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Functionalization of Diazotetronic Acid and Application in a Stereoselective Modular Synthesis of Pulvinone, Aspulvinones A-E, G, Q and their Analogues

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A modular synthesis of aspulvinones A, B, C, D, E, G and the recently isolated aspulvinone Q was developed. The methodology features a highly stereoselective aldol condensation of diazotetronic acid with aldehydes to provide 5-arylidene diazotetronates. Subsequent catalytic intermolecular C-H insertion reactions of the arylidene tetronates with arenes provide a series of naturally occurring aspulvinones including aspulvinones C, D and Q which have not been synthesized before. Variation of the aldehyde and the arene components furnishes synthetic analogues of the aspulvinones.

Introduction

The tetronic acid (4-hydroxy-5*H*-furan-2-one) motif is a characteristic structural unit in many fungal metabolites.[1,2] Among these, the pulvinones (hydroxylated versions of 3-aryl-4-hydroxy-5-arylidene furan-2(5*H*)-ones) constitute a major group of naturally-occurring tetronic acids, which were first isolated as yellow pigments from the mushroom Larch Bolete (*Suillus grevillei*).[3] Subsequently, a significant number of coloured metabolites were isolated from cultures of *Aspergillus terreus*.[4] These were named the aspulvinones presumably because their structures were determined[5,6] to be similar to the pulvinones isolated earlier. Of these, the aspulvinones that were selected for our synthetic studies are shown in Figure 1. The targets are assembled by their structural similarity, and they include pulvinone (**1**),[3] aspulvinone E (**2**),[4] aspulvinone G (**3**),[4] 3',4,4'-trihydroxypulvinone (**4**),[3] aspulvinone Q (**5**),[7] aspulvinone A (**6**),[4] aspulvinone C (**7**),[4] aspulvinone B (**8**)[4] and aspulvinone D (**9**).[4]

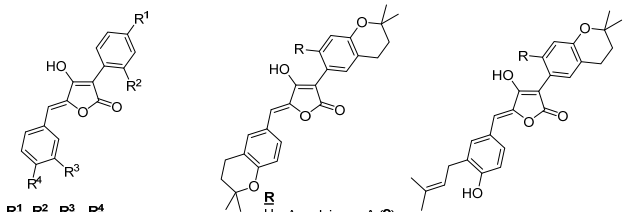

Figure 1. Naturally occurring aspulvinones prepared in this study

Several other aspulvinones are known; aspulvinone F,[4] aspulvinone H,[8] and the more recent additions to the aspulvinone family, aspulvinones I-CR to N-CR from the culture broth of a *Aspergillus* sp. (strain 05545) obtained from a marine sponge,[9] aspulvinone O from the fungal strain *Paecilomyces variotii*,[10] aspulvinone P from *Aspergillus flavipes* PJ03-11[7] and aspulvinone R from *Aspergillus* sp. CPCC 400735.[11] These are all closely related to their congeners in Figure 1 and the synthetic strategy described here is potentially applicable to the entire family of pulvinones. The biological profiles of a large number of naturally occurring as well as synthetic pulvinones have been exhaustively investigated, and several studies have identified pulvinones with anticoagulant,[12] antibacterial,[13] peptidoglycan biosynthesis inhibitory,[14] anti-inflammatory,[15] antidiabetic,[16] anti-epileptic[17] and antifungal[18] activities. In particular, members of the aspulvinone family have antiviral,[19] α-glucosidase inhibitory[20] and firefly luciferase inhibitory[9] activity.

The wide spectrum of biological activity exhibited by pulvinones has contributed to extensive interest in their synthesis and several approaches to the functionalized tetronic acid motif in pulvinones are reported (Figure 2). The salient features of these approaches are: 1) installation of the C5-arylidene portion by aldol reaction of 3-aryl-4-methoxytetronates with aryl aldehydes followed by dehydration (Pattenden),[21] 2) olefination of a dioxolane phosphorane (Ramage),[22] or a dioxolane phosphonate (Brückner)[23] with aryl aldehydes followed by Claisen condensation with arylacetic esters, 3) Wittig reaction of a 3-aryltetronate-derived phosphorane with aryl aldehydes (Campbell),[24] 4) assembly of the lactone moiety by *O*- and *C*-acylation of α-hydroxy dibenzyl ketones with carbonyl diimidazole followed by oxidation of the C5 benzyl group (Gill),[25] 5) aldol condensation of 3-bromotetronates at C5 with aryl aldehydes and subsequent introduction of the C3 aryl group by Suzuki coupling (Antane),[26] 6) Heck reaction of 2-acetoxy acrylates and iodoarenes to provide the corresponding cinnamates, subsequent transesterification with arylacetic acids and Dieckmann cyclization (Brückner),[27] 7) Dieckmann condensation/elimination protocol with functionalized esters of aryl acetic acids (Le Gall)[28] 8) silver catalyzed lactonization of acetylenic acids (Brückner)[29] and 9) silver catalyzed incorporation of carbon dioxide into conjugated ynones under high pressure (Yamada).[30] The majority of these strategies rely on the cyclization of a functionalized precursor to provide the tetronic acid motif and only a few[21,24,26] have relied on the synthesis of an

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appropriate tetronic acid which is subsequently elaborated to the target. Notably, all of these approaches are limited by the requirement of starting materials that contain the substituted arene, or arenes, in the target pulvinones. In addition, some of the above methods generate mixtures of *E*- and *Z*-pulvinones.[23,24,28] In this context, it is noteworthy that the synthesis of aspulvinones C and D (**7**, **9** Figure 1) is not yet reported, and the synthesis of pure aspulvinone B (**8**, Figure 1) has been challenging.[27] We therefore chose to develop a synthesis of pulvinones that is not limited by the availability of arene-bearing starting materials and also provides only the *Z* isomer that is found in all of the naturally occurring pulvinones. We reasoned that a strategy that relied on the direct functionalization of tetronic acid could potentially address these objectives.

