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Regioselective synthesis of sterically encumbered diaryl ethers based on one-pot cyclizations of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes

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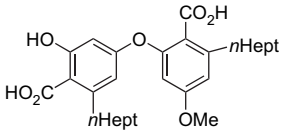
Abstract

Sterically encumbered diaryl ethers are prepared based on formal [3+3] cyclizations of novel 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes.

1. Introduction

Functionalized diaryl ethers are of pharmacological relevance and occur in a variety of natural products.[1] This includes, for example, geodinhydrate methylester, methyl chloroasterrate,[2a,b] 1-desgalloylsanguiin,[2c] dehydrotrigallic acid,[2d] epiphorellic acid,[2e] jolkianin,[2f] remurin A[2g] and micareic acid (Scheme 1).[2h] The most important approach to diaryl ethers relies on the Ullmann[3] and Buchwald–Hartwig[4] reaction and on related transformations.[5] Although these methods are very important, the scope is limited by the availability of the starting materials. In fact, the synthesis of more complex aryl halides or triflates by regioselective functionalizations of arenes is often a difficult task. In addition, the transition metal catalyzed formation of diaryl ethers containing a sterically encumbered ether linkage is often difficult or not possible at all. Some years ago, Chan et al. developed[6] a convenient approach to salicylates based on the cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes[7] with 3-trimethylsilyloxy-2-en-1-ones. We reported the application of this method to the synthesis of a variety of substituted benzene derivatives.[8] Recently, we reported the synthesis of 5-aryloxysalicylates[9] and 5-thioaryloxysalicylates based on reactions of 2-aryloxy- and 2-thioaryloxy-3-trimethylsilyloxy-2-en-1-ones, respectively.[10] Herein, we report, for the first time, the synthesis of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes and their application to the synthesis of diaryl ethers. Noteworthy, the reactions reported herein allow a convenient and regioselective synthesis of sterically encumbered and functionalized diaryl ethers, which are not readily available by other methods.



Scheme 1. Micareic acid.

2. Results and discussion

Ethyl 4-phenoxyacetoacetate (**2a**) was prepared by base-mediated reaction of ethyl 4-chloroacetoacetate and phenol (Scheme 2, Table 1). The methyl 4-phenoxyacetoacetates **2b**,**c** were prepared by Claisen condensation of methyl acetate with the corresponding α-aryloxyacetic chlorides. The silylation of **2a**–**c** gave the 3-silyloxy-2-en-1-ones **3a**–**c**. The novel 4-aryloxy-1,3-bis(silyloxy)-1,3-dienes **4a**–**c** were prepared by

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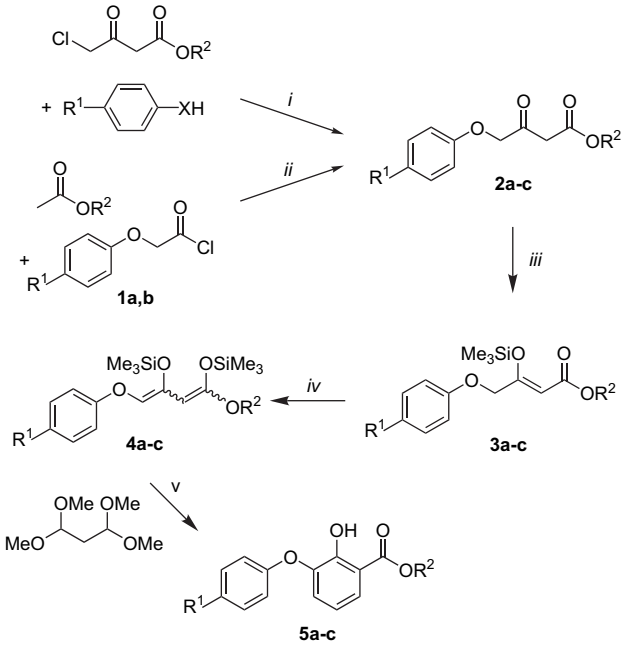
deprotonation (LDA) of **3a–c** at −78 °C and subsequent addition of trimethylchlorosilane. The Me_3SiOTf-catalyzed cyclization of 4-aryloxy-1,3-bis(silyloxy)-1,3-dienes **4a–c** with 1,1,3,3-tetramethoxypropane, following our recently reported protocol,[11] afforded the 3-aryloxysalicylates **5a–c**. During the optimization of cyclization, the concentration and stoichiometry proved to play an important role.



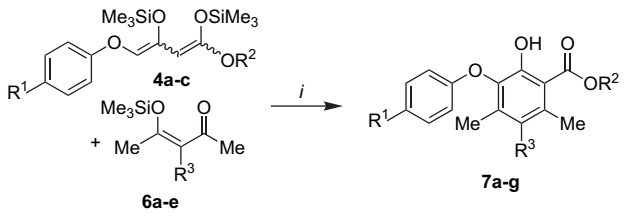
Scheme 2. Synthesis of **5a–c**: (i) NEt_3/KOH, CH_2Cl_2/DMSO, 30 min, 0 °C/5 h, 20 °C; (ii) LDA, THF, −78→20 °C, 14 h; (iii) Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; (iv) LDA, THF, −78→20 °C; (v) Me_3SiOTf, CH_2Cl_2, −78→20 °C, 20 h.

Table 1
Synthesis of diaryl ethers **5a–c**

2–5	R^1	R^2	% (**2**)[a]	% (**3**)[a]	% (**4**)[a]	% (**5**)[a]
a	H	OEt	60	91	82	45
b	Cl	OMe	30	74	82	46
c	Me	OMe	40	75	84	48

[a] Isolated yields.

