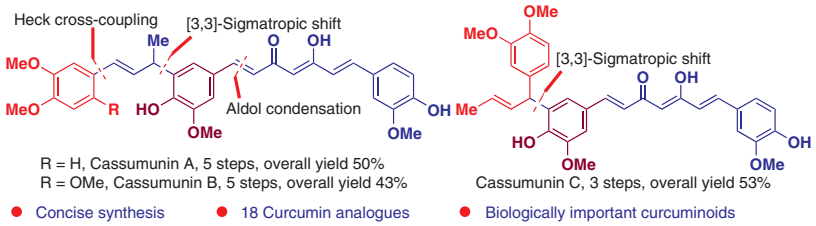
Synthesis M. A. Hussain, F. A. Khan Paper

Total Synthesis of (±)-Cassumunins A–C and Curcumin Analogues

Mulla Althafh Hussain
Faiz Ahmed Khan*

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi, Sangareddy, Telangana, 502285, India
faiz@iith.ac.in



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Abstract A full account of the total synthesis of (±)-cassumunins A–C – superior antioxidants and anti-inflammatory agents – is given. Two novel approaches were developed for synthesizing cassumunins. The total synthesis of cassumunins A and B was accomplished in five linear steps from a known aldehyde in good overall yields of 50 and 43%, respectively, featuring a cascade [3,3]-sigmatropic shift (the Claisen rearrangement) and Heck cross-coupling reaction. Consequently, the total synthesis of cassumunin C was accomplished in three linear steps from a known alcohol with an overall yield of 53%. The key features involved in this synthesis are tandem [3,3]-sigmatropic shift, S_N2' reaction, and aldol condensation. Moreover, a total of eighteen symmetrical and unsymmetrical curcumin analogues were synthesized.

Key words total synthesis, Claisen rearrangement, S_N2' reaction, cassumunins A–C, curcumin, Heck reaction, aldol condensation

Traditionally, curcumin (**1**; Figure 1) is a globally popular herbal drug, isolated from turmeric, the rhizome of *Curcuma longa L.* (Zingiberaceae), by Vogel et al. in 1842.[1] Turmeric contains three curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Out of these three compounds, curcumin is the most abundant and is well known for being an extremely biologically potent component.[2] In the past decade, numerous biological investigations have been carried out on curcumin and it was found to be the best chemopreventive drug that can cure frequently existing cancers such as stomach, lung, breast, duodenal, prostate and colon cancers, and leukemia.[2] Also, it has other biological activities such as antioxidant, anti-inflammatory, antiarthritis, cardiotoxicity, antidiabetic, and neurotoxicity.[2]

In 1993, Masuda et al. isolated three new curcuminoids from the rhizome of tropical ginger, *Zingiber cassumunar* and named as (±)-cassumunins A–C, having superior anti-

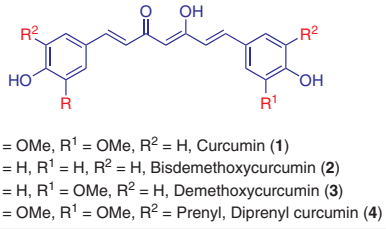


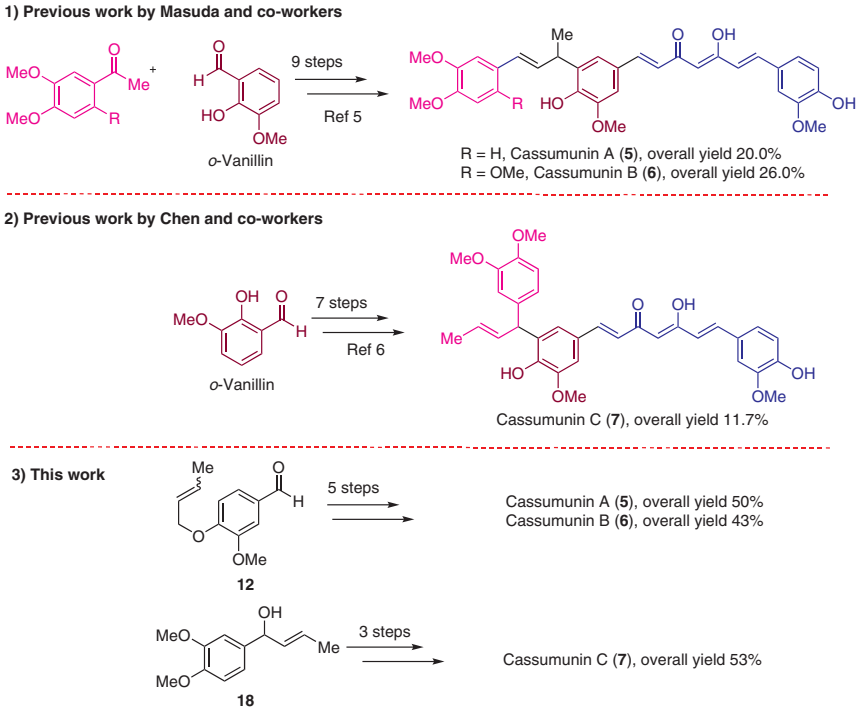
Figure 1 Naturally occurring curcuminoids **1**–**4**[3]

oxidant and anti-inflammatory properties in comparison to curcumin.[4] Subsequently, in 1998, they synthesized cassumunins A and B in nine linear steps in an overall yield of 20 and 26%, respectively (Scheme 1). Cassumunins A–C are more active against cell death in thymocyte system of the rat, induced by H_2O_2 in comparison to curcumin.[5]

In 2014, Chen et al. synthesized cassumunin C in seven linear steps in an overall yield of 11.7% by using aromatic propargylation, stereoselective reduction of alkynylphenol, and Reimer–Tiemann reaction as key steps (Scheme 1).[6] Because of remarkable antioxidant, anti-inflammatory activities, and attractive molecular architecture, we were prompted to synthesize (±)-cassumunins A–C and herein report straightforward as well as efficient approaches leading to good overall yield of 50, 43, and 53%, respectively.

Cassumunins have curcumin core structure with phenylbutenylated moiety.[4,5] Retrosynthetic analysis of **5** and **6** is depicted in Scheme 2. Cassumunins A and B could be assembled via an aldol condensation reaction between **13** and **8** or **9** followed by usual deprotection of *O*-Boc. The compound **8** or **9** could be accessed via Heck cross-coupling of **10** and the corresponding methoxy-substituted bromobenzenes. Compound **10** was expected to be synthesized from **11** through usual Boc protection. Terminal olefin **11** could be obtained by [3,3]-sigmatropic shift (the Claisen rear-

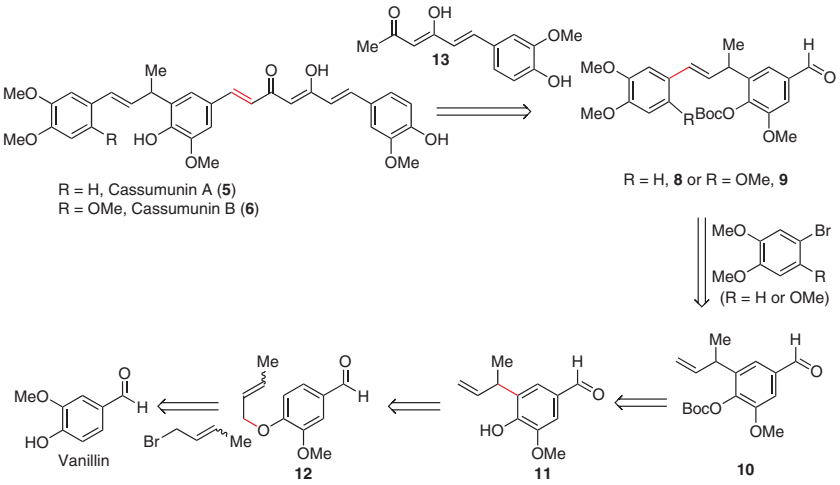
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Scheme 1 1) and 2) Previously reported syntheses of (±)-cassumunins A–C (**5**–**7**).[5,6] 3) Synthesis of (±)-cassumunins A–C (**5**–**7**) described herein.

rangement) of **12**, which was expected to be prepared from commercially available vanillin.

As shown in Scheme 3, we commenced our synthetic investigation towards cassumunins A and B from aldehyde **12**, which was prepared by following the known procedure with slight modification via alkylation between commercially available vanillin and crotyl bromide in the presence of K_2CO_3/DMF in good yield (96%).[7] Aldehyde **12** was subjected to [3,3]-sigmatropic shift (the Claisen rearrangement) at 180 °C in a sealed tube to give **11** in excellent yield (95%).[8] The free hydroxyl group of compound **11** was protected by using $(Boc)_2O$ and DMAP/Et_3N/CH_2Cl_2, which furnished *O*-Boc protected compound **10** in good yield (97%). The corresponding methoxy-substituted aryl group was familiarized by Heck cross-coupling reaction with olefin derivative **10**, in the presence of a catalytic amount of $Pd(OAc)_2$ and Cs_2CO_3/PhMe to afford compound **8** or **9** in good yield of 84 and 82%, respectively.[9] Preparation of cassumunin A (**5**) from **8** through condensation reaction with **13**[10] followed by deprotection of the *O*-Boc group by using

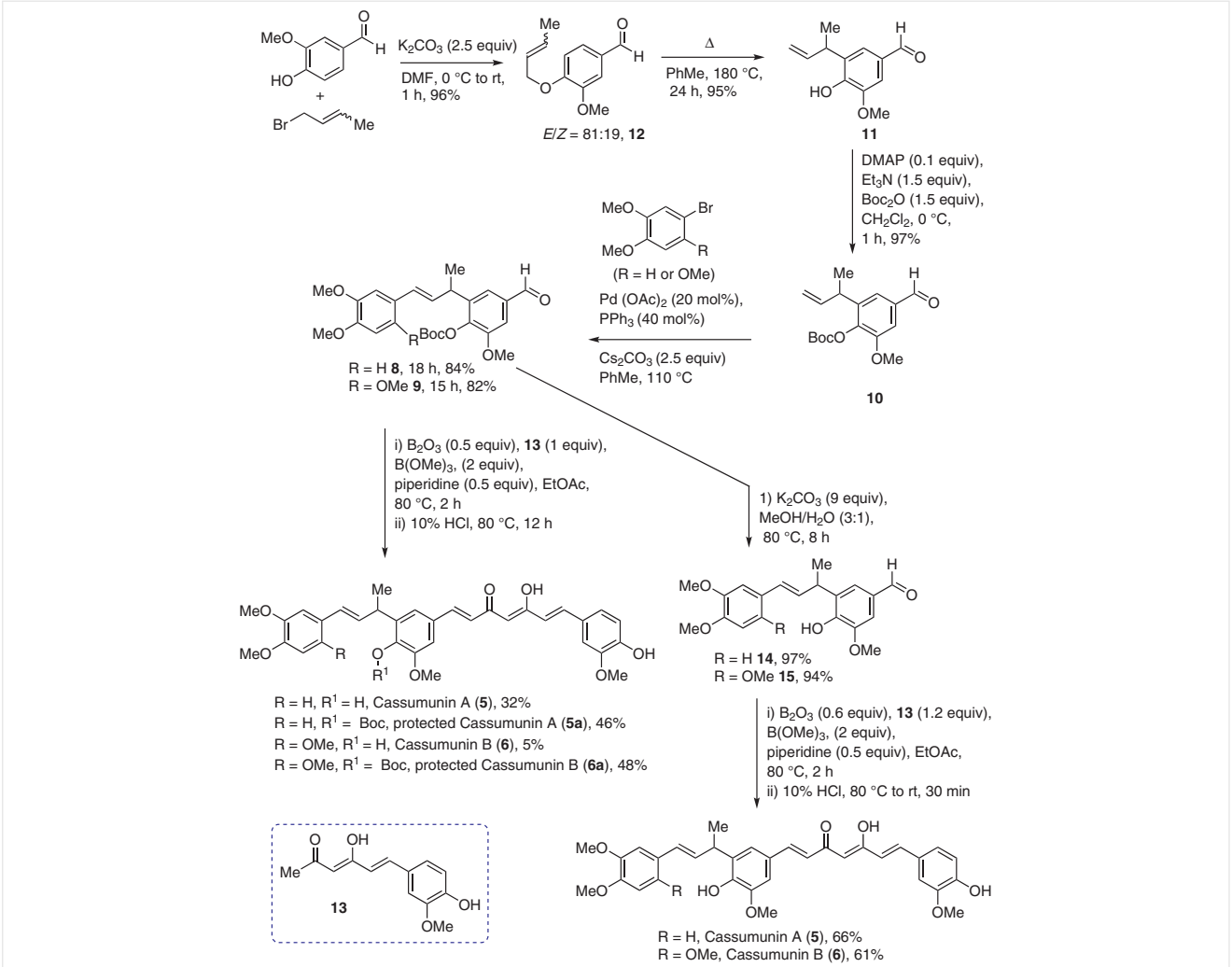


Scheme 2 Retrosynthetic analysis of (±)-cassumunins A and B (**5** and **6**)