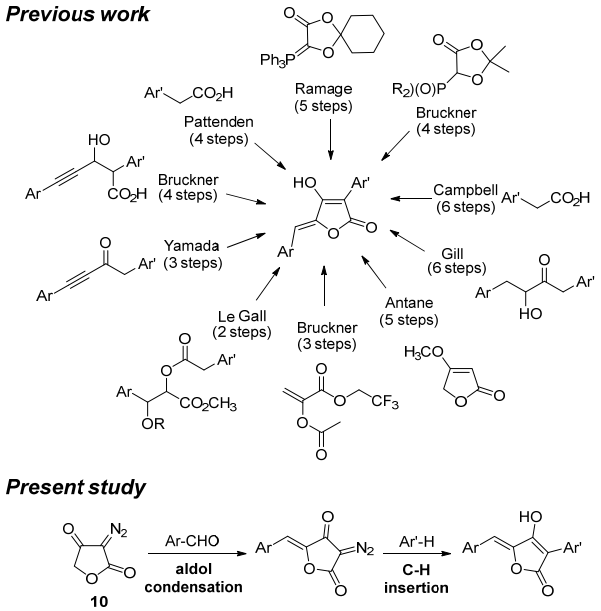


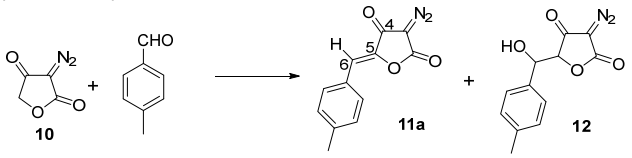
Figure 2. Previous synthetic approaches to pulvinones and our two step strategy.

Results and discussion

Our approach to pulvinones relies on the functionalization of 3-diazotetronic acid (**10**, Figure 2). We have previously shown that C5-functionalized diazotetronates react with arenes in the presence of a metal catalyst and provide the corresponding 3-aryl tetronates as the products of a net C-H insertion reaction of the diazotetronate and the arene C-H bond.[31] This reaction presumably proceeds as an electrophilic aromatic subsbstitution reaction of the arene with the tetronate-derived carbenoid intermediate, and hence it displays the conventional regiochemistry that is anticipated for electrophilic aromatic substitution reactions. Notably, all of the naturally occurring pulvinones have a tetronic acid core that is substituted with an electron rich arene at C3 (Figure 1) which is typically 2-, 2,4-di, or 2,4,5-tri substituted with hydroxy, alkoxy or alkyl groups in relation to the aryl-tetronate linkage. We therefore anticipated that the regiochemistry of our tetronate-arene C-H insertion methodology would be particularly useful for the synthesis of naturally occurring pulvinones and their analogues. In order for the proposed methodology to be successful, a stereoselective aldol condensation at C5 in the diazotetronic acid (**10**), to generate only the *Z*-arylidene functionality found in the pulvinone natural products, is also necessary (Figure 2). Herein, we report the implementation of this two-step procedure for the synthesis of pulvinones from 3-diazotetronic acid (**10**).

The initial focus of our studies was the installation of an arylidene functionality at C5 in diazotetronate **10**, which is easily prepared from commercially available tetronic acid in one step,[32] to potentially provide the immediate precursors of the target pulvinones and their analogs. Our objective was to develop a method that would avoid multistep protocols that were employed in previous studies with tetronic acid derivatives (Figure 2). At the outset, an aldol reaction of **10** and *p*-tolualdehyde was attempted with the titanium enolate of **10** (using the $TiCl_4$-Et_3N reagent,[33] Table 1, entry 1). Interestingly, this directly provided the aldol condensation product[34] **11a** as a single diastereomer, but in low yield (41%). We therefore conducted an optimization of the aldol condensation by employing selected combinations of Lewis acids and bases. Replacing $TiCl_4$ with $BF_3.OEt_2$ (Table 1, entry 2) provided only the aldol addition product **12** as a mixture of diastereomers (dr = 1:1). Changing the base from triethylamine to heteroaromatic bases such as pyridine, *N*-methylimidazole and 2,4,6-collidine prevented the formation of **12** and also improved the yield of **11a**. With *N*-methylimidazole and pyridine (Table 1, entries 3 and 4), **11a** was obtained in good yields (77% and 82% respectively) but the reaction was slow. However, the reaction with 2,4,6-collidine as the base not only provided **11a** in good yield (82%, Table 1, entry 5), but this reaction was significantly faster (80 min) than those with *N*-methylimidazole (~20 h) or pyridine (~43 h) as the base.

Table 1. Optimization of the aldol condensation of **10** with *p*-tolualdehyde.



Entry	Conditions	11a[a]	12[a]
1	$TiCl_4$, -78 °C, 20 min; Et_3N, -78 °C, 40 min to 0 °C, 1.5 h	41	-
2	$BF_3.OEt_2$, -78 °C, 20 min; Et_3N, -78 °C, 40 min; 0 °C, 1 h; rt, 1 h	-	38
3	$TiCl_4$, -78 °C, 20 min; *N*-methylimidazole, -78 °C, 30 min; 0 °C, 80 min; rt, 18 h	77	-
4	$TiCl_4$, -78 °C, 20 min; pyridine, -78 °C, 30 min; 0 °C, 2 h; rt, 41 h	82	-
5	$TiCl_4$, -78 °C, 20 min; 2,4,6-collidine, -78 °C, 30 min; 0 °C, 30 min	82	-

[a] Isolated yields

At this stage, **11a** was assigned the *Z* stereochemistry[35] on the basis of selected ^{13}C-^{1}H coupling constants. The $^{3}J_{C(4)\text{-}H(6)}$ (three bond ^{13}C-^{1}H coupling constant) for the exocyclic methine and the ketone carbonyl in **11a** is 3.9 Hz and $^{2}J_{C(5)\text{-}H(6)}$ (two bond ^{13}C-^{1}H coupling constant) in **11a** is 4.3 Hz. These values are in good agreement with those reported[36] for several *Z*-aurones ($^{3}J_{C\text{-}H}$ = 3.1-3.6 Hz; $^{2}J_{C\text{-}H}$ = 3.7-4.7 Hz) that are structurally related to **11a**. Notably, the reported $^{3}J_{C\text{-}H}$ and $^{2}J_{C\text{-}H}$ values for *E*-aurones are higher (7.0-8.5 Hz).

