9$ Hz), 2.80 (t, 2H, $J = 6.9$ Hz), 2.82 (t, 2H, $J = 6.9$ Hz), 2.95 (t, 2H, $J = 6.9$ Hz), 3.45 (s, 3H), 3.84 (s, 3H), 5.18 (s, 2H), 6.63 (d, 1H, $J = 1.8$ Hz), 6.68 (dd, 1H, $J = 1.5$, 8.2 Hz), 6.75 (d, 1H, $J = 8.2$ Hz), 6.82 (d, 1H, $J = 1.5$ Hz), 6.98 (dd, 1H, $J = 1.8$, 8.2 Hz), 7.12 (d, 1H, $J = 8.2$ Hz), 9.76 (s, 1H), 9.83 (s, 1H); ^{13}C NMR δ 27.5, 27.9, 45.3, 45.4, 56.0, 56.2, 95.5, 112.7, 117.7, 118.7, 118.9, 120.2, 123.2, 134.8, 136.2, 144.0, 146.0, 146.9, 150.3, 201.25, 201.28; HRMS calcd for $C_{21}H_{24}O_6$: (M+H), 373.1650, found *m/z* 373.1657.

4.21. 3-[4-(5-(2-Carboxyethyl)-2-(methoxymethoxy)phenoxy)-3-methoxyphenyl]propanoic acid (26)

A mixture of **25** (70.6 mg, 0.19 mmol) and PDC (708 mg, 1.9 mmol) in DMF (2 mL) was stirred at room temperature overnight. After the addition of H_2O, the mixture was worked up, and purification by a silica gel column ($CHCl_3$/MeOH = 15:1) afforded **26** (39.4 mg, 52%) as a colorless oil: IR (film) 3000–3400 (br), 2933, 1709 cm^{-1}; ^{1}H NMR δ 2.55 (t, 2H, $J = 6.9$ Hz), 2.71 (t, 2H, $J = 7.3$ Hz), 2.81 (t, 2H, $J = 6.9$ Hz), 2.95 (t, 2H, $J = 7.3$ Hz), 3.48 (s, 3H), 3.79 (s, 3H), 5.21 (s, 2H), 6.56 (br, 1H), 6.72 (d, 1H, $J = 8.4$ Hz), 6.81 (complex, 3H), 7.11 (d, 1H, $J = 8.2$ Hz), 10.0 (br, 2H); ^{13}C NMR δ 29.9, 30.6, 35.66, 35.75, 55.9, 56.2, 95.6, 113.0, 117.60, 117.63, 120.0, 120.6, 122.9, 134.9, 136.1, 140.3, 143.7, 145.7, 150.5, 178.91, 178.94; HRMS calcd for $C_{21}H_{24}O_8$: (M−OH), 373.1442, found *m/z* 387.1411.

4.22. *N*-Methoxy-3-[3-methoxy-4-[2-(methoxymethoxy)-5-(2-(*N*-methoxy-*N*-methylcarbamoyl)ethyl)phenoxy]phenyl]-*N*-methylpropanamide (27)

Compound **26** (16.4 mg, 0.041 mmol) was treated with Et_3N (0.25 mL), HOBt (60 mg, 0.45 mmol), WSCI (86 mg, 0.23 mmol), and (MeO)NHMe·HCl (43.6 mg, 0.23 mmol) in CH_2Cl_2 (0.8 mL), as described in the case of **21** to afford **27** (19.0 mg, 96%) as a colorless oil: IR (film) 2937, 1662 cm^{-1}; ^{1}H NMR δ 2.64, (t, 2H, $J = 7.6$ Hz), 2.75 (t, 2H, $J = 7.6$ Hz), 2.82 (t, 2H, $J = 7.8$ Hz), 2.94 (t, 2H, $J = 7.8$ Hz), 3.15 (s, 3H), 3.19 (s, 3H), 3.46 (s, 3H), 3.59 (s, 3H), 3.63 (s, 3H), 3.84 (s, 3H), 5.18 (s, 2H), 6.68 (d, 1H, $J = 2.0$ Hz), 6.72 (dd, 1H, $J = 1.5$, 7.8 Hz), 6.75 (d, 1H, $J = 7.8$ Hz), 6.86 (d, 1H, $J = 1.5$ Hz), 6.88 (dd, 1H, $J = 2.0$, 8.3 Hz), 7.12 (d, 1H, $J = 8.3$ Hz); ^{13}C NMR δ 30.0, 30.5, 32.2 (×2), 33.8 (×2), 56.0, 56.1, 61.2, 61.3, 95.6, 112.9, 117.8, 118.8, 118.9, 120.4, 123.3, 135.9, 137.2, 144.0, 145.9, 147.0, 150.2, 173.4 (×2); HRMS calcd for $C_{25}H_{34}N_2O_8$: (M+H), 491.2390, found *m/z* 491.2355.