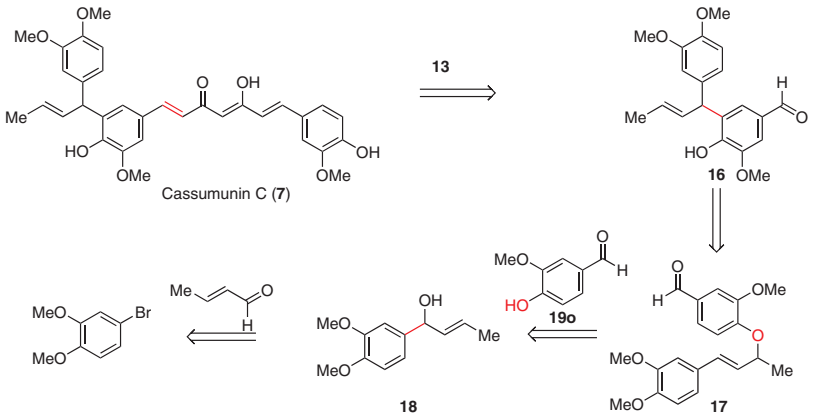
B_2O_3/$B(OMe)_3$/10% HCl furnished two products cassumunin A (**5**) and *O*-Boc protected cassumunin A (**5a**) in 32 and 46% yield, respectively.[11] Similarly, preparation of cassumunin B (**6**) from **9** via aldol condensation reaction with **13**[10] followed by deprotection of *O*-Boc group by using B_2O_3/$B(OMe)_3$/10% HCl[11] gave two products, cassumunin B (**6**) and the *O*-Boc protected cassumunin B (**6a**) in 5 and 48% yield, respectively. Therefore, a small modification in our retrosynthetic synthesis was done by first deprotecting the *O*-Boc group followed by aldol condensation reaction. Compound **8** and **9** were subjected to standard *O*-Boc deprotection condition TFA/CH_2Cl_2, which were unsuccessful. A significant transformation of **8** and **9** to **14** and **15** was observed by using K_2CO_3/MeOH/H_2O[12] (3:1) at 80 °C in excellent yield of 97 and 94%, respectively. Compounds **5** and **6** were accomplished by performing aldol condensation reaction between **13**[10] and **14** or **15** in the presence of B_2O_3/$B(OMe)_3$/10% HCl[11] at 80 °C in good yield of 66 and 61%, respectively.

The retrosynthetic analysis of **7** is depicted in Scheme 4. We anticipated that cassumunin C could be secured via aldol condensation between aldehyde **16** and diketone **13**. Compound **16** could be derived from **17** via [3,3]-sigmatropic shift of **17**, it was expected to be prepared via S_N2' reaction between vanillin and **18** under Mitsunobu reaction conditions.

As shown in Scheme 5, we commenced our synthesis from compound **17**, which was prepared from alcohol **18** via S_N2' reaction under Mitsunobu reaction conditions in the presence of vanillin (**19o**) and Et_3N/DEAD/PPh_3 to furnish aldehyde **17** in excellent yield (91%).[13,14] Alcohol **18** was prepared by following the known procedure by trapping the lithiated arene with crotonaldehyde.[15] Compound **17** was subjected to the rearrangement reaction in a sealed



Scheme 3 Synthesis of (±)-cassumunins A and B (**5** and **6**)

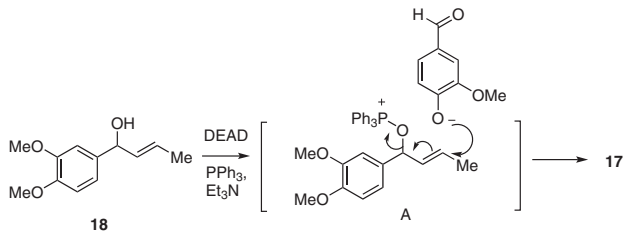


Scheme 4 Retrosynthetic analysis of (±)-cassumunin C (**7**)

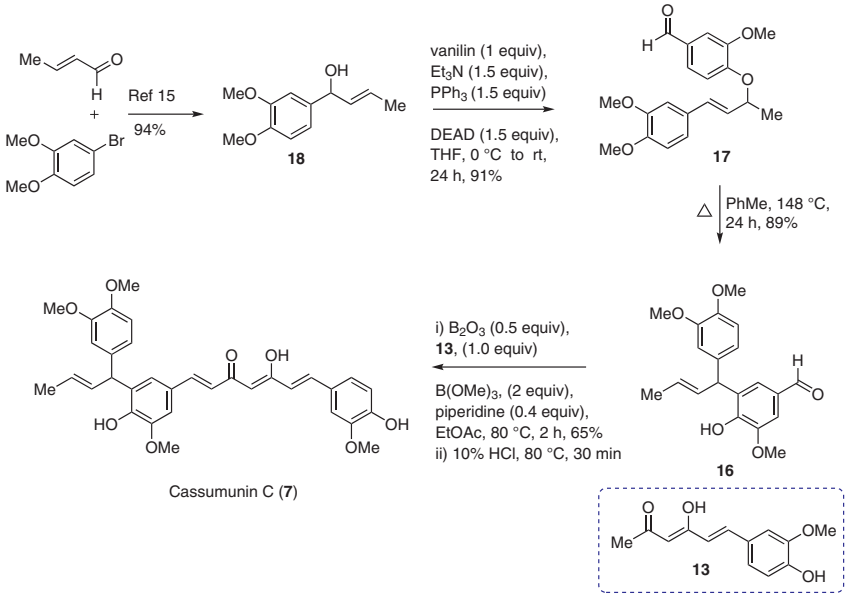
tube at 148 °C/PhMe to afford **16** in excellent yield (89%).[13] Preparation of compound **7** from **16** through aldol condensation with compound **13**[10] in the presence of B_2O_3/$B(OMe)_3$/10% HCl[11] at 80 °C furnished **7** in good yield (65%).

Based on the product formed and previous literature reports,[13,16] a plausible mechanism for the formation **17** is proposed in Scheme 6. First, intermediate A was formed from alcohol **18** under Mitsunobu reaction conditions. After that, vanillin reacted with intermediate A via S_N2' reaction leading to compound **17**.

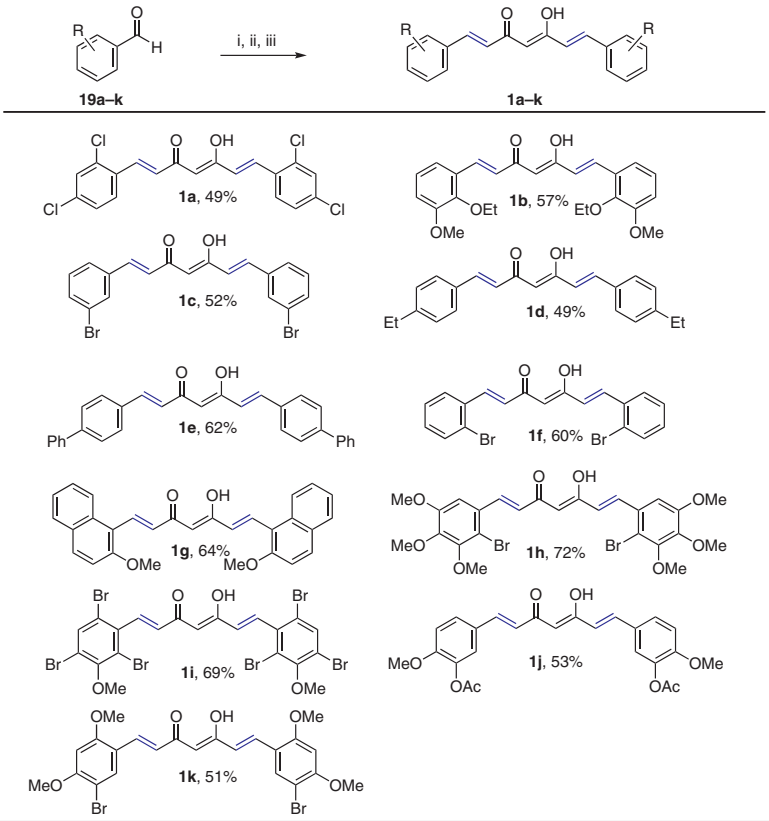
Since cassumunins possess curcumin core, we explored the synthesis of new[17] derivatives of curcumin. Symmetrical curcumin analogues were prepared according to known literature procedure as depicted in Scheme 7.[11a,18] Curcumins **1a–f** were prepared by using commercially available aldehydes **19a–f**. Concisely, in the presence of a base, aldehyde derivatives were condensed with boric anhydride complex, which was prepared in situ from acetylacetone and B_2O_3. Curcumins **1g–k** were prepared from known al-



Scheme 6 Proposed mechanism for compound **17**



Scheme 5 Synthesis of (±)-cassumunin C (**7**)



Scheme 7 Synthesis of symmetrical curcumin analogues **1a–k**. *Reagents and conditions*: (i) acetylacetone (1.0 equiv), B_2O_3 (0.50 equiv), EtOAc, 80 °C, 30 min; (ii) $B(OMe)_3$ (2.0 equiv), aldehyde derivatives **19a–k** (2.0 equiv), *n*-$BuNH_2$ (0.2 equiv), EtOAc, 80 °C, 24 h; (iii) 10% HCl, 80 °C, 30 min. Isolated yields after column chromatography: 49–72%.

dehydes **19g–k**[19–23] having different substituents on the aromatic ring and are present in various natural products and drugs.