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The optimized conditions were employed for the aldol condensation of **10** with a variety of aldehydes. Pleasingly, a selection of electron-rich and electron-deficient aromatic aldehydes, as well as aliphatic aldehydes, provided the 5-arylidene-3-diazofuran-2,4(3*H*,5*H*)-diones **11b-p** as single diastereomers in good yields (16 examples, Figure 3). Notably, the arylidene diazotetronates **11b**, **11d**, **11f**, **11g**, **11h** and **11i**, which are potential intermediates for the synthesis of aspulvinones, were all obtained in good yield (79-92%). The reactions with aliphatic aldehydes are less efficient; cyclopentanecarboxaldehyde and pivalaldehyde provided **11o** and **11p** respectively in modest yield (40% and 43% respectively) and hydrocinnamaldehyde did not provide any of the required product. For reasons that are not clear at this time, the reaction of **10** with pyridine-4-carboxaldehyde was also unsuccessful. The aldol condensation products **11b-p** were assigned the *Z* stereochemistry by analogy to **11a**, and this was also confirmed by the diagnostic C-H coupling constants for **11b** and **11p**.[36] Eventually, this stereochemical assignment was confirmed by conversion of several C5-arylidene derivatives to naturally occurring pulvinones, thus providing unambiguous evidence for their structure.

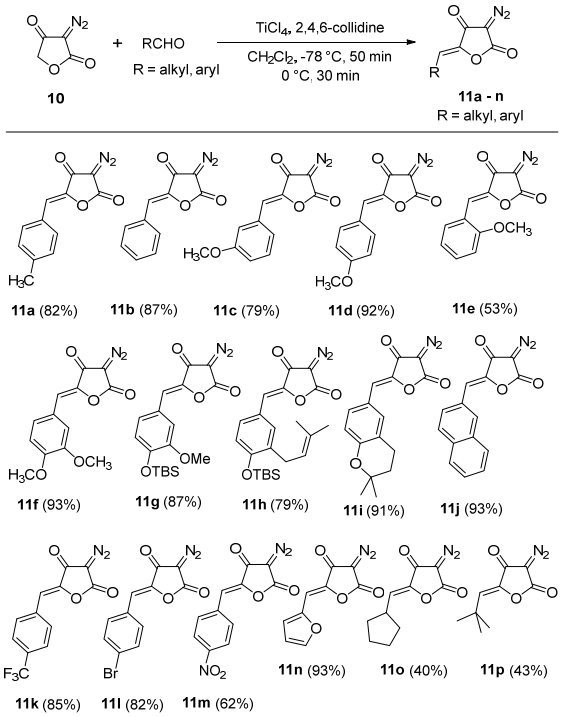
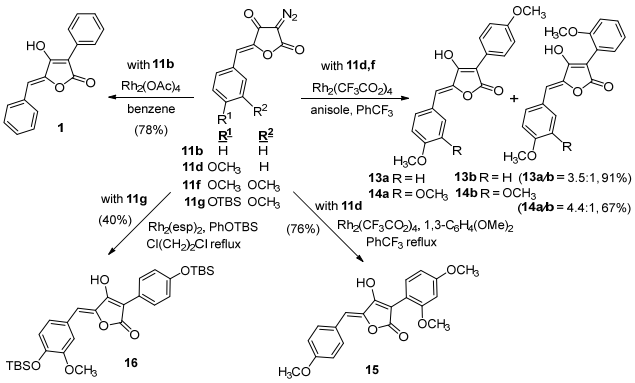


Figure 3. Aldol condensation products of **10** with selected aldehydes.

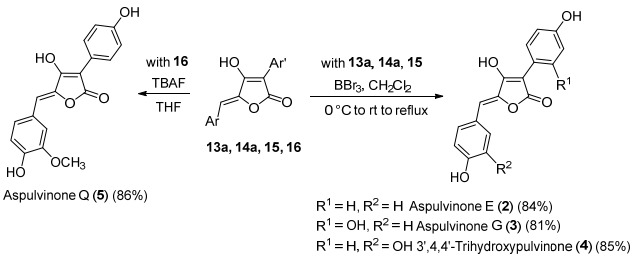
Having established a general synthesis of 5-arylidene diazotetronates **11**, we examined their C-H insertion reactions with a selection of arenes. Since our immediate objective was to confirm the *Z*-geometry of **11**, a C-H insertion reaction of **11b** was conducted in benzene in the presence of $Rh_2(OAc)_4$ to provide the known, naturally occurring, pulvinone **1** (78%, Scheme 1). Spectroscopic data (^{1}H NMR, ^{13}C NMR) of **1** and its acetate derivative[24] were identical with those reported in the literature.[22,24,28] The chemical shift of the methyl group in the acetate derived from *Z*-**1** is reported to be δ 2.35, whereas in *E*-**1** it is δ 1.67.[24] The observed chemical shift (δ 2.42) of the methyl group in the acetate of **1** prepared in our study confirmed the *Z* stereochemistry for **1**. This also supports our earlier conclusion that **11b** has the *Z*-geometry.

Encouraged by the conversion of **11b** to **1**, the synthesis of precursors to aspulvinone E (**2**), aspulvinone G (**3**), 3',4,4'-trihydroxypulvinone (**4**) and aspulvinone Q (**5**) was investigated employing C5-arylidene diazotetronates in which the arene substituent was suitable for the targeted natural product. These C-H insertion reactions were conducted in a solvent, rather than the neat arene, and an excess (4 equiv) of an appropriately substituted arene as the reacting partner. Thus, the $Rh_2(CF_3CO_2)_4$-catalyzed C-H insertion reaction of **11d** with anisole in α,α,α-trifluoromethylbenzene provided the regioisomeric insertion products **13a** and **13b** (**13a**/**13b** = 3.5:1, 91%, Scheme 1). A similar reaction of **11f** provided **14a** and **14b** (**14a**/**14b** = 4.4:1, 67%, Scheme 1). The regioisomeric products (**13a/b** and **14a/b**) were easily separated by flash column chromatography. Although the C-H insertion reaction of **11d** with 1,3-dimethoxybenzene provided **15** (76%) under these conditions, a similar reaction of **11g** with the TBS ether of phenol provided a complex mixture in which the desired product, **16**, could not be detected. Changing the solvent to 1,2-dichloroethane and the use of $Rh_2(esp)_2$,[37] was beneficial and the insertion product **16** was obtained as the only isolable product (40%). Interestingly, the regioisomeric product (ortho C-H insertion, as in **13b** and **14b**) was not obtained in this case.