4.23. MOM-protected *p*-dehydroxyverbenachalcone (28)

Compound **27** (24.9 mg, 0.051 mmol) was reacted with a lithiated **29** (117 mg, 0.54 mmol) in dry THF (2 mL), essentially the same procedure as in the case of **17** to afford **28** (21.9 mg, 67%) as a colorless oil: IR (film) 2933, 1674 cm^{-1}; ^{1}H NMR δ 2.89 (t, 2H, $J = 7.6$ Hz), 3.02 (t, 2H, $J = 7.6$ Hz), 3.21 (t, 2H, $J = 7.6$ Hz), 3.33 (t, 2H,

J = 7.6 Hz), 3.43 (s, 3H), 3.45 (s, 3H), 3.47 (s, 3H), 3.82 (s, 3H), 5.18 (s, 2H), 5.19 (s, 2H), 5.25 (s, 2H), 6.70 (d, 1H, J = 8.3 Hz), 6.72 (br, 1H), 6.73 (d, 1H, J = 7.8 Hz), 6.85 (br, 1H), 6.88 (d, 1H, J = 8.3 Hz), 7.03–7.07 (complex, 2H), 7.11 (d, 1H, J = 7.8 Hz), 7.16 (d, 1H, J = 8.3 Hz), 7.18 (d, 1H, J = 8.3 Hz), 7.39–7.44 (complex, 2H), 7.59 (d, 1H, J = 6.3 Hz), 7.63 (d, 1H, J = 6.3 Hz); ^{13}C NMR δ 29.8, 30.2, 45.3, 45.4, 55.9, 56.2, 56.38, 56.44, 94.3, 94.5, 95.6, 112.9, 114.7, 114.8, 117.7, 118.81, 118.84, 120.3, 121.70, 121.75, 123.3, 129.0, 129.1, 129.9, 130.0, 133.1, 133.2, 136.1, 137.4, 143.9, 145.8, 147.0, 150.2, 155.8, 201.6, 201.7; HRMS calcd for $C_{37}H_{41}O_{10}$: (M+H), 645.2700, found m/z 645.2700.

4.24. *p*-Dehydroxyverbenachalcone (4)

Protecting groups of **28** (10.6 mg, 0.016 mmol) were removed with TsOH (20 mg) in MeOH (1 mL) as in the case of **2** to afford **4** (7.9 mg, 94%) as a yellow oil: IR (film) 3423, 2927, 1639 cm^{-1}; ^{1}H NMR δ 2.92 (t, 2H, J = 7.6 Hz), 3.06 (t, 2H, J = 7.6 Hz), 3.23 (t, 2H, J = 7.6 Hz), 3.35 (t, 2H, J = 7.6 Hz), 3.85 (s, 3H), 6.06 (s, 1H), 6.73 (d, 1H, J = 1.5 Hz), 6.79 (dd, 1H, J = 1.5, 6.4 Hz), 6.84–7.00 (complex, 8H), 7.44–7.49 (complex, 2H), 7.70 (d, 1H, J = 6.8 Hz), 7.76 (d, 1H, J = 6.8 Hz), 12.28 (s, 1H), 12.29 (s, 1H); ^{13}C NMR δ 29.5, 29.9, 40.1, 40.2, 56.0, 112.9, 115.9, 118.0, 118.46, 118.53, 118.8, 118.9, 119.2, 120.7, 120.8, 123.9, 129.7, 129.8, 132.6, 136.3, 136.4, 137.9, 143.5, 144.7, 145.5, 150.6, 162.3, 205.0, 205.3; HRMS calcd for $C_{31}H_{28}O_7$: (M), 512.1832, found m/z 512.1829.