The $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-dienes **4a–c** with 3-silyloxy-2-en-1-ones **6a–e** afforded the 3-aryloxysalicylates **7a–g** (Scheme 3, Table 2). During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution. In addition, the stoichiometry and temperature are important parameters. The



Scheme 3. Synthesis of **7a–g**: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C, 20 h.

Table 2
Synthesis of diaryl ethers **7a–g**

4	6	7	R^1	R^2	R^3	% (**7**)[a]
a	**a**	**a**	H	OEt	H	37
a	**b**	**b**	H	OEt	Me	43
a	**c**	**c**	H	OEt	Cl	38
a	**d**	**d**	H	OEt	ArO[b]	30
a	**e**	**e**	H	OEt	PhS	30
b	**c**	**f**	Me	OMe	Cl	40
c	**b**	**g**	Cl	OMe	Me	40

[a] Isolated yields.
[b] Ar=3,4-$(MeO)_2C_6H_3$.

structure of **7g** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[12]

The $TiCl_4$- and $TiBr_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-diene **4a** with 1,1-diacetylcyclopropane (**8**) afforded the 3-phenoxysalicylates **9a**,**b** containing a remote halide

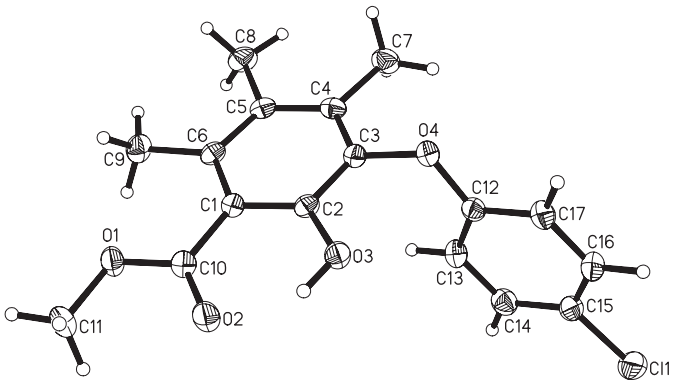
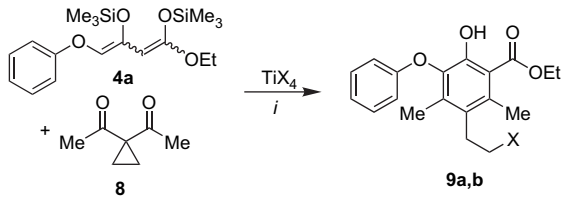


Figure 1. Ortep plot of **7g**.

function (Scheme 4, Table 3). The formation of the products can be explained by means of a domino '[3+3]-cyclization–homo-Michael' reaction.[13] The structures of **9a** and **9b** were independently confirmed by X-ray crystal structure analyses (Figs. 2 and 3).



Scheme 4. Synthesis of **9a**,**b**: (i) TiX_4 (X=Cl, Br), CH_2Cl_2, −78→20 °C, 20 h.

The Me_3SiOTf-catalyzed reaction of 1,3-bis(silyloxy)-1,3-diene **4a** with 3-formylchromone **10** afforded the highly functionalized diaryl ether **11** (Scheme 5). The products are

Table 3
Synthesis of **9a**,**b**

9	X	% (**9**)[a]
a	Cl	40
b	Br	33

[a] Isolated yields.

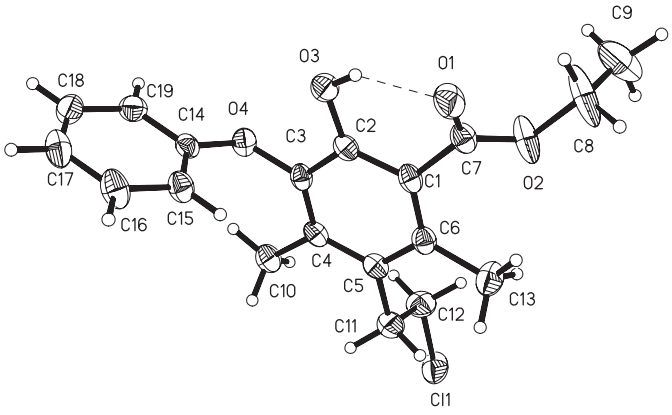


Figure 2. Ortep plot of **9a**.

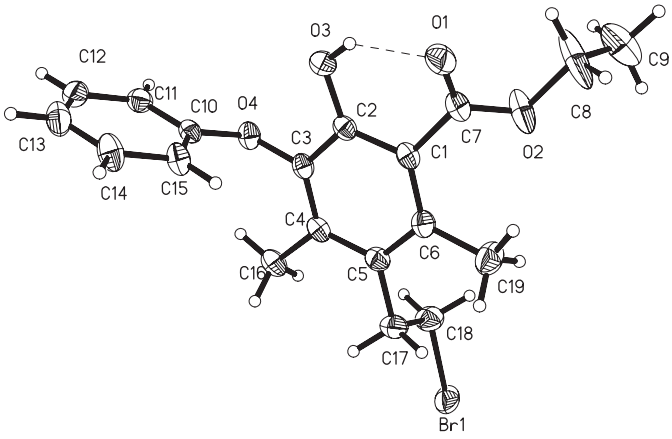
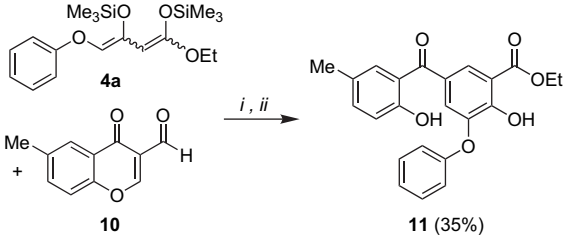


Figure 3. Ortep plot of **9b**.