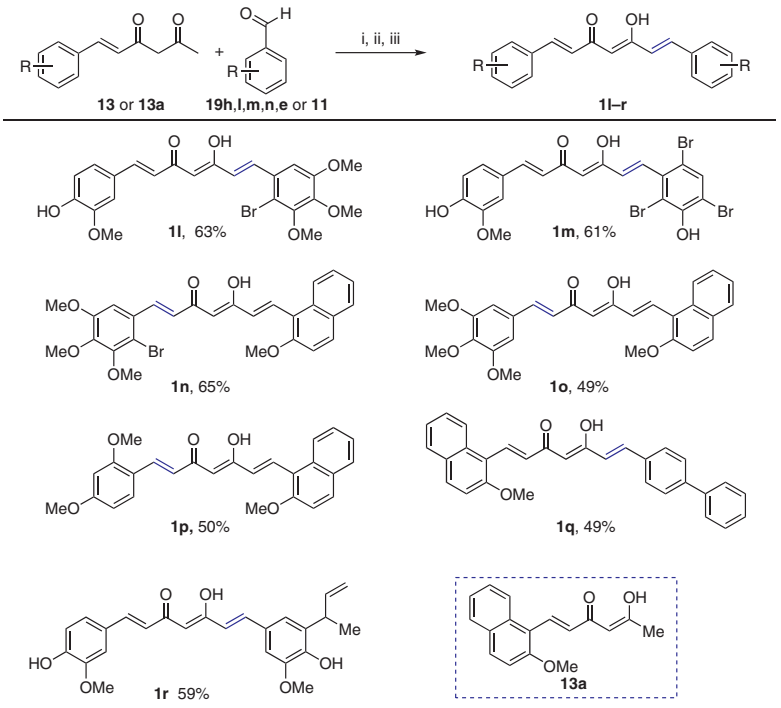
In order to synthesize some novel unsymmetrical curcumin analogues, standard procedure[10,11] as depicted in Scheme 8 was used. The fragment **13** was prepared using known method and the same was extended for the preparation of previously unknown **13a**. Condensation of various aldehydes **19h**,**l**,**m**,**n**,**e** or **11** with **13** or **13a** in the presence of B_2O_3 and base furnished **1l–r**, after acidic workup in moderate to good yields.

In summary, we have accomplished an improved total synthesis for (±)-cassumunins A–C in good overall yields of 50, 43 and 53%, respectively. The key features involved in our approaches are [3,3]-sigmatropic shift (the Claisen rearrangement), Heck cross-coupling reaction, S_N2' reaction, and aldol condensation. Our two approaches are straightforward for (±)-cassumunins A–C with the minimum number of steps and high overall yields. Additionally, we have synthesized new[17] curcumin analogues (18 analogues) by following the known literature procedures.

All reactions were performed in oven-dried glass apparatus. Commercial grade solvents were distilled before use. The reactions were monitored by TLC by using Merck silica gel GF 254 on microscopic slides coated with silica gel and visualization of the spots was accomplished by exposure to UV light and iodine. Melting points were obtained in open capillary tubes using a Gallenkamp instrument and are uncorrected. Purification of products carried out by Biotage flash chromatography or column chromatography using Merck silica gel (100–200 or 200–400) with combinations of EtOAc and hexane solvent system as the eluent. IR spectra were recorded as neat solids or liquids using a Bruker Alpha-p ATR FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded at ambient temperature using a Bruker Avance III 400 MHz spectrometer. The samples for NMR were prepared by dissolving the products in $CDCl_3$ or DMSO-d_6 and TMS was used as an internal standard. Chemical shift (δ) are reported in ppm with reference to the signal for TMS (0 ppm). Coupling constants (*J*) are reported in Hz. Standard abbreviations are used to report the multiplicities. The ^{13}C NMR chemical shifts are assigned by fixing the central signal of $CDCl_3$ at 77.00 ppm. High-resolution mass spectrometry (HRMS) was performed on Agilent spectrometer using electrospray ionization (ESI-TOF).

(*E*)-1-(3,4-Dimethoxyphenyl)but-2-en-1-ol (18)[15]

Compound **18** was prepared according to the known literature procedure.[15] To a stirred solution of bromoveratrole (1.0 g, 4.60 mmol) in anhyd THF (10 mL) at –78 °C under N_2 atmosphere was added drop-



Scheme 8 Synthesis of unsymmetrical curcumin analogues **1l–r**. *Reagents and conditions*: (i) **13** or **13a** (1.0 equiv), B_2O_3 (2.0 equiv), EtOAc, 80 °C, 30 min; (ii) $B(OMe)_3$ (2.0 equiv), aldehyde derivatives **19h**,**l**,**m**,**n**,**e** or **11** (1.0 equiv), piperidine (0.4 equiv), EtOAc, 80 °C, 2 h; (iii) 10% HCl, 80 °C, 30 min. Isolated yields after column chromatography: 49–65%.

wise *n*-BuLi (1.6 M in hexane, 3.0 mL, 5.52 mmol). After stirring for 40 min at –78 °C, a solution of crotonaldehyde (322 mg, 4.60 mmol) in anhyd THF (5 mL) was added dropwise over a period of 10 min. The resulting reaction mixture was stirred for 3 h. After complete conversion of the starting material (monitored by TLC), the reaction mixture was quenched by adding sat. aq NH_4Cl (1 mL) at –78 °C, then the mixture was diluted with H_2O (30 mL) and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100–200 mesh) to afford alcohol **18** as a colorless liquid; yield: 900 mg (94%); R_f = 0.25 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 3619, 2961, 2843, 1688, 1590, 1513, 1454, 1257, 1142 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 2.0 Hz, 1 H), 6.80 (dd, *J* = 8.3, 2.0 Hz, 1 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 5.62 (dd, *J* = 6.4, 5.4 Hz, 2 H), 5.03–4.91 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.85–2.72 (m, 1 H), 1.65 (d, *J* = 4.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 148.0, 136.2, 133.6, 126.6, 118.1, 110.8, 109.2, 77.5, 76.8, 74.5, 55.7, 55.6, 17.5.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_3Na$: 231.0992; found: 231.0996.

(*E*)-4-{[4-(3,4-Dimethoxyphenyl)but-3-en-2-yl]oxy}-3-methoxybenzaldehyde (17)

To a stirred solution of alcohol **18** (350 mg, 1.68 mmol) in anhyd THF (20 mL) at 0 °C under N_2 atmosphere was added vanillin (**19o**; 255 mg, 1.68 mmol), Et_3N (254 mg, 2.52 mmol), and PPh_3 (660 mg, 2.52 mmol). Subsequently, DEAD was added to the reaction mixture (438 mg, 2.52 mmol) over a period of 30 min. The resulting reaction mixture was allowed to warm to rt and stirred for the next 24 h. After complete conversion of the starting material (monitored by TLC), excess of THF was evaporated under reduced pressure. The residue was purified over silica gel column chromatography [before packing the column, 100–200 mesh silica gel was neutralized with 1% Et_3N in hexane (50 mL)] to afford the Mitsunobu product **17** as a colorless liquid; yield: 520 mg (91%); R_f = 0.50 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 2967, 1703, 1591, 1513, 1456, 1259, 1142, 1071 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.76 (s, 1 H), 7.41–7.31 (m, 2 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.93–6.83 (m, 2 H), 6.75 (d, *J* = 8.3 Hz, 1 H), 6.53 (d, *J* = 16.1 Hz, 1 H), 6.13 (dd, *J* = 6.8, 16.1 Hz, 1 H), 5.05 (quint, *J* = 6.4 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 1.58 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 153.0, 150.2, 149.1, 149.0, 131.4, 130.0, 129.1, 127.3, 126.5, 119.9, 113.8, 111.0, 109.4, 108.7, 76.1, 55.9, 55.88, 55.80, 21.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}O_5$: 343.1540; found: 343.1544.

(*E*)-3-[1-(3,4-Dimethoxyphenyl)but-2-en-1-yl]-4-hydroxy-5-methoxybenzaldehyde (16)

The Mitsunobu product **17** (400 mg, 1.17 mmol) was taken in a sealed tube and PhMe was added (5 mL) to it at rt under N_2 atmosphere. The resulting reaction mixture was heated to 148 °C and allowed to stir for 24 h. After complete conversion of the starting material (monitored by TLC), excess of PhMe was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [before packing the column, 100–200 mesh silica gel was neutralized

with 1% Et_3N in hexane (50 mL)] to afford the rearrangement product **16** as a colorless liquid; yield: 358 mg (89%); R_f = 0.45 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 3384, 2934, 2842, 1677, 1591, 1505, 1448, 1250, 11376, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.31 (s, 2 H), 6.95–6.65 (m, 3 H), 6.38 (br s, 1 H), 5.92 (ddd, *J* = 16.0, 7.0, 2.0 Hz, 1 H), 5.44 (ddd, *J* = 16.0, 7.0, 2.0 Hz, 1 H), 5.05 (d, *J* = 7.3 Hz, 1 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 1.75 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 148.9, 148.8, 147.6, 147.0, 135.4, 132.0, 130.4, 129.0, 127.5, 127.2, 120.2, 111.9, 111.0, 106.9, 56.3, 55.88, 55.85, 46.2, 18.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}O_5$: 343.1540; found: 343.1533.

(±)-Cassumunin C (7)[4,6]

To a stirred solution of B_2O_3 (10.0 mg, 0.146 mmol) was added diketone **13** (34 mg, 0.15 mmol) in anhyd EtOAc (3 mL) at rt under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 30 min, whereupon a yellow precipitate was observed. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehyde **16** (100 mg, 0.29 mmol), EtOAc (3 mL) and $B(OMe)_3$ (60 mg, 1.17 mmol), then reaction mixture was heated to 80 °C and allowed to stir for 30 min. After 30 min, piperidine [10 mg dissolved in EtOAc (0.5 mL), 0.012 mmol], was added dropwise at 80 °C to the mixture. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and stirred for 30 min at 80 °C. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 200–400 mesh) to afford cassumunin C (**7**) as a yellow colored solid foam; yield: 106 mg (65%); mp 89–91 °C; R_f = 0.35 (35% EtOAc in hexane, silica gel TLC).

IR (neat): 3398, 2935, 1575, 1502, 1436, 1260, 1132, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.07 (br s, 1 H), 7.57 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 16.0 Hz, 1 H), 7.09 (dd, *J* = 8.1, 2.2 Hz, 1 H), 7.03 (d, *J* = 1.5 Hz, 1 H), 6.97 (d, *J* = 1.7 Hz, 1 H), 6.95 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.76 (s, 2 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 6.43 (d, *J* = 16.0 Hz, 1 H), 6.08 (br s, 2 H), 5.91 (ddd, *J* = 15.0, 7.0, 1.5 Hz, 1 H), 5.80 (s, 1 H), 5.46 (ddd, *J* = 15.0, 7.0, 1.5 Hz, 1 H), 5.01 (br d, *J* = 7.3 Hz, 1 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 1.75 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.5, 183.1, 148.8, 147.9, 147.5, 146.9, 146.8, 145.4, 141.1, 140.5, 135.8, 132.3, 130.5, 127.7, 127.2, 126.7, 123.3, 122.9, 121.8, 121.5, 120.3, 114.9, 112.0, 111.0, 109.7, 107.3, 101.1, 56.1, 56.0, 55.9, 46.3, 18.1.

HRMS (ESI-TOF): *m*/*z* [M + K]$^+$ calcd for $C_{33}H_{34}O_8K$: 597.1885; found: 597.1895.

4-(But-2-en-1-yloxy)-3-methoxybenzaldehyde (12)[7]

Compound **12** was prepared according to the known literature procedure.[7] To a stirred solution of vanillin (**19o**; 1.0 g, 6.58 mmol) in anhyd DMF (10 mL) at 0 °C under N_2 atmosphere was added K_2CO_3 (1.82 g, 13.14 mmol). After stirring for 10 min at 0 °C, ~85% *trans*-crotyl bromide (1.15 g, 8.54 mmol) was added. The resulting mixture was allowed to warm to rt and stirred for next 1 h. Then it was quenched H_2O (30 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200–400 mesh) to afford the alkylation product mixture **12** as *E*:*Z* (81:19); colorless liquid; yield: 1.30 g (96%); R_f = 0.60 (10% EtOAc in hexane, silica gel TLC).