Scheme 1. Arene C-H insertion reactions for the synthesis of pulvinones **1**, **13-16**.

Selected insertion products shown in Scheme 1 were readily converted into a series of naturally occurring aspulvinones. Demethylation of **13a**, **14a** and **15** with BBr_3, according to the reported procedure,[27] provided aspulvinone E (**2**, 84%), aspulvinone G (**3**, 81%), and 3',4,4'-trihydroxypulvinone (**4**, 85%, Scheme 2). Removal of the TBS protecting groups in **16** with TBAF provided aspulvinone Q (**5**) in good yield (86%).



Scheme 2. Synthesis of aspulvinones E, G, Q and 3',4,4'-trihydroxypulvinone.

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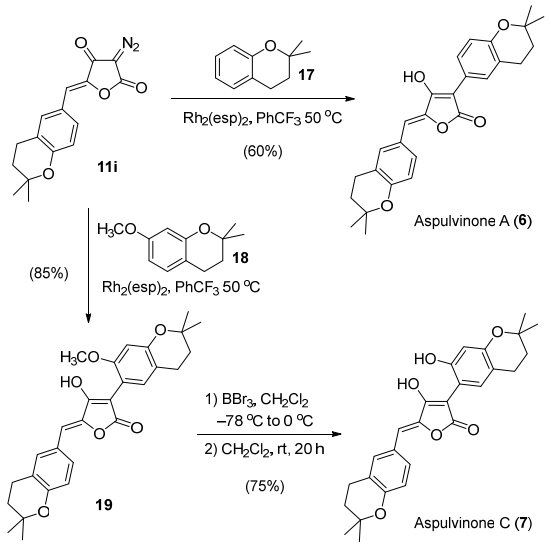
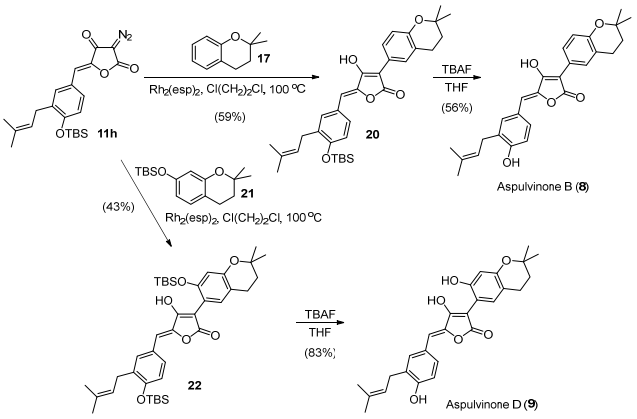
Having achieved the synthesis of the naturally occuring pulvinones **2**, **3**, **4** and **5**, we next targeted the naturally occurring aspulvinone A (**6**), aspulvinone C (**7**), aspulvinone B (**8**) and aspulvinone D (**9**). In initial studies, $Rh_2(CF_3COO)_4$ and $Rh_2(OAc)_4$ were screened as catalysts in the C-H insertion reactions of **11i** with chromane **17**[38] (4 equiv.) in $PhCF_3$ as the solvent at 100 °C. However, in both cases, poor yields (29%, 38% respectively) of **6** were observed. Changing the catalyst to $Rh_2(esp)_2$ and lowering the reaction temperature to 50 °C improved the yield of aspulvinone A (**6**) to 60%. These conditions were also used for the insertion reaction of **11i** with the 7-methoxy-2,2-dimethylchromane (**18**)[39] to provide the pulvinone **19** in good yield (85%, Scheme 3). Attempted demethylation of **19** by treatment with BBr_3 resulted in concomitant C-O bond cleavage in the chromane moieties to provide a bis-tertiary bromide intermediate. This material spontaneously cyclized[40] back to the bis-chromane in CH_2Cl_2 solution at ambient temperature to provide aspulvinone C (**7**) in 75% yield from **19**.



Scheme 3. Synthesis of aspulvinones A and C.

The synthesis of aspulvinones B and D was examined next using the diazotetronate **11h** as the starting material, and a notable difference in the reactivities of **11i** and **11h** was immediately apparent. A change of solvent from $PhCF_3$ to 1,2-dichloroethane, and higher reaction temperature (100 °C) was necessary with **11h**. With these modifications, the C-H insertion reaction of **11h** and chromane (**17**) provided **20** (59%). Subsequent removal of the TBS protection in **20** provided aspulvinone B (**8**, 56%). The synthesis of aspulvinone D was first initiated with an insertion reaction of **11h** and 7-methoxy-2,2-dimethylchromane (**18**). While this reaction was successful (44% yield), subsequent demethylation of the insertion product was complicated by unwanted side reactions, and hence the TBS-protected chromane derivative **21**[41] was employed as the insertion partner. Thus the reaction of **11h** and **21** provided **22** (43%), which was deprotected to provide aspulvinone D (**9**, 83%, Scheme 4).



Scheme 4. Synthesis of aspulvinones B and D.

Over the years, interest in the biological activity of pulvinones and aspulvinones has resulted in intense investigation of the synthesis of structural variants of the natural isolates.[9,12-20,42] It may be noted that the described methodology is particularly amenable to the synthesis of a wide variety of non-natural pulvinones by variation of the aldehyde component in the aldol condensation that provides **11** and subsequent variation of the arene component in the C-H insertion reactions of **11**. The potential of this strategy was demonstrated by the two-step synthesis of the non-natural pulvinones **23** (from **11o** and **17**), **24** (from **11j** and **17**) and **25** (from **11i** and 5-bromoindole, Figure 4).