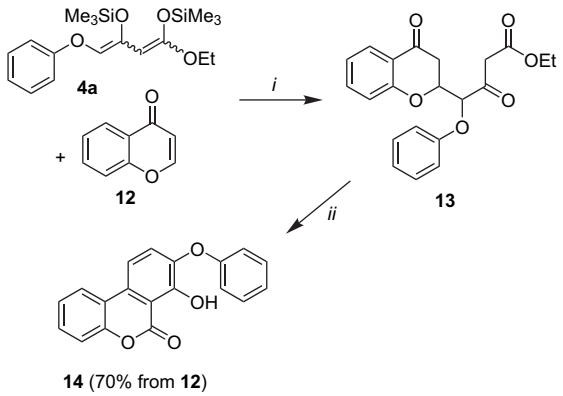
formed by a domino 'Michael–retro-Michael–Mukaiyama-Aldol' reaction.[14]



Scheme 5. Synthesis of **11**: (i) Me_3SiOTf (0.3 equiv), 20 °C, 10 min; (ii) (1) **4a** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (2) HCl (10%).

The Me_3SiOTf-catalyzed reaction of **4a** with chromone (**12**) afforded product **13**, which was transformed (without purification) into the diaryl ether **14** (Scheme 6). The transformation of **13** into **14** proceeds by a domino 'Michael–retro-Michael–lactonization' reaction.[15] The structure of **14** was independently confirmed by X-ray crystal structure analysis (Fig. 4).

In conclusion, a variety of sterically encumbered diaryl ethers were prepared based on formal [3+3] cyclizations of novel 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes. The products are not readily available by other methods.



Scheme 6. Synthesis of **14**: (i) (1) Me_3SiOTf (0.3 equiv), 20 °C, 1 h; (2) **4a** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (3) HCl (10%); (ii) NEt_3 (2.0 equiv), EtOH, 20 °C, 12 h.

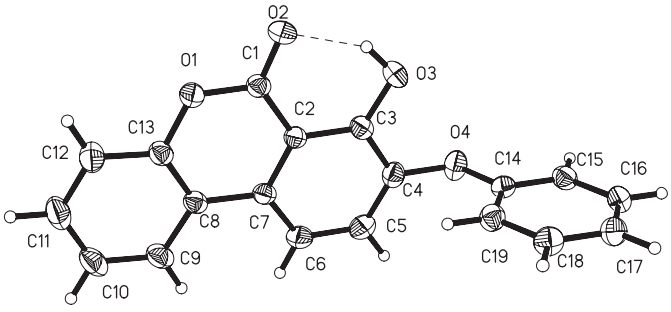


Figure 4. Ortep plot of **14**.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.2. General procedure for the synthesis of aryloxyacetoacetates **2a–c**

Method A: To a mixture of potassium hydroxide (2.0 mmol) in 2 mL of DMSO was dropwise added a solution of phenol (1.0 mmol) in 0.2 mL of DMSO. The mixture was stirred at room temperature for 30 min and then ethyl 4-chloroacetoacetate (1.0 mmol) was added. The mixture was stirred at room temperature overnight and then acidified by addition of hydrochloric acid (4 M). The mixture was extracted with EtOAc and the organic layer was washed with water and then with brine, and dried over Na_2SO_4. The solution was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc/*n*-heptane).

Method B: A THF solution of 2.3 equiv of LDA was prepared by addition of *n*-BuLi (0.93 mL, 2.3 mmol, 2.5 M solution in hexanes) to a THF solution (6 mL) of diisopropylamine (0.32 mL, 2.3 mmol) at 0 °C. After stirring of the solution for 30 min, methyl acetate (0.09 mL, 1.1 mmol) was added at 0 °C. After stirring for 45–60 min, to the solution was added a THF solution (4 mL) of the acid chloride (205 mg, 1.0 mmol) at −78 °C. The temperature was allowed to rise to 20 °C during 5–6 h and the solution was stirred at 20 °C for 8 h. To the solution was added a diluted aqueous solution of HCl and the mixture was extracted with EtOAc (3×200 mL). The organic layers were dried and filtered, the solvent of the filtrate was removed in vacuo, and the residue was purified by chromatography (silica gel, EtOAc/*n*-heptane).

3.2.1. Ethyl 4-phenoxyacetoacetate (**2a**)

Starting with 4-chloroacetoacetate (14.4 mL, 106.3 mmol), phenol (10.00 g, 106.3 mmol), KOH (11.80 g, 212.7 mmol) and DMSO (212 mL), **2a** was isolated as a colourless oil (14.30 g, 60%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (t, 3H, J=7.0 Hz, CH_3), 3.67 (s, 2H, CH_2), 4.21 (q, 2H, J=7.0 Hz, OCH_2), 4.68 (s, 2H, CH_2), 6.85–6.96 (m, 2H, ArH), 7.02–7.07 (m, 1H, ArH), 7.25–7.34 (m, 2H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.1 (CH_3), 46.5, 62.0, 72.8 (CH_2), 114.6 (2C, CH), 122.4 (CH), 129.9 (2C, CH) 157.4, 166.9, 200.7 (C); IR (neat): $\tilde{\nu}$=3043 (w), 2983 (m), 2937 (w), 1724 (s), 1599 (s), 1496 (s), 1322 (s), 1244 (s), 1175 (s), 1032 (s), 813 (m), 755 (s), 692 (s), 508 (w); MS (EI, 70 eV): *m*/*z* (%): 222 (M^+, 84), 176 (67), 134 (66), 129 (72), 107 (100), 94 (45), 77 (97), 51 (39); HRMS (EI): calcd for $C_{12}H_{14}O_4$ [M^+]: 222.08881, found 222.08866.