IR (neat): 2936, 1681, 1586, 1507, 1455, 1400, 1255, 1127, 973 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ (*E*:*Z* mixture) = 9.85–9.84 (m, 2 H), 7.52–7.37 (m, 4 H), 6.98 (d, *J* = 7.8 Hz, 2 H), 5.99–5.81 (m, 2 H), 5.81–5.61 (m, 2 H), 4.70–4.51 (m, 4 H), 3.93 (s, 6 H), 1.84–1.61 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 153.7, 149.9, 149.8, 131.8, 130.0, 130.0, 129.3, 126.7, 125.0, 124.7, 111.7, 109.1, 77.4, 77.1, 76.8, 69.7, 64.8, 56.0, 17.9, 13.4.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_3$: 207.1016; found: 207.1016.

3-(But-3-en-2-yl)-4-hydroxy-5-methoxybenzaldehyde (11)

The alkylation product **12** (390 mg, 1.89 mmol), was taken in a sealed tube and PhMe was added (1 mL) under N_2 atmosphere. The resulting reaction mixture was heated to 180 °C and stirred for 24 h. After complete conversion of the starting material (as monitored by TLC), excess of PhMe was evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel, 200–400 mesh) and isolated with 8–10% EtOAc in hexane as eluent to afford the rearrangement product **11** as a colorless liquid; yield: 372 mg (95%); R_f = 0.50 (10% EtOAc in hexane, silica gel TLC).

IR (neat): 3156, 2967, 1663, 1637, 1588, 1427, 1365, 1263, 1193, 1143, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.34 (d, *J* = 1.5 Hz, 1 H), 7.30 (d, *J* = 1.5 Hz, 1 H), 6.41 (br s, 1 H), 6.06 (ddd, *J* = 5.9, 10.5, 16.9 Hz, 1 H), 5.26–5.02 (m, 2 H), 3.98–3.93 (m, 4 H, OCH_3 merged with 1 H), 1.38 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 148.9, 146.9, 141.4, 131.4, 129.1, 125.8, 113.8, 106.8, 56.2, 35.7, 19.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_3$: 207.1016; found: 207.1019.

2-(But-3-en-2-yl)-4-formyl-6-methoxyphenyl *tert*-Butyl Carbonate (10)

To a stirred solution of the rearrangement product **11** (350 mg, 1.70 mmol) in anhyd CH_2Cl_2 (5 mL) under N_2 atmosphere was added DMAP (20 mg, 0.17 mmol), Et_3N (257 mg, 2.55 mmol), and Boc_2O (0.6 mL, 2.55 mmol) at 0 °C for 1 h. After complete conversion of the starting material (as monitored by TLC), all volatiles were evaporated under reduced pressure and the residue was purified by flash chromatography (silica gel, 200–400 mesh) to afford the Boc protected product **10** as a colorless liquid; yield: 502 mg (97%); R_f = 0.50 (10% EtOAc in hexane, silica gel TLC).

IR (neat): 2977, 1761, 1695, 1594, 1463, 1427, 1381, 1254, 1123, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.89 (s, 1 H), 7.33 (s, 1 H), 7.35 (s, 1 H), 5.95 (ddd, *J* = 6.1, 10.5, 17.1 Hz, 1 H), 5.15–5.00 (m, 2 H), 3.88 (s, 3 H), 3.79 (quint, *J* = 8.0 Hz, 1 H), 1.52 (s, 9 H), 1.34 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 152.2, 150.3, 143.0, 140.8, 139.4, 134.5, 123.6, 114.4, 108.6, 83.8, 56.2, 36.2, 27.5, 19.3.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}O_5$: 307.1540; found: 307.1547.

tert-Butyl (*E*)-{2-[4-(3,4-Dimethoxyphenyl)but-3-en-2-yl]-4-formyl-6-methoxyphenyl} Carbonate (8)

To a stirred solution of olefin **10** (200 mg, 0.65 mmol) in anhyd PhMe (5 mL) under N_2 atmosphere was added bromoveratrole (170 mg, 0.78 mmol), Cs_2CO_3 (425 mg, 1.30 mmol), $Pd(OAc)_2$ (29 mg, 0.13 mmol), and PPh_3 (70 mg, 0.26 mmol) at rt. The resulting reaction mixture was heated to 110 °C and stirred for 18 h. After complete conversion of the starting material (as monitored by TLC), the crude reaction mixture was filtered through a short Celite pad and the residue was purified by flash chromatography (silica gel 200–400 mesh) to afford the Heck coupled product **8** as a colorless liquid; yield: 242 mg (84%); R_f = 0.25 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2975, 1761, 1695, 1593, 1513, 1460, 1383, 1256, 1131, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.92 (s, 1 H), 7.44 (d, *J* = 1.5 Hz, 1 H), 7.37 (d, *J* = 1.5 Hz, 1 H), 6.94–6.85 (m, 2 H), 6.84–6.74 (m, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 6.20 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.99–3.93 (m, 1 H), 3.92 (s, 3 H), 3.90–3.85 (m, 6 H), 1.50 (s, 9 H), 1.48 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 152.3, 150.4, 149.0, 148.5, 143.1, 139.7, 134.6, 130.7, 130.3, 129.2, 123.6, 119.3, 111.1, 108.6, 83.9, 56.2, 55.9, 55.8, 35.7, 27.5, 20.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{31}O_7$: 443.2064; found: 443.2067.

tert-Butyl (*E*)-{4-Formyl-2-methoxy-6-[4-(2,4,5-trimethoxyphenyl)but-3-en-2-yl]phenyl} Carbonate (9)

To a stirred solution of olefin **10** (200 mg, 0.65 mmol) in anhyd PhMe (5 mL) under N_2 atmosphere was added 1-bromo-2,4,5-trimethoxybenzene (193 mg, 0.79 mmol), Cs_2CO_3 (425 mg, 1.30 mmol), $Pd(OAc)_2$ (29 mg, 0.13 mmol), and PPh_3 (69 mg, 0.26 mmol) at rt. Then, the resulting reaction mixture was heated to 110 °C and stirred for 15 h. After complete conversion of the starting material (as monitored by TLC), the crude reaction mixture was filtered through a short Celite pad and the residue was purified by flash chromatography (silica gel 200–400 mesh) to afford the Heck coupled product **9** as a colorless liquid; yield: 253 mg (82%); R_f = 0.25 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2970, 2841, 1760, 1696, 1595, 1511, 1457, 1386, 1260, 1130, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.92 (s, 1 H), 7.45 (d, *J* = 2.0 Hz, 1 H), 7.36 (d, *J* = 2.0 Hz, 1 H), 6.94 (s, 1 H), 6.78 (dd, *J* = 16.0, 2.0 Hz, 1 H), 6.49 (s, 1 H), 6.20 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.04–3.94 (m, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 1.51 (s, 9 H), 1.48 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.5, 152.3, 151.1, 150.5, 149.2, 143.4, 143.1, 140.2, 134.6, 130.9, 123.8, 123.6, 118.1, 109.7, 108.5, 97.8, 83.8, 56.7, 56.5, 56.2, 56.1, 36.2, 27.5, 20.2.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{33}O_8$: 473.2170; found: 473.2168.

(±)-Cassumunin A (5)[4,5] and *tert*-Butyl {2-[(*E*)-4-(3,4-Dimethoxyphenyl)but-3-en-2-yl]-4-[(1*E*,4*Z*,6*E*)-5-hydroxy-7-(4-hydroxy-3-methoxyphenyl)-3-oxohepta-1,4,6-trien-1-yl]-6-methoxyphenyl)} Carbonate (5a)

To a stirred solution of B_2O_3 (16.0 mg, 0.23 mmol) in anhyd EtOAc (5 mL) was added diketone **13**[10] (105 mg, 0.45 mmol) at rt under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 30 min, whereupon a yellow precipitate was observed. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehyde **8** (200 mg, 0.45 mmol), EtOAc (5 mL), and $B(OMe)_3$ (94 mg, 0.90 mmol) at the same temperature under N_2 atmosphere and the mixture was heated to 80 °C and stirred for 15 min. Then piperidine [19 mg dissolved in EtOAc (0.5 mL), 0.23 mmol] was added dropwise at the same temperature and stirred for 2 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and stirred for 30 min. The mixture was allowed to stir at 80 °C for 12 h. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200–400 mesh) to afford cassumunin A (**5**) and the *O*-Boc protected cassumunin A **5a**.

Compound 5

Yellow colored solid foam; yield: 80 mg (32%); mp 96–98 °C; R_f = 0.35 (35% EtOAc in hexane, silica gel TLC).

For the spectral data of **5**, vide infra.

Compound 5a

Yellow colored solid foam; yield: 138 mg (46%); mp 88–90 °C; R_f = 0.45 (35% EtOAc in hexane, silica gel TLC).

IR (neat): 3413, 2966, 2841, 1756, 1579, 1507, 1452, 1254, 1130, 1030 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.92 (br s, 1 H), 7.60 (d, *J* = 16.0 Hz, 1 H), 7.58 (d, *J* = 16.0 Hz, 1 H), 7.12 (dd, *J* = 8.1, 2.0 Hz, 1 H), 7.08 (d, *J* = 2.0 Hz, 1 H), 7.07–7.03 (m, 1 H), 7.00 (d, *J* = 2.0 Hz, 1 H), 6.96–6.86 (m, 3 H), 6.83–6.76 (m, 1 H), 6.53 (d, *J* = 16.0 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 6.21 (dd, *J* = 16.0, 6.1 Hz, 1 H), 5.93 (br s, 1 H), 5.83 (s, 1 H), 3.94–3.90 (m, 4 H, OCH_3 merged with 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 1.50 (s, 9 H), 1.45 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.4, 182.0, 151.8, 151.0, 149.0, 148.5, 148.0, 146.8, 141.0, 139.8, 139.3, 133.4, 131.2, 130.5, 128.8, 127.5, 124.0, 123.0, 121.8, 120.3, 119.3, 114.9, 111.1, 109.7, 108.9, 108.7, 101.4, 83.6, 56.1, 56.0, 55.9, 55.8, 35.8, 27.6, 20.0.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{38}H_{43}O_{10}$: 659.2851; found: 659.2846.

(±)-Cassumunin B (6)[4,5] and *tert*-Butyl {4-[(1*E*,4*Z*,6*E*)-5-Hydroxy-7-(4-hydroxy-3-methoxyphenyl)-3-oxohepta-1,4,6-trien-1-yl]-2-methoxy-6-[(*E*)-4-(2,4,5-trimethoxyphenyl)but-3-en-2-yl]phenyl} Carbonate (6a)

To a stirred solution of B_2O_3 (13 mg, 0.80 mmol) in anhyd EtOAc (5 mL) was added diketone **13**[10] (84 mg, 0.36 mmol) at rt under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 30 min, whereupon a yellow precipitate was observed. Excess of EtOAc was evaporated under reduced pressure and the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehyde **9** (170 mg, 0.36 mmol), EtOAc (5 mL), and $B(OMe)_3$ (75 mg, 0.72 mmol) at the same temperature and the mixture was stirred at 80 °C for 15 min. Then piperidine [15 mg dissolved in EtOAc (0.5 mL), 0.18 mmol] was added dropwise at the same temperature and stirred for 2 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and stirred for 30 min. The reaction mixture was allowed to stir from 80 °C for 12 h. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concen-

trated under reduced pressure. The residue was purified by silica gel flash column chromatography (200–400 mesh) to afford cassumunin B **6** and the *O*-Boc protected cassumunin B **6a**.