4.25. MOM-protected *o*-dehydroxyverbenachalcone (30)

Compound **27** (24.9 mg, 0.051 mmol) was reacted with a lithiated **31** (123 mg, 0.57 mmol) in dry THF (2 mL), essentially the same procedure as in the case of **17** to afford **30** (27.4 mg, 84%) as a colorless oil: IR (film) 2933, 2827, 1678 cm^{-1}; ^{1}H NMR δ 2.91 (t, 2H, J = 7.8 Hz), 3.03 (t, 2H, J = 7.6 Hz), 3.15 (t, 2H J = 7.8 Hz), 3.26 (t, 2H, J = 7.6 Hz), 3.46 (s, 3H), 3.48 (s, 3H), 3.48 (s, 3H), 3.83 (s, 3H), 5.18 (s, 2H), 5.23 (s, 2H), 5.23 (s, 2H), 6.70 (d, 1H, J = 2.0 Hz), 6.74 (complex, 2H), 6.86 (br, 1H), 6.90 (dd, 1H, J = 2.0, 8.3 Hz), 7.05 (d, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 8.8 Hz), 7.13 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 8.8 Hz), 7.95 (d, 1H, J = 8.8 Hz); ^{13}C NMR δ 29.7, 30.1, 40.16, 40.24, 55.9, 56.2, 56.3 (×2), 94.0 (×2), 95.6, 112.8, 115.6, 115.7, 117.7, 118.8, 118.9, 120.3, 123.3, 130.08, 130.11, 130.66, 130.70, 135.9, 137.2, 143.9, 145.9, 147.0, 150.2, 160.88, 160.91, 197.69, 197.74; HRMS calcd for $C_{37}H_{41}O_{10}$: (M+H), 645.2700, found m/z 645.2690.

4.26. *o*-Deoxyverbenachalcone (5)

Protecting groups of **30** (15.8 mg, 0.025 mmol) were removed with TsOH (23 mg) in MeOH (1 mL) to afford **5** (13.9 mg, 100%) as a yellow oil: IR (film) 3334, 2927, 1660 cm^{-1}; ^{1}H NMR δ 2.89 (t, 2H, J = 7.8 Hz), 3.04 (t, 2H, J = 7.3 Hz), 3.14 (t, 2H, J = 7.8 Hz), 3.24 (t, 2H, J = 7.3 Hz), 3.80 (s, 3H), 6.27 (br, 1H), 6.65 (br, 1H), 6.76 (d, 1H, J = 8.3 Hz), 6.83–6.91 (complex, 7H), 7.84 (d, 1H, J = 8.3 Hz), 7.86 (d, 2H, J = 8.3 Hz), 8.34 (br, 1H), 8.43 (br, 1H); ^{13}C NMR δ 29.9, 30.6, 39.7, 40.1, 55.9, 112.9, 115.3, 115.7, 117.6., 120.5, 120.7, 123.6, 129.0, 129.2, 130.5, 133.1, 138.3, 143.3, 144.6, 145.2, 150.4, 161.19, 161.24, 198.3, 198.5; HRMS calcd for $C_{31}H_{28}O_7$: (M+H), 513.1911, found m/z 513.1938.

4.27. Bioassay

PC12D cells were trypsinized for dissociation and seeded on 48-well culture plates (2×10^4 cells/well). After 24 h, the medium was replaced with fresh medium containing 12% FBS and 2% CS. NGF at final concentration of 5 ng/mL and verbenachalcone or its congeners at 10 and 30 μM were added to the medium. After 48 h, the morphology of PC12D cells was observed by microscope. Cells with process-length of more than twice the diameter of a cell body were scored as neurite-bearing cells.

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