3.2.2. Methyl 4-(4-chlorophenoxy)acetoacetate (**2b**)

Starting with 2-(4-chlorophenoxy)acetyl chloride (5.00 g, 24.0 mmol) and methyl acetate (2.14 mL, 26.8 mmol), **2b** was isolated as a colourless solid (2.00 g, 30%), mp 57 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.55 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 4.55 (s, 2H, CH_2), 6.74 (d, 2H, J=9.1 Hz, ArH), 7.16 (d, 2H, J=9.1 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=45.7 (CH_2), 52.4 (CH_3), 72.6 (CH_2), 115.8 (2C, CH), 126.6 (C), 129.4 (2C, CH) 156.0, 167.1, 199.6 (C); IR (KBr): $\tilde{\nu}$=3008 (w), 2958 (w), 2931 (w), 1737 (s), 1595 (m), 1493 (s), 1326 (s), 1233 (s), 1158 (s), 1024(s), 986 (m), 823 (s), 636 (m), 512 (m), 495 (w); MS (EI, 70 eV): *m*/*z* (%): 244 (M^+, ^{37}Cl, 11), 242 (M^+, ^{35}Cl, 39), 210 (28), 168 (13), 141 (76), 128 (17), 115 (92), 101 (39), 85.9 (80), 83.9 (100), 59 (23); HRMS (EI): calcd for $C_{11}H_{11}ClO_4$ [M^+, ^{35}Cl]: 242.03335, found 242.03404.

3.2.3. Methyl 4-(4-methylphenoxy)acetoacetate (**2c**)

Starting with 2-(4-methylphenoxy)acetyl chloride (10.00 g, 54.3 mmol), and methyl acetate (4.8 mL, 59.7 mmol), **2c** was isolated as a colourless oil (4.80 g, 40%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.21 (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 3.64 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2), 6.70 (d, 2H, J=8.6 Hz, ArH), 7.01 (distorted d, 2H, J=8.6 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=20.3 (CH_3), 46.1 (CH_2), 52.4 (CH_3), 72.6 (CH_2), 114.4 (2C, CH), 130.1 (2C, CH), 131.5, 155.1, 167.3, 200.8 (C); IR (neat): $\tilde{\nu}$=3030 (w), 2954 (w), 2926 (w), 1731 (s), 1613 (m), 1511 (s), 1437 (m), 1236 (s), 1178 (s), 1066(s), 1039 (m), 817 (s), 510 (w); *m*/*z* (%): 222 (M^+, 92), 206 (7), 190 (71), 148 (34), 128 (55), 121 (100), 101 (41), 86 (82), 77 (49), 59 (28); HRMS (EI): calcd for $C_{12}H_{14}O_4$ [M^+]: 222.08869, found 222.08866.

3.3. General procedure for the synthesis of diaryl ethers **5a–c**

To a dichloromethane solution (2 mL/mmol of **4**) of **4** (1.0 mmol) and of 1,1,3,3-tetramethoxypropane was added TMSOTf (0.1 mmol) at −78 °C. The solution was allowed to warm to 20 °C within 20 h. To the solution was added a saturated aqueous solution of HCl (15 mL). The organic and the aqueous layer were separated and the latter was extracted with dichloromethane (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo and the residue was purified by chromatography.

3.3.1. Ethyl 3-phenoxysalicylate (**5a**)

Starting with tetramethoxypropane (0.3 mL, 1.8 mmol), 1,3-bis(silyl enol ether) **4a** (660 mg, 1.8 mmol) and TMSOTf (0.03 mL, 0.18 mmol), **5a** was isolated as a highly viscous colourless oil (210 mg, 45%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.35 (t, 3H, J=7.1 Hz, CH_3), 4.35 (q, 2H, J=7.1 Hz, OCH_2), 6. 77 (t, 1H, J=7.9 Hz, ArH), 6.91 (dd, 2H, J=1.1, 8.6 Hz, ArH), 6.99 (m, 1H, ArH), 7.11 (m, 1H, ArH), 7.20 (m, 2H, ArH), 7.62 (dd, 1H, J=1.5, 8.0 Hz, ArH), 10.95 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.1 (CH_3), 61.7 (CH_2), 114.2 (C), 117.0 (2C, CH), 118.7, 122.7, 125.7, 126.7 (CH), 129.6 (2C, CH), 144.2, 154.0, 157.6, 170.0 (C); IR (neat): $\tilde{\nu}$=3072 (w), 2983 (w), 1674 (s), 1585 (s), 1460 (s), 1323 (s), 1253 (s), 1150 (s), 1025 (s), 854 (m), 752 (s), 690 (m), 580 (w), 498 (w); MS (EI, 70 eV): *m*/*z* (%): 258 (M^+, 65), 212 (100), 184 (46), 128 (13), 105 (31), 77 (15), 51 (12); elemental analysis: calcd (%) for $C_{15}H_{14}O_4$: C 69.76, H 5.46; found: C 69.68, H 5.63.