Compound 6

Yellow colored solid foam; yield: 10 mg (5%); mp 98–100 °C; R_f = 0.35 (35% EtOAc in hexane, silica gel TLC).

For the spectral data of **6**, vide infra.

Compound 6a

Yellow colored solid foam; yield: 120 mg (48%); mp 86–88 °C; R_f = 0.45 (35% EtOAc in hexane, silica gel TLC).

IR (neat): 3392, 2952, 2838, 1747, 1677, 1592, 1508, 1452, 1255, 1139, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.96 (br s, 1 H), 7.60 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 16.0 Hz, 1 H), 7.09 (dt, *J* = 1.8, 4.2 Hz, 2 H), 7.04–7.01 (m, 1 H), 7.00–6.94 (m, 2 H), 6.94–6.87 (m, 1 H), 6.84–6.74 (m, 1 H), 6.57–6.40 (m, 3 H), 6.21 (dd, *J* = 6.2, 15.8 Hz, 1 H), 6.04 (br s, 1 H), 5.82 (s, 1 H) 3.91 (s, 4 H, OCH_3 merged with 1 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 1.51 (s, 9 H), 1.46 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.3, 182.0, 151.7, 151.1, 151.0, 149.1, 148.0, 146.8, 143.4, 141.0, 139.9, 139.7, 139.6, 133.4, 131.4, 127.5, 123.9, 123.2, 122.9, 121.7, 120.4, 118.3, 114.9, 109.7, 108.8, 101.3, 97.9, 83.5, 56.7, 56.5, 56.1, 56.0, 55.9, 36.2, 27.5, 20.1.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{45}O_{11}$: 689.2956; found: 689.2946.

(*E*)-3-[4-(3,4-Dimethoxyphenyl)but-3-en-2-yl]-4-hydroxy-5-methoxybenzaldehyde (14)

To a stirred solution of compound **8** (100 mg, 0.23 mmol) in MeOH/H_2O (3:1, 2 mL) under N_2 atmosphere was added K_2CO_3 (280 mg, 2.03 mmol). Then, the resulting reaction mixture was heated to 80 °C and stirred for 8 h. After complete conversion of the starting material (as monitored by TLC), excess of MeOH was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200–400 mesh, 40% EtOAc in hexane) to afford **14** as a colorless liquid; yield: 75 mg (97%); R_f = 0.35 (33% EtOAc in hexane, silica gel TLC).

IR (neat): 2955, 1676, 1591, 1506, 1449, 1251, 1136, 1026, 964 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.41 (d, *J* = 1.5 Hz, 1 H), 7.30 (d, *J* = 2.2 Hz, 1 H), 6.94–6.86 (m, 2 H), 6.79 (d, *J* = 8.1 Hz, 1 H), 6.60 (br s, 1 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 6.29 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.10 (quint, *J* = 6.8 Hz, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 1.48 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 149.03, 149.01, 148.5, 147.0, 131.7, 131.4, 130.5, 129.1, 128.7, 125.6, 119.2, 111.2, 108.7, 106.9, 56.2, 55.9, 55.8, 35.3, 19.7.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}O_5$: 343.1540; found: 343.1546.

(*E*)-4-Hydroxy-3-methoxy-5-[4-(2,4,5-trimethoxyphenyl)but-3-en-2-yl]benzaldehyde (15)

To a stirred solution of compound **9** (80 mg, 0.17 mmol) in MeOH/H_2O (3:1, 2 mL), under N_2 atmosphere was added K_2CO_3 (210 mg, 1.50 mmol). Then the resulting reaction mixture was heated to 80 °C for 8 h. After complete conversion of the starting material (as monitored by TLC), excess of MeOH was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 200–400 mesh, 30% EtOAc in hexane) to afford **15** as a colorless liquid; yield: 59 mg (94%); R_f = 0.30 (33% EtOAc in hexane, silica gel TLC).

IR (neat): 2925, 1678, 1593, 1507, 1452, 1274, 1203, 1137, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 7.42 (d, *J* = 2.0 Hz, 1 H), 7.30 (d, *J* = 2.0 Hz, 1 H), 6.97 (s, 1 H), 6.78 (dd, *J* = 16.0, 1.5 Hz, 1 H), 6.49 (s, 1 H), 6.40 (br s, 1 H), 6.28 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.11 (quint, *J* = 8.0 Hz, 1 H), 3.96 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 1.49 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 151.1, 149.2, 148.9, 147.0, 143.4, 132.0, 131.6, 129.1, 125.9, 123.2, 118.3, 109.7, 106.8, 97.9, 56.7, 56.6, 56.3, 56.1, 35.9, 19.9.

HRMS (ESI-TOF): *m*/*z* [M + K]$^+$ calcd for $C_{21}H_{24}O_6K$: 411.1204; found: 411.1205.

(±)-Cassumunin A (5)[4,5]

To a stirred solution of B_2O_3 (7 mg, 0.01 mmol) was added diketone **13**[10] (48 mg, 0.20 mmol) in anhyd EtOAc (3 mL) was added at rt under N_2 atmosphere. Then the reaction mixture was heated to 80 °C and stirred for 30 min, whereupon a yellow precipitate was observed. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehyde **14** (60 mg, 0.17 mmol), EtOAc (3 mL), and $B(OMe)_3$ (35 mg, 0.34 mmol) at rt under N_2 atmosphere, then reaction mixture was heated to 80 °C for 15 min. Then piperidine [7 mg dissolved in EtOAc (0.5 mL), 0.08 mmol], was added dropwise at 80 °C and stirred for 2 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and the mixture was stirred for 30 min at 80 °C. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200–400 mesh, 45% EtOAc in hexane) to afford cassumunin A (**5**) as a yellow solid foam; yield: 63 mg (66%); mp 96–98 °C; R_f = 0.35 (35% EtOAc in hexane, silica gel TLC).

IR (neat): 3400, 2950, 2840, 1573, 1500, 1435, 1256, 1128, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.07 (br s, 1 H), 7.58 (d, *J* = 16.0 Hz, 1 H), 7.56 (d, *J* = 16.0 Hz, 1 H), 7.09 (d, *J* = 2.2 Hz, 1 H), 7.07 (s, 1 H), 7.01 (s, 1 H), 6.93 (s, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.79 (d, *J* = 8.8 Hz, 1 H), 6.46 (dd, *J* = 15.8, 7.0 Hz, 2 H), 6.38 (br s, 1 H), 6.29 (dd, *J* = 16.0, 5.9 Hz, 1 H), 6.12 (br s, 2 H), 5.80 (s, 1 H), 4.05 (quint, *J* = 8.0 Hz, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 1.46 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.4, 183.2, 149.0, 148.4, 147.9, 146.9, 146.7, 145.3, 141.0, 140.5, 131.9, 131.8, 130.7, 128.5, 127.6, 127.0, 122.7, 122.9, 121.7, 121.5, 119.2, 114.9, 111.2, 109.7, 108.7, 107.3, 101.2, 56.1, 56.0, 55.9, 35.5, 19.8.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{35}O_8$: 559.2326; found: 559.2341.

(±)-Cassumunin B (6)[4,5]

To a stirred solution of B_2O_3 (7.0 mg, 0.01 mmol) in anhyd EtOAc (3 mL) was added diketone **13**[10] (45 mg, 0.19 mmol) at rt under N_2 atmosphere. Then, the reaction mixture was heated to 80 °C and stirred for 30 min, whereupon a yellow precipitate was observed. Excess of

EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehyde **15** (60 mg, 0.16 mmol), EtOAc (3 mL), and $B(OMe)_3$ (34 mg, 0.32 mmol) at rt under N_2 atmosphere and the mixture was stirred at 80 °C for 15 min. Then, piperidine [7 mg, dissolved in EtOAc (0.5 mL), 0.08 mmol] was added dropwise at 80 °C and stirred for 2 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL), and the mixture was stirred for 30 min at 80 °C . The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 200–400 mesh, 45% EtOAc in hexane) to afford cassumunin B (**6**) as a yellow solid foam; yield: 58 mg (61%); mp 98–100 °C; R_f = 0.35 (35% EtOAc in hexane, silica gel TLC).

IR (neat): 3406, 2938, 2844, 1754, 1508, 1504, 1446, 1266, 1200, 1126, 1028 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.07 (br s, 1 H), 7.59 (d, *J* = 16.0 Hz, 1 H), 7.57 (d, *J* = 16.0 Hz, 1 H), 7.11 (d, *J* = 2.2 Hz, 1 H), 7.09 (s, 1 H), 7.03 (d, *J* = 1.5 Hz, 1 H), 6.99 (s, 1 H), 6.94 (d, *J* = 1.8 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.79 (dd, *J* = 16.1, 1.5 Hz, 1 H), 6.51 (s, 1 H), 6.46 (d, *J* = 16.0 Hz, 2 H), 6.30 (dd, *J* = 16.0, 6.6 Hz, 1 H), 6.14 (br s, 1 H), 6.05 (br s, 1 H), 5.80 (s, 1 H), 4.07 (quint, *J* = 8.0 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 1.48 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.5, 183.1, 151.1, 149.1, 147.9, 146.8, 146.7, 145.3, 143.5, 141.1, 140.4, 132.2, 132.1, 127.7, 127.0, 126.9, 122.8, 121.7, 121.5, 118.5, 114.8, 109.7, 107.3, 101.09, 97.94, 56.8, 56.6, 56.1 (2 C), 55.95, 36.0, 20.0.

HRMS (ESI-TOF): *m*/*z* $[M + K]^+$ calcd for $C_{34}H_{36}O_9K$: 627.1991; found: 627.1982.

Compounds 1a–k; General Procedure A

To a stirred solution of acetylacetone (1.0 equiv) in anhyd EtOAc (2.5 mL) was added B_2O_3 (0.50 equiv). The solution was stirred for 30 min at 80 °C to get a white boric anhydride complex. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane (2 mL), and dried under reduced pressure. To the resulting boric anhydride complex was added the respective aldehyde **19a–k** (2.0 equiv), EtOAc (2 mL), and $B(OMe)_3$ (2.0 equiv) at ambient temperature under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 15 min to obtain a transparent solution. After 15 min, *n*-$BuNH_2$ [0.2 equiv, dissolved in EtOAc (0.5 mL)] was added dropwise at the same temperature. Then the reaction allowed to stir for 24 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and stirred for 30 min. The aqueous layer was extracted with EtOAc (3 × 15–25 mL), the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100–200 mesh), by using combinations of solvents such as MeOH, EtOAc, CH_2Cl_2, and hexane as eluents to afford **1a–k**.

(1*E*,4*Z*,6*E*)-1,7-Bis(2,4-dichlorophenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1a)

General procedure **A** described above was followed when acetylacetone (34 mg, 0.35 mmol), B_2O_3 (12 mg, 0.17 mmol), and $B(OMe)_3$ (71 mg, 0.69 mmol) reacted with 2,4-dichlorobenzaldehyde (**19a**; 120 mg, 0.69 mmol) and *n*-$BuNH_2$ (5 mg, 0.07 mmol) at 80 °C to afford **1a** as a yellow solid; yield: 71 mg (49%); mp 177–179 °C; R_f = 0.50 (15% CH_2Cl_2 in hexane, silica gel TLC).