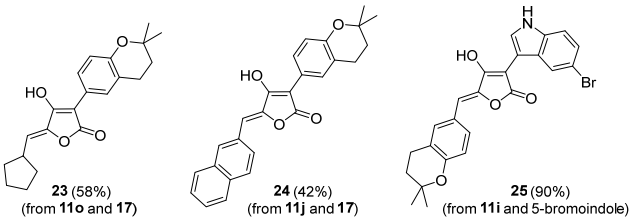


Figure 4. Non-natural pulvinones prepared in this study.

Conclusion

In conclusion a two-step synthesis of 3-aryl-5-arylidene tetronates was developed from diazotetronic acid as the starting material. The utility of the methodology was demonstrated by application in the synthesis of two naturally occurring pulvinones (**1** and **4**, Figure 1), seven aspulvinones (**2**, **3**, **5**, **6**, **7**, **8** and **9**, Figure 1) as well as three non-natural pulvinones. This strategy provides the shortest route to functionalized tetronates and has potential for the rapid synthesis of focused libraries of aspulvinone-like natural product analogues. Current efforts focus on these and other applications of **10**.

Experimental

General: All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Commercially available α,α,α-trifluorotoluene was used

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as received. CH_2Cl_2 and $Cl(CH_2)_2Cl$ (DCE) were distilled from CaH_2. Commercial precoated silica gel plates were used for TLC. All melting points are uncorrected. Silica gel for flash column chromatography was 230-400 mesh. IR spectra were recorded on a Bruker TENSOR 27 FT-IR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 300 or an AVANCE 500 instrument. Mass spectra were obtained on an Agilent 6200 LC/MSD (TOF) chromatographic system.

3-Diazofuran-2,4(3*H*,5*H*)-dione (10): To a solution of tetronic acid (1.50 g, 15.0 mmol) in acetonitrile (20 mL) at 0 °C was added tosyl azide (2.90 g, 15.0 mmol) followed by dropwise addition of triethylamine (2.09 mL, 15.0 mmol) over 10 min at 0 °C. The mixture gradually turned black and it was stirred at room temperature for 1 h. Removal of the solvent under reduced pressure provided a black residue. This was applied to a column (3 cm x 17 cm) of flash silica gel packed in dichloromethane and the column was eluted with dichloromethane (~300 mL). The residue obtained by concentration of the eluate was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 98:2) to provide 773 mg (41%) of **10** as a white solid. R_f = 0.41 (CH_2Cl_2/EtOAc, 9.5:0.5). Spectroscopic data for **10** is in agreement with reported data.[31]

General procedure for the aldol condensation of diazotetronate 10 and aldehydes: To a solution of **10** (1.0 equiv) and aldehyde (1.0 equiv) in CH_2Cl_2 was added $TiCl_4$ (3.0 equiv) at -78 °C. The solution was stirred for 20 min, 2,4,6-collidine (3.0 equiv) was added and the mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. Saturated aqueous NH_4Cl (~ 3 mL) was added followed by cold water (~ 2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to provide the arylidene- or alkylidene diazotetronates **11a-p**.

(*Z*)-3-Diazo-5-(4-methylbenzylidene)furan-2,4(3*H*,5*H*)-dione (11a): The reaction of **10** (126 mg, 1.00 mmol), 4-methylbenzaldehyde (118 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 188 mg (82%) of **11a** as a white solid.
R_f = 0.32 (hexanes/EtOAc, 8.5:1.5); mp: 147-150 °C; IR (neat): 2157, 1758, 1689, 1634, 1602, 1362, 1339, 1313, 1251, 1078, 1048, 962, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, 2H, *J* = 8.1 Hz, Ar*H*), 7.23 (d, 2H, *J* = 8.1 Hz, Ar*H*), 6.68 (s, 1H, ArC*H*=C), 2.39 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.5 (O*C*=O), 141.6 (O-*C*=CHAr or Ar*C*$_{ipso}$), 141.3 (O-*C*=CHAr or Ar*C*$_{ipso}$), 131.6 (2 × Ar*C*), 129.9 (2 × Ar*C*), 128.3 (Ar*C*$_{ipso}$), 112.2 (Ar*C*H=C), 21.8 (*C*H$_3$); HRMS (APPI, pos.): *m/z* 228.0537 (228.0535 calc. for $C_{12}H_8N_2O_3$, $(M)^+$).

(*Z*)-5-Benzylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (11b): The reaction of **10** (70 mg, 0.56 mmol), benzaldehyde (57 µL, 0.56 mmol), $TiCl_4$ (0.18 mL, 1.7 mmol) and 2,4,6-collidine (0.22 mL, 1.7 mmol) in CH_2Cl_2 (3 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5), 104 mg (87%) of **11b** as a white solid.
R_f = 0.51 (hexanes/EtOAc, 7:3); mp: 147-154 °C; IR (neat): 2921, 2852, 2151, 1763, 1699, 1639, 1358, 1337, 1244, 1082, 1051, 963 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.72 (m, 2H, Ar*H*), 7.49-7.39 (m, 3H, Ar*H*), 6.69 (s, 1H, PhC*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (*C*=O), 160.3 (O*C*=O), 142.1 (PhHC=*C*-O), 131.5 (2 × Ar*C*), 131.0 (Ar*C*$_{ipso}$), 130.5 (Ar*C*), 129.1 (2 × Ar*C*), 111.9 (Ph*C*H=C); HRMS (APPI, pos.): *m/z* 214.0378 (214.0378 calc. for $C_{11}H_6N_2O_3$, $(M)^+$).