3.3.2. Methyl 3-(4-chlorophenoxy)salicylate (**5b**)

Starting with tetramethoxypropane (0.25 mL, 1.5 mmol), 1,3-bis(silyl enol ether) **4b** (582 mg, 1.5 mmol) and TMSOTf (0.027 mL, 0.15 mmol), **5b** was isolated as a highly viscous colourless oil (192 mg, 46%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.88 (s, 3H, OCH_3), 6.81 (m, 3H, ArH), 7.15 (m, 3H, ArH), 7.61 (dd, 1H, J=1.5, 8.0 Hz, ArH), 10.23 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=52.5 (CH_3), 114.1 (C), 118.0 (2C, CH), 118.9, 125.8, 127.0 (CH), 127.6 (C) 129.5 (2C, CH), 143.8, 153.9, 156.3, 170.3 (C); IR (neat): $\tilde{\nu}$=3099 (w), 2954 (m), 2854 (w), 1680 (s), 1583 (s), 1485 (s), 1329 (s), 1254 (s), 1007 (s), 824 (s), 662 (m), 499 (m), 441 (w); MS (EI, 70 eV): *m*/*z* (%): 280 (M^+, ^{37}Cl, 24), 278 (M^+, ^{35}Cl, 71), 246 (100), 218 (26), 211 (50), 155 (9), 139 (34), 107 (20), 75 (9); HRMS (EI): calcd for $C_{14}H_{11}ClO_4$ [M^+, ^{35}Cl]: 278.03435, found 278.03404.

*3.3.3. Methyl 3-(4-methylphenoxy)salicylate (**5c**)*

Starting with tetramethoxypropane (0.25 mL, 1.5 mmol), 1,3-bis(silyl enol ether) **4c** (554 mg, 1.5 mmol) and TMSOTf (0.027 mL, 0.15 mmol), **5c** was isolated as a highly viscous oil (186 mg, 48%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.24 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 6.72–6.82 (m, 3H, ArH), 7.02–7.09 (m, 3H, ArH), 7.56 (dd, 1H, J=1.5, 8.0 Hz, ArH), 10.87 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=20.5, 52.5 (CH_3), 112.8 (C), 116.2 (2C, CH), 117.7, 126.7, 127.5 (CH), 129.2 (2C, CH), 131.3, 143.9, 152.7, 154.1, 169.5 (C); IR (neat): $\tilde{\nu}$=2955 (w), 2924 (m), 2855 (w), 1680 (s), 1505 (s), 1440 (s), 1329 (s), 1252 (s), 1150 (s), 1006 (m), 815 (m), 718 (w), 501 (w); MS (EI, 70 eV): *m/z* (%): 258 (M^+, 75), 226 (100), 198 (37), 119 (34), 107 (14), 91 (11), 65 (8), 51 (5); HRMS (EI): calcd for $C_{15}H_{15}O_4$ [M^+]: 258.08868, found 258.08866.

*3.4. General procedure for the synthesis of diaryl ethers **7a–g***

To a dichloromethane solution (2 mL/mmol of **4**) of **4** (1.0 mmol) and of **6** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at −78 °C. The solution was allowed to warm to 20 °C within 20 h. To the solution was added a saturated aqueous solution of $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc/*n*-heptane=1:4).

*3.4.1. Ethyl 4,6-dimethyl-3-(phenoxy)salicylate (**7a**)*

Starting with 3-(silyloxy)alk-2-en-1-one **6a** (600 mg, 3.48 mmol), 1,3-bis(silyl enol ether) **4a** (1.27 g, 3.48 mmol) and $TiCl_4$ (0.38 mL, 3.48 mmol), **7a** was isolated as a colourless solid (354 mg, 37%), mp 69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.35 (t, 3H, J=7.2 Hz, CH_3), 2.08 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.35 (q, 2H, J=7.0 Hz, OCH_2), 6.54 (s, 1H, ArH), 6.78 (d, 2H, J=8.7 Hz, ArH), 6.90 (t, 1H, J=7.4 Hz, ArH), 7.18 (t, 2H, J=8.1 Hz, ArH), 11.43 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.1, 16.3, 23.7 (CH_3), 61.6 (CH_2), 111.4 (C), 114.6 (2C, CH), 121.6, 124.3 (CH), 129.4 (2C, CH), 137.1, 138.1, 138.9, 155.9, 157.8, 171.2 (C); IR (KBr): $\tilde{\nu}$=2988 (m), 2930 (w), 1651 (s), 1590 (m), 1494 (s), 1377 (s), 1300 (s), 1213(s), 1164 (s), 1029 (m), 842 (w), 793 (s), 692 (s), 577 (w), 421 (w); MS (EI, 70 eV): *m/z* (%): 286 (M^+, 42), 240 (100), 211 (13), 197 (9), 135 (10), 105 (43), 77 (16); elemental analysis: calcd (%) for $C_{17}H_{18}O_4$ (286.1): C 71.31, H 6.43; found: C 71.18, H 6.66.

*3.4.2. Ethyl 4,5,6-trimethyl-3-phenoxysalicylate (**7b**)*

Starting with 3-(siloxy)alk-2-en-1-one **6b** (600 mg, 3.2 mmol), 1,3-bis(silyl enol ether) **4a** (1.18 g, 3.2 mmol) and $TiCl_4$ (0.35 mL, 3.2 mmol), **7b** was isolated as a colourless solid (414 mg, 43%), mp 75 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.28 (t, 3H, J=7.1 Hz, CH_3), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.30 (q, 2H, J=7.0 Hz, OCH_2), 6.71 (dd, 2H, J=1.1, 8.6 Hz, ArH), 6.84 (m, 1H, ArH), 7.09–7.15 (m, 2H, ArH), 10.08 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=13.8, 14.1, 15.8, 18.8 (CH_3), 61.7 (CH_2), 113.4 (C), 114.6 (2C, CH), 121.6 (CH), 127.7 (C), 129.5 (2C, CH), 134.3, 136.7, 138.4, 151.6, 158.0, 171.0 (C); IR (KBr): $\tilde{\nu}$=2992 (w), 2923 (w), 1663 (s), 1591 (s), 1414 (s), 1312 (s), 1251 (s), 1189 (s), 1018 (s), 801 (m), 753 (s), 693 (m), 507 (w), 418 (w); MS (EI, 70 eV): *m/z* (%): 300 (M^+, 46), 254 (100), 239 (27), 211 (15), 149 (15), 105 (57), 77 (22); elemental analysis: calcd (%) for $C_{18}H_{20}O_4$ (300.1): C 71.98, H 6.71; found: C 71.66, H 6.77.