IR (neat): 3088, 2355, 2204, 2162, 1949, 1635, 1578, 1468, 1384, 1306, 1140, 1103, 1048, 970, 1864, 815 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.67 (br s, 1 H), 7.98 (d, *J* = 16.0 Hz, 2 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 2.4 Hz, 2 H), 7.29–7.27 (m, 2 H), 6.60 (d, *J* = 15.8 Hz, 2 H), 5.88 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.8, 136.2, 135.7, 135.4, 131.7, 130.1, 128.2, 127.5, 126.7, 102.0.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{13}Cl_4O_2$ $[M + H]^+$: 412.9664; found: 412.9655.

(1*E*,4*Z*,6*E*)-1,7-Bis(2-ethoxy-3-methoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1b)

General procedure **A** described above was followed when acetylacetone (28 mg, 0.28 mmol), B_2O_3 (10 mg, 0.14 mmol), and $B(OMe)_3$ (40 mg, 0.55 mmol) reacted with 2-ethoxy-3-methoxybenzaldehyde (**19b**; 100 mg, 0.55 mmol) and *n*-$BuNH_2$ (4 mg, 0.06 mmol) at 80 °C h to afford **1b** as a yellow solid; yield: 68 mg (57%); mp 100–102 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2974, 2934, 2892, 1621, 1573, 1471, 1444, 1386, 1296, 1259, 1212, 1179, 1137, 1070, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.89 (br s, 1 H), 7.99 (d, *J* = 16.0 Hz, 2 H), 7.19 (d, *J* = 7.8 Hz, 2 H), 7.05 (t, *J* = 8.0 Hz, 2 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 6.68 (d, *J* = 16.0 Hz, 2 H), 5.86 (s, 1 H), 4.08 (q, *J* = 7.3 Hz, 4 H), 3.86 (s, 6 H), 1.42 (t, *J* = 7.3 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.6, 153.3, 147.6, 135.6, 129.5, 125.3, 124.0, 119.1, 113.7, 101.4, 69.7, 55.8, 15.6.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{29}O_6$ $[M + H]^+$: 425.1959; found: 425.1957.

(1*E*,4*Z*,6*E*)-1,7-Bis(3-bromophenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1c)[17]

General procedure **A** described above was followed when acetylacetone (40 mg, 0.40 mmol), B_2O_3 (14 mg, 0.20 mmol), and $B(OMe)_3$ (83 mg, 0.81 mmol) reacted with 3-bromobenzaldehyde (**19c**; 150 mg, 0.81 mmol) and *n*-$BuNH_2$ (6 mg, 0.08 mmol) at 80 °C to afford **1c** as a yellow solid; yield: 90 mg (52%); mp 139–141 °C; R_f = 0.60 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 3057, 2340, 2150, 1633, 1563, 1471, 1412, 1306, 1270, 1199, 1137, 1069 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.75 (br s, 1 H), 7.69 (s, 2 H), 7.57 (d, *J* = 15.5 Hz, 2 H), 7.47 (dd, *J* = 15.8, 7.7 Hz, 4 H), 7.28–7.24 (m, 2 H), 6.60 (d, *J* = 15.8 Hz, 2 H), 5.83 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9, 139.0, 137.0, 132.9, 130.6, 130.4, 126.9, 125.2, 123.1, 102.3.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{15}Br_2O_2$ $[M + H]^+$: 432.9433; found: 432.9428.

(1*E*,4*Z*,6*E*)-1,7-Bis(4-ethylphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1d)

General procedure **A** described above was followed when acetylacetone (112 mg, 1.1 mmol), B_2O_3 (39 mg, 0.56 mmol), and $B(OMe)_3$ (230 mg, 2.23 mmol) reacted with 4-ethylbenzaldehyde (**19d**; 300 mg, 2.23 mmol) and *n*-$BuNH_2$ (16 mg, 0.22 mmol) at 80 °C to afford **1d** as a yellow solid; yield: 182 mg (49%); mp 169–171 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2966, 2389, 2304, 2196, 2121, 2068, 2002, 1940, 1628, 1594, 1325, 1182, 1138 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.99 (br s, 1 H), 7.64 (d, *J* = 15.8 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 4 H), 7.22 (m, 4 H), 6.58 (d, *J* = 15.9 Hz, 2 H), 5.8 (s, 1 H), 2.67 (q, *J* = 7.6 Hz, 4 H), 1.24 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.4, 146.8, 140.5, 132.5, 128.5, 128.2, 123.1, 101.6, 28.8, 15.3.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{25}O_2$ [M + H]$^+$: 333.1849; found: 333.1847.

(1*E*,4*Z*,6*E*)-1,7-Di(biphenyl-4-yl)-5-hydroxyhepta-1,4,6-trien-3-one (1e)

General procedure **A** described above was followed when acetylacetone (36 mg, 0.36 mmol), B_2O_3 (12 mg, 0.18 mmol), and $B(OMe)_3$ (74 mg, 0. 72 mmol) reacted with [1,1′-biphenyl]-4-carbaldehyde (**19e**; 130 mg, 0.72 mmol) and *n*-$BuNH_2$ (5 mg, 0.07 mmol) at 80 °C to afford **1e** as a yellow solid; yield: 95 mg (62%); mp 258–260 °C; R_f = 0.50 (15% CH_2Cl_2 in hexane, silica gel TLC).

IR (neat): 3033, 2924, 2853, 1636, 1596, 1553, 1485, 1453, 1408, 1136 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.96 (br s, 1 H), 7.37 (d, *J* = 15.6 Hz, 2 H), 7.65–7.62 (m, 12 H), 7.46 (t, *J* = 7.3 Hz, 4 H), 7.38 (d, *J* = 7.3 Hz, 2 H), 6.68 (d, *J* = 15.7 Hz, 2 H), 5.88 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.2, 142.8, 140.1, 133.9, 128.9, 128.6, 127.8, 127.5, 127.0, 123.9, 101.9.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{31}H_{25}O_2$ [M + H]$^+$: 429.1849; found: 429.1857.

(1*E*,4*Z*,6*E*)-1,7-Bis(2-bromophenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1f)

General procedure **A** described above was followed when acetylacetone (41 mg, 0.40 mmol), B_2O_3 (14 mg, 0.20 mmol), and $B(OMe)_3$ (83 mg, 0.81 mmol) reacted with 2-bromobenzaldehyde (**19f**; 150 mg, 0.81 mmol) and *n*-$BuNH_2$ (6 mg, 0.08 mmol) at 80 °C to afford **1f** as a yellow solid; yield: 105 mg (60%); mp 138–140 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2089, 2050, 1994, 1629, 1556, 1523, 1463, 1431, 1021 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.71 (br s, 1 H), 8.02 (d, *J* = 15.8 Hz, 2 H), 7.63 (dd, *J* = 9.9, 8.4 Hz, 4 H), 7.33 (t, *J* = 7.7 Hz, 2 H), 7.25–7.19 (m, 2 H), 6.57 (dd, *J* = 15.8, 1.7 Hz, 2 H), 5.91 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.0, 139.1, 134.9, 133.5, 131.0, 127.7, 126.7, 125.6, 101.7.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{14}Br_2O_2Na$ [M + Na]$^+$: 454.9253; found: 454.9267.

(1*E*,4*Z*,6*E*)-5-Hydroxy-1,7-bis(2-methoxynaphthalen-1-yl)hepta-1,4,6-trien-3-one (1g)[17]

General procedure **A** described above was followed when acetylacetone (27 mg, 0.27 mmol), B_2O_3 (9 mg, 0.14 mmol), and $B(OMe)_3$ (55 mg, 0.54 mmol) reacted with 2-methoxy-1-naphthaldehyde[19] (**19g**; 100 mg, 0.54 mmol) and *n*-$BuNH_2$ (4 mg, 0.05 mmol) at 80 °C to afford **1g** as a yellow solid; yield: 75 mg (64%); mp 155–157 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2932, 2849, 2509, 2357, 2197, 1616, 1553, 1510, 1463, 1261, 1141, 1093 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 16.25 (br s, 1 H), 8.36 (d, *J* = 16.0 Hz, 2 H), 8.25 (d, *J* = 8.8 Hz, 2 H), 7.84–7.76 (m, 4 H), 7.52 (ddd, *J* = 8.6, 6.6, 1.5 Hz, 2 H), 7.37 (t, *J* = 7.8 Hz, 2 H), 7.28–7.23 (m, 2 H), 6.91 (d, *J* = 16.8 Hz, 2 H), 5.92 (s, 1 H), 4.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.1, 156.8, 133.5, 132.8, 131.5, 129.3, 129.0, 128.6, 127.4, 123.9, 123.5, 117.4, 112.8, 102.4, 56.2.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{25}O_4$ [M + H]$^+$: 437.1747; found: 437.1745.

(1*E*,4*Z*,6*E*)-1,7-Bis(2-bromo-3,4,5-trimethoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1h)

General procedure **A** described above was followed when acetylacetone (22 mg, 0.22 mmol), B_2O_3 (7 mg, 0.11 mmol), and $B(OMe)_3$ (45 mg, 0.44 mmol) reacted with 2-bromo-3,4,5-trimethoxybenzaldehyde[20] (**19h**; 120 mg, 0.44 mmol) and *n*-$BuNH_2$ (4 mg, 0.05 mmol) at 80 °C to afford **1h** as a yellow solid; yield: 98 mg (72%); mp 137–139 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2937, 2834, 1625, 1568, 1477, 1424, 1391, 1342, 1285, 1200, 1106, 1004 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.74 (br s, 1 H), 7.99 (d, *J* = 16.0 Hz, 2 H), 6.95 (s, 2 H), 6.47 (d, *J* = 16.0 Hz, 2 H), 5.93 (s, 1 H), 3.92 (s, 6 H), 3.90 (6 H), 3.89 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.0, 152.8, 151.2, 144.8, 139.1, 130.2, 126.0, 113.2, 105.9, 101.0, 61.2, 61.0, 56.2.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{27}Br_2O_8$ [M + H]$^+$: 613.0067; found: 613.0062.

(1*E*,4*Z*,6*E*)-5-Hydroxy-1,7-bis(2,4,6-tribromo-3-methoxyphenyl)-hepta-1,4,6-trien-3-one (1i)

General procedure **A** described above was followed when acetylacetone (27 mg, 0.27 mmol), B_2O_3 (9 mg, 0.13 mmol), and $B(OMe)_3$ (56 mg, 0.54 mmol) reacted with 2,4,6-tribromo-3-methoxybenzaldehyde[21] (**19i**; 200 mg, 0.54 mmol) and *n*-$BuNH_2$ (4 mg, 0.05 mmol) at 80 °C to afford **1i** as a yellow solid; yield: 150 mg (69%); mp 209–211 °C; R_f = 0.50 (30% MeOH in CH_2Cl_2, silica gel TLC).

IR (neat): 3409, 2926, 2253, 2127, 1643, 1448, 1411, 1350, 1022 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6, 3:1): δ = 7.69 (s, 2 H), 7.38 (d, *J* = 16.0 Hz, 2 H), 6.41 (d, *J* = 16.1 Hz, 2 H), 5.77 (s, 1 H), 3.73 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6, 3:1): δ = 182.2, 154.1, 138.1, 136.8, 135.9, 132.4, 120.3, 118.1, 102.6, 60.5.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{15}Br_6O_4$ [M + H]$^+$: 804.6065; found: 804.6035.