(*Z*)-3-Diazo-5-(3-methoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (11c): The reaction of **10** (150 mg, 1.19 mmol), 3-methoxybenzaldehyde (145 µL, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 7:3), 231 mg (79%) of **11c** as a yellow solid.
R_f = 0.46 (hexanes/EtOAc, 7:3); mp: 159-161°C; IR (neat): 2923, 2844, 2132, 1764, 1705, 1647, 1582, 1357, 1302, 1215, 1176, 1092, 1074, 1036, 981, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H, Ar*H*), 7.31-7.28 (m, 1H, Ar*H*), 7.00-6.92 (m, 1H, Ar*H*), 6.65 (s, 1H, ArC*H*=C), 3.84 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 160.1 (O*C*=O or Ar*C*$_{ipso}$), 159.8 (O*C*=O or Ar*C*$_{ipso}$), 142.1 (O-*C*=CHAr), 132.1 (Ar*C*$_{ipso}$), 129.9 (Ar*C*), 124.1 (Ar*C*), 116.6 (Ar*C*), 116.0 (Ar*C*), 111.7 (Ar*C*H=C), 55.4 (O*C*H$_3$); HRMS (APPI, pos.): *m/z* 244.0481 (244.0484 calc. for $C_{12}H_8N_2O_4$, $(M)^+$).

(*Z*)-3-Diazo-5-(4-methoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (11d): The reaction of **10** (126 mg, 1.00 mmol), 4-methoxybenzaldehyde (121 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (6 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 4:1), 224 mg (92%) of **11d** as a yellow solid.
R_f = 0.33 (hexanes/EtOAc, 7:3); mp: 141-145 °C; IR (neat): 2970, 2917, 2845, 2158, 1774, 1690, 1646, 1598, 1565, 1508, 1366, 1341, 1305, 1250, 1174, 1134, 1070, 1021, 957 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.94 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 3.86 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 161.4 (O*C*=O or Ar*C*$_{ipso}$), 160.4 (O*C*=O or Ar*C*$_{ipso}$), 140.5 (O-*C*=CHAr), 133.4 (2 × Ar*C*), 123.7 (Ar*C*$_{ipso}$), 114.5 (2 × Ar*C*), 112.0 (Ar*C*H=C), 55.4 (O*C*H$_3$); HRMS (APPI, pos.): *m/z* 244.0484 (244.0484 calc. for $C_{12}H_8N_2O_4$, $(M)^+$).

(*Z*)-3-Diazo-5-(2-methoxybenzylidene)furan-2,4(3H,5H)-dione (11e): The reaction of **10** (75 mg, 0.59 mmol), 2-methoxybenzaldehyde (81 mg, 0.59 mmol), $TiCl_4$ (0.2 mL, 1.78 mmol) and 2,4,6-collidine (0.2 mL, 1.78 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 77 mg (53%) of **11e** as a yellow solid.
R_f = 0.23 (hexanes/EtOAc, 9:1); mp: 210-211 °C; IR (neat): 3080, 2923, 2840, 2152, 1775, 1699, 1648, 1592, 1483, 1462, 1359, 1305, 1283, 1254, 1233, 1193, 1138, 1070, 1045, 1018, 955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (dd, 2H, *J* = 7.6, 1.7 Hz, ArH), 7.37 (ddd, 1H *J* = 8.3, 7.6, 1.7 Hz), 7.28 (s, 1H, ArC*H*), 7.01 (br t, 1H, *J* = 7.6 Hz, Ar*H*), 6.91 (br d, 1H, *J* = 8.3 Hz, Ar*H*), 3.88 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O-*C*=O), 158.7 (Ar*C*$_{ipso}$), 141.8 (Ar*C*$_{ipso}$), 132.1 (O-*C*=CHAr), 131.7 (Ar*H*), 121.0 (Ar*H*), 119.9 (Ar*C*H=C), 110.8 (Ar*H*), 106.2 (Ar*H*), 55.6 (OCH_3); HRMS (APPI, pos.): m/z 244.0847 (244.0484 calc. for $C_{12}H_8N_2O_4$ (M^+)), 245.0560 (245.0562 calc. for $C_{12}H_9N_2O_4$ $(M+H)^+$).

(*Z*)-3-Diazo-5-(3,4-dimethoxybenzylidene)furan-2,4(3*H*,5*H*)-dione (11f): The reaction of **10** (80 mg, 0.64 mmol), 3,4-dimethoxybenzaldehyde (106 mg, 0.640 mmol), $TiCl_4$ (0.21 mL, 1.9 mmol) and 2,4,6-collidine (0.25 mL, 1.9 mmol) in CH_2Cl_2 (4 mL) according to the general procedure provided, after purification by

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flash column chromatography on silica gel (hexanes/EtOAc, 7:3 to 1:1), 161 mg (93%) of **11f** as a yellow solid.
R_f = 0.19 (hexanes/EtOAc, 7:3); mp: 177-183 °C; IR (neat): 2961, 2936, 2913, 2836, 2143, 1779, 1693, 1643, 1594, 1513, 1360, 1321, 1266, 1219, 1145, 1129, 1081, 1063, 1018, 979, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H, Ar*H*), 7.35 (dd, 1H, *J* = 8.6, 2.0 Hz, Ar*H*), 6.91 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 3.94 (s, 6H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O*C*=O), 151.4 (ArC_{ipso}), 149.3 (ArC_{ipso}), 140.7 (O-*C*=CHAr), 126.2 (Ar*C*), 124.1 (ArC_{ipso}), 113.5 (Ar*C* or Ar*C*H=C), 112.4 (Ar*C* or Ar*C*H=C), 111.3 (Ar*C* or Ar*C*H=C), 56.1 (2 × OCH_3); HRMS (APPI, pos.): *m/z* 274.0597 (274.0590 calc for $C_{13}H_{10}N_2O_5$ $(M)^+$).