*3.4.3. Ethyl 4,6-dimethyl-5-chloro-3-phenoxysalicylate (**7c**)*

Starting with 3-(siloxy)alk-2-en-1-one **6c** (400 mg, 1.93 mmol), 1,3-bis(silyl enol ether) **4a** (707 mg, 1.93 mmol) and $TiCl_4$ (0.21 mL, 1.93 mmol), **7c** was isolated as a colourless solid (234 mg, 38%), mp 47 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.1 Hz, CH_3), 2.20 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 4.38 (q, 2H, J=7.1 Hz, CH_2), 6.75 (d, 2H, J=7.9 Hz, ArH), 6.91 (t, 1H, J=7.3 Hz, ArH), 7.18 (m, 2H, ArH), 10.68 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=13.3, 14.0, 18.6 (CH_3), 61.1 (CH_2), 112.4 (C), 113.0 (2C, CH), 120.9 (CH), 125.7 (C), 128.5 (2C, CH), 133.3, 136.0, 138.3, 152.2, 156.5, 169.5 (C); IR (Nujol): $\tilde{\nu}$=3069 (w), 1664 (s), 1591 (m), 1490 (s), 1401 (s), 1376 (s), 1347 (m), 1246 (s), 1184 (s), 1074 (m), 854 (w), 749 (s), 686 (m), 433 (w); MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 15), 320 (M^+, ^{35}Cl, 43), 274 (100), 245 (15), 211 (13), 169 (8), 139 (34), 105 (43), 77 (21); elemental analysis: calcd (%) for $C_{17}H_{17}ClO_4$ (320.08): C 63.65, H 5.34; found: C 63.23, H 5.70.

*3.4.4. Ethyl 4,6-dimethyl-3-phenoxy 5-(3,4-dimethoxyphenoxy)salicylate (**7d**)*

Starting with 3-(siloxy)alk-2-en-1-one **6d** (600 mg, 1.83 mmol), 1,3-bis(silyl enol ether) **4a** (671 mg, 1.83 mmol) and $TiCl_4$ (0.2 mL, 1.83 mmol), **7d** was isolated as a highly viscous oil (207 mg, 30%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.35 (t, 3H, J=7.1 Hz, CH_3), 1.95 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.36 (q, 2H, J=7.2 Hz, OCH_2), 6.02 (dd, 1H, J=2.8, 8.6 Hz, ArH), 6.44 (d, 1H, J=2.8 Hz, ArH), 6.64 (d, 1H, J=8.8 Hz, ArH), 6.77–6.81 (m, 2H, ArH), 6.88–6.95 (m, 1H, ArH), 7.16–7.23 (m, 2H, ArH), 11.09 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=10.9, 14.1, 15.1, 55.9, 56.3 (CH_3), 62.0 (CH_2), 100.0, 104.1, 111.9 (CH), 112.0 (C), 114.5 (2C, CH), 121.8 (CH), 129.5 (2C, CH), 130.4, 133.8, 139.4, 143.7, 143.9, 150.1, 152.4, 153.1, 157.7, 171.1 (C); IR (neat): $\tilde{\nu}$=2999 (w), 2936 (w), 1601 (s), 1508 (s), 1452 (s), 1301 (s), 1261 (s), 1192 (s), 1027 (s), 833 (m), 753 (w), 653 (w), 475 (w); MS (EI, 70 eV): MS (EI, 70 eV): *m/z* (%): 438.1 (M^+, 100), 392.1 (87), 377.1 (49), 287.1 (3), 255 (3), 138 (13), 105 (59), 77 (16); HRMS (EI): calcd for $C_{25}H_{26}O_7$ [M^+]: 438.16708, found 438.16730.

*3.4.5. Ethyl 4,6-dimethyl-3-phenoxy-5-thiophenoxysalicylate (**7e**)*

Starting with 3-(siloxy)alk-2-en-1-one **6e** (500 mg, 1.8 mmol), 1,3-bis(silyl enol ether) **4a** (647 mg, 1.8 mmol)

and $TiCl_4$ (0.19 mL, 1.8 mmol), **7e** was isolated as a colourless solid (210 mg, 30%), mp 103 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.0 Hz, CH_3), 2.26 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.37 (q, 2H, J=7.2 Hz, OCH_2), 6.77 (distorted d, 2H, J=7.8 Hz, ArH), 6.86 (dd, 2H, J=1.3, 8.1 Hz, ArH), 6.92–7.02 (m, 2H, ArH), 7.11–7.22 (m, 4H, ArH), 10.99 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.1, 16.0, 21.1 (CH_3), 62.2 (CH_2), 114.0 (C), 114.6 (2C, CH), 121.9 (CH), 123.2 (C), 124.6, 124.8 (CH), 125.3 (2C, CH), 129.0 (2C, CH), 129.1 (2C, CH), 137.9, 139.5, 143.2, 144.2, 155.6, 157.5, 170.9 (C); IR (KBr): $\tilde{\nu}$=3069 (w), 2978 (w), 2928 (m), 2851 (m), 1662 (s), 1599 (s), 1476 (s), 1374 (s), 1244 (s), 1159 (s), 1077 (m), 752 (m), 686 (m), 488 (w); MS (EI, 70 eV): *m/z* (%): 394 (M^+, 93), 349 (37), 348 (100), 247 (22), 333 (16), 290 (5), 270 (7), 211 (10), 177 (28), 161 (19), 105 (28), 57 (31); HRMS (EI): calcd for $C_{23}H_{22}O_4S$ [M^+]: 394.12333, found 394.12343.