(1*E*,3*Z*,6*E*)-3-Hydroxy-5-oxohepta-1,3,6-triene-1,7-diyl)bis(2-methoxy-5,1-phenylene) Diacetate (1j)

General procedure **A** described above was followed when acetylacetone (39 mg, 0.39 mmol), B_2O_3 (13 mg, 0.19 mmol), and $B(OMe)_3$ (79 mg, 0.77 mmol) reacted with 5-formyl-2-methoxyphenyl acetate[22] (**19j**; 150 mg, 0.77 mmol) and *n*-$BuNH_2$ (6 mg, 0.08 mmol) at 80 °C to afford **1j** as a yellow solid; yield: 93 mg (53%); mp 155–157 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 2941, 1763, 1630, 1593, 1508, 1460, 1415, 1369, 1297, 1259, 1195, 1154, 1125, 1031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 15.99 (br s, 1 H), 7.54 (d, *J* = 16.0 Hz, 2 H), 7.34 (dd, *J* = 8.4, 1.8 Hz, 2 H), 7.26 (d, *J* = 2.2 Hz, 2 H), 6.93 (d, *J* = 8.1 Hz, 2 H), 6.43 (d, *J* = 16.0 Hz, 2 H), 5.71 (s, 1 H), 3.83 (s, 6 H), 2.32 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.1, 168.8, 151.3, 140.0 139.3, 128.2, 127.8, 127.7, 122.7, 121.8, 101.7, 55.9, 20.6.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{25}O_8$ [M + H]$^+$: 453.1544; found: 453.1542.

(1*E*,4*Z*,6*E*)-1,7-Bis(5-bromo-2,4-dimethoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (1k)

General procedure **A** described above was followed when acetylacetone (41 mg, 0.40 mmol), B_2O_3 (14 mg, 0.20 mmol), and $B(OMe)_3$ (83 mg, 0.81 mmol) reacted with 5-bromo-2,4-dimethoxybenzaldehyde[23] (**19k**; 200 mg, 0.81 mmol) and *n*-$BuNH_2$ (6 mg, 0.08 mmol) at 80 °C to afford **1k** as a yellow solid; yield: 114 mg (51%); mp 192–195 °C; R_f = 0.40 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 2941, 2842, 1589, 1498, 1460, 1386, 1295, 1208, 1144, 1059, 1026, 972, 816 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.08 (br s, 1 H), 7.83 (d, *J* = 16.0 Hz, 2 H), 7.70 (s, 2 H), 6.54 (d, *J* = 16.0 Hz, 2 H), 6.44 (s, 2 H), 5.77 (s, 1 H), 3.93 (s, 6 H), 3.31 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.4, 159.0, 158.0, 133.8, 132.1, 123.0, 118.1, 102.6, 101.6, 96.0, 56.3, 55.8.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{23}Br_2O_6$ $[M + H]^+$: 552.9856; found: 552.9844.

Compounds 13 and 13a; General Procedure B

To a stirred solution of acetylacetone (2.2 equiv) in anhyd EtOAc (30 mL) was added B_2O_3 (2.0 equiv). The solution was stirred for 30 min at 80 °C to get a white boric anhydride complex. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added aldehydes **19o** or **19g**[19] (1.0 equiv) EtOAc (30 mL) and $B(OMe)_3$ (0.4 equiv) at rt under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 15 min to obtain a transparent solution. After 15 min, *n*-$BuNH_2$ [0.35 equiv dissolved in EtOAc (2.0 mL)], was added dropwise at the same temperature. Afterwards, the mixture was heated to 110 °C for 3 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aqa 10% HCl (5 mL) and stirred for 30 min. The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100–200 mesh) using EtOAc and hexane as eluents to afford **13** and **13a**.

(1*E*,4*Z*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)hexa-1,4-dien-3-one (13)[10]

General procedure **B** described above was followed when acetylacetone (3.3 mL 32.0 mmol), B_2O_3 (2.0 g, 28.94 mmol), and $B(OMe)_3$ (600 mg, 5.90 mmol) reacted with vanillin (**19o**; 2.2 g 14.47 mmol) and *n*-$BuNH_2$ (390 mg, 5.06 mmol) at 80 to 110 °C afford **13** as a yellow solid; yield: 1.7 g (50%); mp 140–142 °C (Lit.[10] mp 143.5–145.5 °C); R_f = 0.50 (20% EtOAc in hexane, silica gel TLC).

IR (neat): 3213, 1626, 1566, 1509, 1421, 1272, 1148, 1021, 930 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.49 (br s, 1 H), 7.53 (d, *J* = 16.1 Hz, 1 H), 7.17–7.04 (m, 1 H), 7.01 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.32 (d, *J* = 15.4 Hz, 1 H), 6.01 (br s, 1 H), 5.63 (s, 1 H), 3.92 (s, 3 H), 2.15 (s, 3 H).

(1*E*,4*Z*)-5-Hydroxy-1-(2-methoxynaphthalen-1-yl)hexa-1,4-dien-3-one (13a)

General procedure **B** described above was followed when acetylacetone (2.6 mL 25.52 mmol), B_2O_3 (1.6 g, 23.20 mmol), and $B(OMe)_3$ (480 mg, 4.64 mmol) reacted with 2-methoxy-1-naphthaldehyde[19] (**19g**; 2.160 g, 11.60 mmol) and *n*-$BuNH_2$ (300 mg, 4.06 mmol) at 80 to 110 °C to afford **13a** as a yellow solid; yield: 1.0 g (32%); mp 142–144 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 3056, 2839, 1620, 1581, 1506, 1459, 1430, 1336, 1246, 1148, 1083, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.52 (br s, 1 H), 8.34–8.09 (m, 2 H), 7.88–7.72 (m, 2 H), 7.52 (ddd, *J* = 1.5, 7.0, 8.7 Hz, 1 H), 7.37 (dt, *J* = 1.0, 7.3 Hz, 1 H), 7.33–7.15 (m, 1 H), 6.82 (d, *J* = 16.1 Hz, 1 H), 5.69 (s, 1 H), 4.00 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 177.9, 156.5, 133.0, 132.7, 131.3, 129.0, 128.6, 127.9, 127.3, 123.9, 123.3, 117.4, 112.8, 101.2, 56.2, 27.0.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{17}H_{17}O_3$ $[M + H]^+$: 269.1172; found: 269.1170.

Compounds 1l–r; General Procedure C

To a stirred solution of diketone derivative **13** or **13a** (1.0 equiv) in anhyd EtOAc (2.5 mL) was added B_2O_3 (2.0 equiv). The solution was stirred for 30 min at 80 °C to get an orange-red boric anhydride complex. Excess of EtOAc was evaporated under reduced pressure, the residue was rinsed with hexane, and dried under reduced pressure. To the resulting boric anhydride complex was added the respective aldehyde **19h**,**l**,**m**,**n**,**e** or **11** (1.0 equiv) EtOAc (2 mL) and $B(OMe)_3$ (2.0 equiv) at r.t. under N_2 atmosphere and the reaction mixture was heated to 80 °C and stirred for 15 min to obtain a transparent orange-red solution. After 15 min, piperidine [0.4 equiv dissolved in EtOAc (0.5 mL)] was added dropwise at the same temperature. Then the reaction mixture was stirred for 2 h. After complete conversion of the starting material (as monitored by TLC), the reaction was quenched with aq 10% HCl (5 mL) and stirred for 30 min. The aqueous layer was extracted with EtOAc (3 × 15–25 mL), the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100–200 mesh) using EtOAc and hexane as eluents to afford **1l–r**.

(1*E*,4*Z*,6*E*)-7-(2-Bromo-3,4,5-trimethoxyphenyl)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one (1l)

General procedure **C** described above was followed when compound **13** (120 mg, 0.51 mmol), B_2O_3 (70 mg, 1.02 mmol), and $B(OMe)_3$ (105 mg, 1.02 mmol) reacted with 2-bromo-3,4,5-trimethoxybenzaldehyde[20] (**19h**; 140 mg, 0.51 mmol) and piperidine (17 mg, 0.20 mmol) at 80 °C to afford **1l** as a yellow solid; yield: 160 mg (63%); mp 149–151 °C; R_f = 0.50 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 3403, 2939, 2054, 1625, 1577, 1511, 1475, 1427, 1390, 1344, 1273, 1205, 1166, 1134, 1110, 1004 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.91 (br s, 1 H), 7.91 (d, *J* = 15.8 Hz, 1 H), 7.61 (d, *J* = 15.8 Hz, 1 H), 7.12 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.05 (d, *J* = 1.0 Hz, 1 H), 6.96–6.92 (m, 2 H), 6.48 (dd, *J* = 15.40, 9.5 Hz, 2 H), 5.93 (br s, 1 H), 5.87 (s, 1 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.3, 181.9, 152.8, 151.2, 148.0, 146.8, 144.7, 141.2, 138.6, 130.4, 127.5, 126.0, 123.0, 121.7, 114.8, 113.1, 109.6, 105.9, 101.2, 61.2, 61.0, 56.2, 55.9.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{24}BrO_7$ $[M + H]^+$: 491.0700; found: 491.0696.

(1*E*,4*Z*,6*E*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(2,4,6-tribromo-3-hydroxyphenyl)hepta-1,4,6-trien-3-one (1m)

General procedure **C** described above was followed when compound **13** (80 mg, 0.34 mmol), B_2O_3 (47 mg, 0.68 mmol), and $B(OMe)_3$ (70 mg, 0.68 mmol) reacted with 2,4,6-tribromo-3-hydroxybenzalde-

hyde[21] (**19l**; 122 mg, 0.34 mmol) and piperidine (12 mg, 0.14 mmol) at 80 °C to afford **1m** as a yellow solid; yield: 120 mg (61%); mp 99–101 °C; R_f = 0.50 (50% EtOAc in hexane, silica gel TLC).

IR (neat): 3482, 3073, 2962, 1627, 1572, 1510, 1432, 1374, 1268, 1204, 1175, 1133, 1029 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$/DMSO-d_6, 3:1): δ = 15.98 (br s, 1 H), 8.78 (br s, 1 H), 8.30 (br s, 1 H), 7.94 (d, *J* = 3.0 Hz, 1 H), 7.82 (d, *J* = 16.0 Hz, 1 H), 7.68 (dd, *J* = 16.0, 2.6 Hz, 1 H), 7.56 (d, *J* = 3.0 Hz, 1H), 7.29 (s, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 16.0 Hz, 2 H), 6.06 (s, 1 H), 4.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6, 3:1): δ = 186.0, 179.2, 150.7, 149.1, 147.6, 142.0, 137.2, 136.1, 135.1, 132.3, 126.6, 123.2, 121.1, 115.5, 113.1, 112.6, 111.1, 110.1, 102.0, 55.8.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{20}H_{16}Br_3O_5$ $[M + H]^+$: 572.8542; found: 572.8517.