(*Z*)-5-(4-(*tert*-butyldimethylsilyloxy)-3-methoxybenzylidene)-3-diazofuran-2,4(3H,5H)-dione (11g): The reaction of **10** (100 mg, 0.79 mmol), 4-(tert-butyldimethylsilyloxy)-3-methoxybenzaldehyde (211 mg, 0.79 mmol), $TiCl_4$ (0.25 mL, 2.38 mmol) and 2,4,6-collidine (0.3 mL, 2.38 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9.2:0.8), 257 mg (87%) of **11g** as a yellow solid.
R_f = 0.30 (hexanes/EtOAc, 9.2:0.8); IR (neat): 2957, 2931, 2856, 2147, 1786, 1708, 1649, 1591, 1508, 1463, 1419, 1364, 1344, 1310, 1276, 1248, 1169, 1132, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 1H, *J* = 2.1 Hz, Ar*H*), 7.24 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.88 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.65 (s, 1H, ArC*H*), 3.86 (s, 3H, OCH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.5 (O-*C*=O), 151.4 (ArC_{ipso}), 148.0 (ArC_{ipso}), 140.7 (ArC_{ipso}), 126.1 (Ar*C*), 124.9 (O-*C*=CHAr), 121.4 (Ar*H*), 114.5 (Ar*C*H), 112.6 (Ar*C*), 55.7 (OCH_3), 25.8 (C(*C*H$_3$)$_3$), 18.7 (*C*(CH$_3$)$_3$), -4.4 (Si(*C*H$_3$)$_2$); HRMS (ESI, pos.): *m/z* 374.1295 (374.1298 calc. for $C_{18}H_{22}N_2O_5Si$ $(M)^+$), 397.1187 (397.1196 calc. for $C_{18}H_{22}N_2NaO_5Si$ $(M+Na)^+$).

(*Z*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (11h): The reaction of **10** (350 mg, 2.78 mmol), 4-((tert-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (846 mg, 2.78 mmol), $TiCl_4$ (0.90 mL, 8.3 mmol) and 2,4,6-collidine (1.10 mL, 8.33 mmol) in CH_2Cl_2 (12 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 19:1), 902 mg (79%) of **11h** as a yellow solid.
R_f = 0.63 (hexanes/EtOAc, 7:3); mp: 118-121 °C; IR (neat): 2961, 2929, 2858, 2137, 1782, 1708, 1648, 1598, 1497, 1364, 1276, 1076, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar*H*), 7.49 (d, 1H, *J* = 2.3 Hz, Ar*H*), 6.82 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.66 (s, 1H, ArC*H*=C), 5.24-5.33 (m, 1H, (CH$_3$)$_2$C=C*H*), 3.30 (d, 2H, *J* = 7.1 Hz, C=CHCH_2), 1.77 (br d, 3H, *J* = 1.0 Hz, CH_3), 1.71 (br s, 3H, CH_3), 1.02 (s, 9H, 3 × CH_3), 0.27 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.4 (O*C*=O), 156.0 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 133.61 (Ar*C*), 133.57 (ArC_{ipso} or (CH$_3$)$_2$*C*=CH), 133.1 (ArC_{ipso} or (CH$_3$)$_2$*C*=CH), 130.6 (Ar*C* or (CH$_3$)$_2$C=*C*H), 123.9 (ArC_{ipso} or (CH$_3$)$_2$*C*=CH), 121.7 (Ar*C* or Ar*C*H=C), 118.9 (Ar*C*), 112.6 (Ar*C*H=C), 28.4 (*C*H$_2$), 25.7 (4 × *C*H$_3$), 18.3 (Si-*C*(CH$_3$)$_3$), 17.9 (*C*H$_3$), -4.1 (2 × Si*C*H$_3$); HRMS (APPI, pos.): *m/z* 412.1827 (412.1818 calc. for $C_{22}H_{28}N_2O_4Si$, $(M)^+$) and 413.1859 (413.1897 calc. for $C_{22}H_{29}N_2O_4Si$, $(M+H)^+$).

(*Z*)-3-Diazo-5-((2,2-dimethylchroman-6-yl)methylene)furan-2,4(3*H*,5*H*)-dione (11i): The reaction of **10** (200 mg, 1.59 mmol), 2,2-dimethylchroman-6-carbaldehyde (302 mg, 1.59 mmol), $TiCl_4$ (0.52 mL, 4.8 mmol) and 2,4,6-collidine (0.63 mL, 4.8 mmol) in CH_2Cl_2 (9 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 7:3), 430 mg (91%) of **11i** as a yellow-orange solid.
R_f = 0.46 (hexanes/EtOAc, 7:3); mp: 156-161 °C; IR (neat): 2979, 2926, 2163, 1774, 1702, 1641, 1598, 1570, 1490, 1364, 1308, 1269, 1116, 1074, 1054, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (br s, 1H, Ar*H*), 7.50 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar*H*), 6.81 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.64 (s, 1H, ArC*H*=C), 2.81 (t, 2H, *J* = 6.7 Hz, ArCH_2CH$_2$), 1.83 (t, 2H, *J* = 6.7 Hz, ArCH$_2$CH_2), 1.36 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (*C*=O), 160.6 (O*C*=O), 156.6 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 133.3 (Ar*C*), 131.4 (Ar*C*), 122.6 (ArC_{ipso}), 121.7 (ArC_{ipso}), 118.1 (Ar*C*), 112.7 (Ar*C*H=C), 75.5 (Ar-O-*C*(CH$_3$)$_2$), 32.5 (ArCH$_2$CH$_2$), 26.9 (2 × CH$_3$), 22.4 (ArCH$_2$CH$_2$); HRMS (ESI, pos.): *m/z* 298.0939 (298.0954 calc. for $C_{16}H_{14}N_2O_4$, $(M)^+$), 299.1012 (299.1032 calc. for $C_{16}H_{15}N_2O_4$, $(M+H)^+$) and 321.0827 (321.0851 calc. for $C_{16}H_{14}N_2NaO_4$, $(M+Na)^+$).

(*Z*)-3-Diazo-5-(naphthalen-2-ylmethylene)furan-2,4(3*H*,5*H*)-dione (11j): The reaction of **10** (150 mg, 1.19 mmol), 2-naphthaldehyde (186 mg, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 1:1), 292 mg (93%) of **11j** as an orange-yellow solid.
R_f = 0.40 (hexanes/EtOAc, 7:3); mp: 156-160 °C; IR (neat): 2922, 2134, 1762, 1710, 1645, 1358, 1322, 1078, 1048, 976, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, Ar*H*), 7.94-7.80 (m, 4H, Ar*H*), 7.59-7.49 (m, 2H, Ar*H*), 6.86 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (*C*=O), 160.4 (O*C*=O), 142.2 (O-*C*=CHAr), 134.0 (ArC_{ipso}), 133.3 (ArC_{ipso}), 132.6 (Ar*C*), 129.0 (Ar*C*), 128.9 (Ar*C*), 128.6 (ArC_{ipso}), 128.0 (Ar*C*), 127.9 (Ar*C*), 127.4 (Ar*C*), 126.9 (Ar*C*), 112.2 (Ar*C*H=C); HRMS (APPI, pos): *m/z* 264.0539 (264.0535 calc for $C_{15}H_8N_2O_3$ $(M)^+$).