*3.4.6. Methyl 4,6-dimethyl-5-chloro-3-(4-methylphenoxy)salicylate (**7f**)*

Starting with 3-(siloxy)alk-2-en-1-one **6c** (400 mg, 1.9 mmol), 1,3-bis(silyl enol ether) **4b** (711 mg, 1.9 mmol) and $TiCl_4$ (0.21 mL, 1.93 mmol), **7f** was isolated as a highly viscous oil (248 mg, 40%); ^1H NMR (300 MHz, $CDCl_3$): δ=2.20 (s, 6H, CH_3), 2.53 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 6.65 (d, 2H, J=8.5 Hz, ArH), 6.97 (d, 2H, J=8.8 Hz, ArH), 10.55 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 18.6, 19.5, 51.5 (CH_3), 112.3 (C), 113.3 (2C, CH), 125.7 (C), 129.0 (2C, CH), 130.3, 133.0, 136.1, 138.5, 152.1, 154.4, 169.9 (C); IR (neat): $\tilde{\nu}$=297 (m), 2927 (m), 2871 (w), 1661 (s), 1506 (s), 1444 (s), 1248 (s), 1164 (s), 1040 (m), 846 (m), 707 (w), 612 (w), 503 (w); MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 15), 320 (M^+, ^{35}Cl, 46), 288 (100), 273 (9), 259 (15), 169 (10), 119 (87), 91 (22), 77 (18); HRMS (EI): calcd for $C_{17}H_{17}ClO_4$ [M^+, ^{35}Cl]: 320.08106, found 320.08099.

*3.4.7. Methyl 4,5,6-trimethyl-3-(4-chlorophenoxy)-salicylate (**7g**)*

Starting with 3-(silyloxy)alk-2-en-1-one **6b** (400 mg, 2.1 mmol), 1,3-bis(silyl enol ether) **4c** (814 mg, 2.1 mmol) and $TiCl_4$ (0.23 mL, 2.1 mmol), **7g** was isolated as a colourless solid (272 mg, 40%), mp 98 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=2.01 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.65 (d, 2H, J=8.9 Hz, ArH), 7.05 (d, 2H, J=8.8 Hz, ArH), 10.23 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=13.8, 15.9, 18.8, 52.3 (CH_3), 113.1 (C), 116.0 (2C, CH), 126.4, 127.8 (C), 129.4 (2C, CH), 134.7, 136.7, 138.3, 151.6, 156.6, 171.6 (C); IR (KBr): $\tilde{\nu}$=3005(w), 2952 (w), 2926 (w), 1667 (s), 1595 (m), 1485 (s), 1318 (s), 1248 (s), 1298 (s), 1064 (s), 994 (m), 823 (s), 626 (w), 457 (w); MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 21), 320 (M^+, ^{35}Cl, 62), 288 (70), 273 (13), 253 (71), 225 (11), 139 (100), 91 (13), 77 (18); elemental analysis: calcd (%) for $C_{17}H_{17}ClO_4$ (320.08): C 63.65, H 5.34; found: C 63.59, H 5.39.

*3.4.8. Ethyl 4,6-dimethyl-5-(2-chloroethyl)-3-phenoxy-salicylate (**9a**)*

Starting 1,1-diacetylclopropane (**15**) (300 mg, 2.4 mmol), 1,3-bis(silyl enol ether) **4a** (1.200 g, 3.3 mmol), $TiCl_4$ (0.52 mL, 4.8 mmol) and CH_2Cl_2 (110 mL), **9a** was isolated as colourless crystals (328 mg, 40%), mp 75 °C; ^1H NMR (250 MHz, $CDCl_3$): δ=1.34 (t, 3H, J=7.25 Hz, CH_3), 2.14 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.07 (t, 2H, J=6.45 Hz, CH_2), 3.45 (t, 2H, J=7.5 Hz, CH_2), 4.37 (q, 2H, J=6.5 Hz, CH_2), 6.76 (m, 2H, ArH), 6.94 (m, 1H, ArH), 7.76 (m, 2H, ArH), 10.41 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=12.4, 13.1, 17.3 (CH_3), 32.2, 41.1, 60.9 (CH_2), 112.9 (C), 113.6 (2C CH), 120.7 (CH), 126.4 (C), 128.5 (2C CH), 133.9 136.0, 138.0, 151.9, 156.7, 169.8 (C); IR (Nujol): $\tilde{\nu}$=3381 (w), 2981 (s), 1728 (m), 1669 (m), 1590 (m), 1491 (m), 1301 (m), 1218 (m), 1167 (m), 1036 (m), 788 (w) 750 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 450 (M^+, ^{37}Cl, 13), 448 (M^+, ^{35}Cl, 41), 403 (73), 267 (83), 253 (43), 105 (100), 77 (22); HRMS (EI): calcd for $C_{19}H_{21}O_4Cl$ [M^+, ^{35}Cl]: 448.11229, found 448.11180.