(1*E*,4*Z*,6*E*)-1-(2-Bromo-3,4,5-trimethoxyphenyl)-5-hydroxy-7-(2-methoxynaphthalen-1-yl)hepta-1,4,6-trien-3-one (1n)

General procedure **C** described above was followed when compound **13a** (100 mg, 0.37 mmol), B_2O_3 (52 mg, 0.75 mmol), and $B(OMe)_3$ (77 mg, 0.75 mmol) reacted with 2-bromo-3,4,5-trimethoxybenzaldehyde[20] (**19h**; 102 mg, 0.37 mmol) and piperidine (13 mg, 0.15 mmol) at 80 °C to afford **1n** as a yellow solid; yield: 126 mg (65%); mp 118–122 °C; R_f = 0.40 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 2939, 2839, 1769, 1620, 1560, 1512, 1473, 1428, 1391, 1344, 1269, 1200, 1105, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 15.98 (br s, 1 H), 8.37 (d, *J* = 16.0 Hz, 1 H), 8.24 (d, *J* = 8.6 Hz, 1 H), 8.01 (d, *J* = 15.6 Hz, 1 H), 7.86 (d, *J* = 9.2 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.54–7.51 (m, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.31–7.25 (m, 1 H), 7.02–6.97 (m, 2 H), 6.51 (d, *J* = 15.5 Hz, 1 H), 5.94 (s, 1 H), 4.03 (s, 3 H), 3.89 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 182.3, 156.9, 152.8, 151.2, 144.7, 138.6, 134.1, 132.8, 131.7, 130.5, 129.1, 129.0, 128.67, 127.4, 126.2, 123.9, 123,4, 117.2, 113.2, 112.7, 105.9, 101.8, 61.2, 61.0, 56.28, 56.23.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{27}H_{26}BrO_6$ $[M + H]^+$: 525.0907; found: 525.0901.

(1*E*,4*Z*,6*E*)-5-Hydroxy-7-(2-methoxynaphthalen-yl)-1-(3,4,5-trimethoxyphenyl)hepta-1,4,6-trien-3-one (1o)

General procedure **C** described above was followed when compound **13a** (100 mg, 0.37 mmol) B_2O_3 (52 mg, 0.75 mmol), and $B(OMe)_3$ (77 mg, 0.75 mmol) reacted with 3,4,5-trimethoxybenzaldehyde (**19m**; 72 mg, 0.37 mmol) and piperidine (13 mg, 0.15 mmol) at 80 °C to afford **1o** as a yellow solid; yield: 81 mg (49%); mp 145–148 °C; R_f = 0.50 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 2938, 2837, 2312, 2270, 2188, 2168, 1985, 1625, 1582, 1504, 1460, 1263, 1129 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.08 (br s, 1 H), 8.35 (d, *J* = 15.9 Hz, 1 H), 8.22 (d, *J* = 8.6 Hz, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 15.8 Hz, 1 H), 7.53–7.50 (m, 1 H), 7.40–7.36 (m, 1 H), 7.29–7.25 (m, 1 H), 6.98 (d, *J* = 16.0 Hz, 1 H), 6.77 (s, 2 H), 6.55 (d, *J* = 15.6 Hz, 1 H), 5.89 (s, 1 H), 4.01 (s, 3 H), 3.89 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2, 182.9, 156.8, 153.4, 140.2, 139.9, 133.8, 132.8, 131.6, 130.6, 129.1, 129.0, 128.6, 127.4, 123.9, 123.6, 123.4, 117.2, 112.7, 105.1, 102.0, 61.0, 56.2, 56.1.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{27}H_{27}O_6$ $[M + H]^+$: 447.1802; found: 447.1799.

(1*E*,4*Z*,6*E*)-1-(2,4-Dimethoxyphenyl)-5-hydroxy-7-(2-methoxynaphthalen-1-yl)hepta-1,4,6-trien-3-one (1p)

General procedure **C** described above was followed when compound **13a** (80 mg, 0.30 mmol), B_2O_3 (41 mg, 0.60 mmol), and $B(OMe)_3$ (62 mg, 0.60 mmol) reacted with 2,4-dimethoxybenzaldehyde (**19n**; 50 mg, 0.30 mmol) and piperidine (10 mg, 0.12 mmol) at 80 °C to afford **1p** as a yellow solid; yield: 62 mg (50%); mp 141–144 °C; R_f = 0.50 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 3056, 3004, 2939, 2837, 1599, 1506, 1460, 1269, 1206, 1130, 1033, 968 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.21 (br s, 1 H), 8.31 (d, *J* = 16.0 Hz, 1 H), 8.24 (d, *J* = 8.6 Hz, 1 H), 7.93 (d, *J* = 15.9 Hz, 1 H), 7.85–7.78 (m, 2 H), 7.54–7.48 (m, 2 H), 7.38 (t, *J* = 7.7 Hz, 1 H), 7.30 (d, *J* = 9.5 Hz, 1 H), 6.96 (d, *J* = 16.0 Hz, 1 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.52 (dd, *J* = 8.8, 2.2 Hz, 1 H), 6.46 (d, *J* = 2.2 Hz, 1 H), 5.86 (s, 1 H), 4.02 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.0, 182.7, 162.7, 159.9, 156.6, 136.0, 133.0, 132.8, 131.3, 130.2, 129.4, 129.1, 128.6, 127.3, 123.9, 123.5, 122.5, 117.6, 117.2, 112.8, 105.4, 101.7, 98.4, 56.2, 55.52, 55.50.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{26}H_{24}O_5Na$ $[M + Na]^+$: 439.1516; found: 439.1516.

(1*E*,4*Z*,6*E*)-7-(Biphenyl-4-yl)-5-hydroxy-1-(2-methoxynaphthalen-1-yl)hepta-1,4,6-trien-3-one (1q)

General procedure **C** described above was followed when compound **13a** (85 mg, 0.32 mmol), B_2O_3 (44 mg, 0.63 mmol), and $B(OMe)_3$ (65 mg, 0.63 mmol) reacted with [1,1′-biphenyl]-4-carbaldehyde (**19e**; 58 mg, 0.32 mmol) and piperidine (11 mg, 0.13 mmol) at 80 °C to afford **1q** as a yellow solid; yield: 68 mg (49%); mp 187–190 °C; R_f = 0.50 (15% EtOAc in hexane, silica gel TLC).

IR (neat): 3035, 2938, 2839, 2160, 1622, 1557, 1510, 1463, 1348, 1267, 1184, 1138, 972 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 16.0 (br s, 1 H), 8.37 (d, *J* = 15.9 Hz, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 9.0 Hz, 1 H), 7.76 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 15.9 Hz, 1 H), 7.63–7.61 (m, 6 H), 7.54 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1 H), 7.46 (t, *J* = 7.3 Hz, 2 H), 7.41–7.35 (m, 2 H), 7.30 (d, *J* = 9.0 Hz, 1 H), 7.01 (d, *J* = 16.0 Hz, 1 H), 6.68 (d, *J* = 16.0 Hz, 1 H), 5.91 (s, 1 H), 4.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.5, 182.8, 156.8, 142.7, 140.2, 139.7, 134.1, 133.9,132.8, 131.6, 129.2, 129.0, 128.9, 128.66, 128.60, 127.8, 127.5, 127.4, 127.0, 124.1, 123.9, 123.4, 117.3, 112.7, 102.1, 56.2.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{25}O_3$ $[M + H]^+$: 433.1798; found: 433.1796.

(1*E*,4*Z*,6*E*)-7-[3-(But-3-en-2-yl)-4-hydroxy-5-methoxyphenyl]-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-trien-3-one (1r)

General procedure **C** described above was followed when compound **13** (50 mg, 0.21 mmol), B_2O_3 (30 mg, 0.43 mmol), and $B(OMe)_3$ (44 mg, 0.43 mmol) reacted with 3-(but-3-en-2-yl)-4-hydroxy-5-methoxybenzaldehyde (**11**; 43 mg, 0.21 mmol) and piperidine (7.0 mg, 0.08 mmol) at 80 °C to afford **1r** as a yellow solid; yield: 52 mg (59%); mp 179–181 °C; R_f = 0.50 (30% EtOAc in hexane, silica gel TLC).

IR (neat): 3417, 2961, 1578, 1503, 1442, 1278, 1205, 1136, 965, 837 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 16.37 (br s, 1 H), 9.69 (s, 1 H), 9.25 (s, 1 H), 7.56 (dd, *J* = 16.1, 2.2 Hz, 2 H), 7.33 (d, *J* = 1.5 Hz, 1 H), 7.24 (d, *J* = 1.5 Hz, 1 H), 7.16 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.07 (d, *J* = 2.2 Hz, 1 H),

6.84 (d, *J* = 8.8 Hz, 1 H), 6.78 (d, *J* = 5.9 Hz, 1 H), 6.74 (d, *J* = 5.1 Hz, 1 H), 6.11 (s, 1 H), 6.09–6.02 (m, 1 H), 5.08–5.01 (m, 2 H), 3.88 (s, 3 H), 3.85 (s, 4 H, CH_3O merged with 1 H), 1.28 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.2, 183.1, 149.3, 147.9, 147.6, 146.0, 142.2, 140.9, 140.6, 131.9, 126.3, 125.7, 123.0, 121.3, 121.1, 121.0, 115.6, 113.1, 111.3, 108.6, 100.6, 55.9, 55.6, 35.4, 19.2.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{25}H_{27}O_6$ $[M + H]^+$: 423.1802; found: 423.1805.

2-Methoxy-1-naphthaldehyde (19g)[19]

Compound **19g** was prepared according to the known literature procedure.[19]

Mp 80–82 °C (Lit.[19] mp 82.2–83.1 °C).

IR (neat): 3004, 2954, 2881, 1657, 1582, 1511, 1430, 1252, 949 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.85 (s, 1 H), 9.26 (d, *J* = 8.8 Hz, 1 H), 7.99 (d, *J* = 9.3 Hz, 1 H), 7.73 (d, *J* = 8.3 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.46–7.28 (m, 1 H), 7.21 (d, *J* = 9.3 Hz, 1 H), 3.98 (s, 3 H).

2-Bromo-3,4,5-trimethoxybenzaldehyde (19h)[20]

Compound **19h** was prepared according to the known literature procedure.[20]

Mp 68–70 °C (Lit.[20] mp 70.5–71.5 °C).

IR (neat): 3075, 2993, 2937, 2851, 1680, 1566, 1460, 1381, 1317, 991 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.26 (s, 1 H), 7.28 (s, 1 H), 3.96 (s, 3 H), 3.89 (s, 6 H).

2,4,6-Tribromo-3-methoxybenzaldehyde (19i)[21]

Compound **19i** was prepared according to the known literature procedure.[21]

Mp 109–111 °C (Lit.[21] mp 113 °C).

IR (neat): 3068, 2942, 2881, 2781, 1697, 1530, 1451, 1407, 1329, 1022, 919 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.15 (s, 1 H), 7.88 (s, 1 H), 3.91 (s, 1 H).

5-Formyl-2-methoxyphenyl Acetate (19j)[22]

Compound **19j** was prepared according to the known literature procedure.[22]

Mp 84–86 °C (Lit.[22] mp 85–86 °C).

IR (neat): 2840, 1764, 1687, 1600, 1509, 1439, 1374, 1270, 1186, 1112, 908 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 1 H), 7.73 (dd, *J* = 8.6, 2.2 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.05 (d, *J* = 8.8 Hz, 1 H), 3.89 (s, 3 H), 2.31 (s, 3 H).

2,4,6-Tribromo-3-hydroxybenzaldehyde (19l)[21]

Compound **19l** was prepared according to the known literature procedure.[21]

Mp 117–119 °C (Lit.[21] mp 119.5 °C).

IR (neat): 3383, 2878, 1694, 1544, 1434, 1364, 1287, 1172, 867 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.17 (s, 1 H), 7.84 (s, 1 H), 6.39 (br s, 1 H).

5-Bromo-2,4-dimethoxybenzaldehyde (19k)[23]

Compound **19k** was prepared according to the known literature procedure.[23]

Mp 130–132 °C (Lit.[23] mp 134–138 °C).

IR (neat): 2944, 2856, 1660, 1584, 1460, 1394, 1269, 1156, 1012, 891 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.19 (s, 1 H), 7.94 (s, 1 H), 6.41 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690794.

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