*3.4.9. Ethyl 4,6-dimethyl-5-(2-bromoethyl)-3-phenoxy-salicylate (**9b**)*

Starting with 1,1-diacetylcyclopropane **15** (300 mg, 2.4 mmol), 1,3-bis(silyl enol ether) **4a** (1.20 g, 3.3 mmol), $TiBr_4$ (873 mg, 2.4 mmol) and CH_2Cl_2 (110 mL), **9b** was isolated as colourless crystals (315 mg, 33%), mp 103 °C; ^1H NMR (250 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz, CH_3), 2.03 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 4.27 (q, 2H, J=7.1 Hz, CH_2), 6.65 (m, 2H, ArH), 6.83 (m, 1H, ArH), 7.08 (m, 2H, ArH), 10.23 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=11.4, 12.2, 16.3 (CH_3), 27.6, 31.6, 59.9 (CH_2), 111.9 (C), 112.6 (2C CH), 119.5 (CH), 126.5 (C), 127.6 (2C CH), 132.8, 134.9, 137.0, 151.0, 155.7, 168.8 (C); IR (Nujol): $\tilde{\nu}$=3375 (w), 2978 (s), 1734 (m), 1675 (m), 1590 (m), 1490 (m), 1319 (m), 1219 (m), 1176 (m), 1029 (m), 751 (w) 690 (m) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 393 (M^+, ^{81}Br, 40), 391 (M^+, ^{79}Br, 40), 347 (62), 313 (26), 267 (100), 253 (33), 105 (89), 77 (34); HRMS (EI): calcd for $C_{19}H_{21}O_4Br$ ([(M+1)$^+$, ^{79}Br]: 392.06177, found 392.06199.

*3.4.10. Synthesis of ethyl-5-(2-hydroxy-3-methylbenzoyl)-3-phenoxysalicylate (**11**)*

Me_3SiOTf (0.3 equiv) was added to the 3-formylchromone (1.0 equiv) at 20 °C. After stirring for 10 min, CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis-(silyl enol ether) (1.3 equiv) was added. The mixture was stirred at 20 °C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4. The mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc/*n*-heptane). Starting with 3-formylchromone **10** (411 mg, 2.2 mmol), 1,3-bis(silyl enol ether) **4a** (800 mg, 2.2 mmol) and Me_3SiOTf (0.65 mL, 1.2 mmol), **11** was isolated as a highly viscous oil (300 mg,

35%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.35 (t, 3H, J=7.1 Hz, CH_3), 2.17 (s, 3H, CH_3), 4.39 (q, J=7.1 Hz, 2H, CH_2), 6.88 (m, 1H, ArH), 6.94–7.06 (m, 3H, ArH), 7.21–7.30 (m, 4H, ArH), 7.44 (d, J=2.1 Hz, 1H, ArH), 8.02 (d, J=2.2 Hz, 1H, ArH), 11.45 (s, 1H, OH), 11.49 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.1, 20.4 (CH_3), 62.3 (CH_2), 113.8 (C), 116.9 (C), 117.7 (2C, CH), 118.3 (CH), 118.5 (C), 123.6, 126.1, 127.0 (CH), 127.8, 128.6 (C), 129.8 (2C, CH), 132.5, 137.3 (CH), 144.8, 156.8, 156.9, 160.9, 169.6, 198.3 (C); IR (neat): $\tilde{\nu}$=2982 (w), 2926 (w), 2869 (w), 1678 (s), 1587 (s), 1401 (s), 1376 (s), 1212 (s), 1109 (m), 1028 (s), 827 (m), 788 (s), 691(m), 475 (w) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 392 (M^+, 100), 347 (43), 258 (31), 212 (44), 184 (13), 135 (54), 105 (24), 77 (27); HRMS (EI) calcd for $C_{23}H_{20}O_6$ [M^+]: 392.12554, found 392.12544.

*3.4.11. Synthesis of 8-phenoxy-7-hydroxy-6H-benzo[c]chromen-6-one (**14**)*

Me_3SiOTf (1.3 equiv) was added to the chromone (1.0 equiv) at 20 °C. After stirring for 1 h, CH_2Cl_2 (8 mL) was added, the solution was cooled to 0 °C and the 1,3-bis-(silyl enol ether) (1.3 equiv) was added. The mixture was stirred at 20 °C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3×15 mL) and dried over Na_2SO_4. The mixture was filtered and the solvent of the filtrate was removed under reduced pressure to give crude product **13**. To an EtOH solution (10 mL) of the latter was added NEt_3 (2.0 equiv) and the mixture was stirred for 12 h at 20 °C. To the solution was added hydrochloric acid (1 M) and then EtOAc. The organic and the aqueous layer were separated and the latter was extracted with EtOAc and dried over Na_2SO_4. The mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc/*n*-heptane). Starting with chromone **12** (500 mg, 3.42 mmol), 1,3-bis(silyl enol ether) **4a** (1.62 g, 4.4 mmol), Me_3SiOTf (0.8 mL, 4.4 mmol) and NEt_3 (0.95 mL, 6.8 mmol), **14** was isolated as a colourless solid (728 mg, 70%), mp 151 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ=6.93 (dd, 2H, J=1.1, 8.6 Hz, ArH), 7.03 (m, 1H, ArH), 7.20–7.28 (m, 4H, ArH), 7.32–7.36 (m, 2H, ArH), 7.43 (distorted d, J=8.6 Hz, 1H, ArH), 7.86 (dd, J=1.8, 8.6 Hz, 1H, ArH), 11.42 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ=107.5 (C), 112.2 (CH), 117.4 (2C, CH), 117.6 (CH), 118.1 (C), 122.9, 123.3, 125.3, 128.5 (CH), 129.7 (2C, CH), 130.2 (CH), 130.5, 143.6, 150.1, 153.9, 157.1, 165.3 (C); IR (KBr): $\tilde{\nu}$=3138 (w), 3070 (w), 2923 (w), 1684(s), 1586 (s), 1481 (s), 1318 (m), 1220 (s), 1128 (s), 1081 (m), 869 (m), 756 (s), 717 (m), 456 (w) cm^{-1}; GC–MS (EI, 70 eV): *m/z* (%): 304 (M^+, 100), 287 (15), 199 (22), 171 (7), 115 (9), 77 (7), 51 (4); HRMS (EI) calcd for $C_{19}H_{12}O_4$ [M^+]: 304.07316, found 304.07301.

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