(*Z*)-3-Diazo-5-(4-(trifluoromethyl)benzylidene)furan-2,4(3*H*,5*H*)-dione (11k): The reaction of **10** (126 mg, 1.00 mmol), 4-(trifluoromethyl)benzaldehyde (134 µL, 1.00 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol) and 2,4,6-collidine (0.40 mL, 3.0 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 4:1), 239 mg (85%) of **11k** as a yellow solid.
R_f = 0.56 (hexanes/EtOAc, 7:3); mp: 158-162 °C; IR (neat): 3072, 2924, 2168, 1783, 1710, 1653, 1355, 1317, 1170, 1120, 1045, 1013, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.65 (d, 2H, *J* = 8.3 Hz, Ar*H*), 6.67 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (*C*=O), 159.8 (O*C*=O), 143.4 (O-*C*=CHAr), 134.3 (q, $^5J_{C-F}$ = 1.4 Hz, ArC_{ipso}), 131.6 (q, $^2J_{C-F}$ = 32.7 Hz, ArC_{ipso}), 131.3 (2 × Ar*C*), 125.85 (q, $^3J_{C-F}$ = 3.8 Hz, 2 × Ar*C*), 123.7 (q, $^1J_{C-F}$ = 272.3 Hz, *C*F$_3$), 109.5 (Ar*C*H=C); HRMS (APPI, neg.): *m/z* 282.0254 (282.0252 calc. for $C_{12}H_5F_3N_2O_3$, $(M)^-$).

(*Z*)-5-(4-Bromobenzylidene)-3-diazofuran-2,4(3*H*,5*H*)-dione (11l): The reaction of **10** (150 mg, 1.19 mmol), 4-bromobenzaldehyde (220 mg, 1.19 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.5:1.5 to 4:1), 287 mg (82%) of **11l** as a yellow solid.
R_f = 0.36 (hexanes/EtOAc, 7:3); mp: 214-218 °C; IR (neat): 2163, 1780, 1702, 1638, 1579, 1484, 1354, 1306, 1244, 1131, 1064, 1045, 1003, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, 2H, *J* = 8.6 Hz, Ar*H*), 7.55 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.62 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (*C*=O), 159.9 (O*C*=O), 142.3 (O-*C*=CHAr), 132.7 (2 × Ar*C*), 132.3 (2 × Ar*C*), 129.8 (ArC_{ipso}), 125.0 (ArC_{ipso}), 110.4 (Ar*C*H=C); HRMS (APPI, pos.): *m/z* 291.9481 (291.9484 calc. for $C_{11}H_5{}^{79}BrN_2O_3$, $(M)^+$) and 293.9455 (293.9463 calc. for $C_{11}H_5{}^{81}BrN_2O_3$, $(M)^+$).

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(*Z*)-3-Diazo-5-(4-nitrobenzylidene)furan-2,4(3H,5H)-dione (11m): The reaction of **10** (75 mg, 0.59 mmol), 4-nitrobenzaldehyde (90 mg, 0.59 mmol), $TiCl_4$ (0.2 mL, 1.78 mmol) and 2,4,6-collidine (0.2 mL, 1.78 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 95 mg (62%) of **11m** as a light brown solid. R_f = 0.20 (hexanes/EtOAc, 4:1); mp: 188-190 °C; IR (neat): 2922, 2850, 2162, 1767, 1706, 1643, 1504, 1362, 1338, 1296, 1240, 1070, 962, 911, 857, 828, 750 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.34 (d, 2H, *J* = 8.9 Hz, Ar*H*), 8.09 (d, 2H, *J* = 8.9 Hz, Ar*H*), 6.92 (s, 1H, ArC*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 174.4 (*C*=O), 160.1 (O-*C*=O), 147.2 (ArC_{ipso}), 144.5 (ArC_{ipso}), 137.8 (O-*C*=CHAr), 131.7 (2 x Ar*H*), 124.0 (2 x Ar*H*), 106.5 (Ar*C*H=C); HRMS (APPI, pos.): m/z 259.0224 (259.0229 calc. for $C_{11}H_5N_3O_5$ (M^+)), 260.0296 (260.0307 calc. for $C_{11}H_6N_3O_6$ $(M+H)^+$).

(*Z*)-3-Diazo-5-(furan-2-ylmethylene)furan-2,4(3*H*,5*H*)-dione (11n): The reaction of **10** (150 mg, 1.19 mmol), 2-furaldehyde (99 µL, 1.2 mmol), $TiCl_4$ (0.39 mL, 3.6 mmol) and 2,4,6-collidine (0.47 mL, 3.6 mmol) in CH_2Cl_2 (7 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 8.5:1.5), 227 mg (93%) of **11n** as an orange-yellow solid.

R_f = 0.29 (hexanes/EtOAc, 9:1); mp: 163-167 °C; IR (neat): 2923, 2853, 2166, 1761, 1698, 1641, 1353, 1315, 1242, 1070, 1014, 964 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, 1H, *J* = 1.7, 0.5 Hz, Ar*H*), 7.03 (br dt, 1H, *J* = 3.5, 0.5 Hz, Ar*H*), 6.70 (br s, 1H, ArC*H*=C), 6.57 (ddd, 1H, *J* = 3.5, 1.7, 0.5 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (*C*=O), 160.0 (O*C*=O), 147.5 (O-*C*=CHAr or ArC_{ipso}), 145.6 (Ar*C*), 139.8 (O-*C*=CHAr or ArC_{ipso}), 117.6 (Ar*C*), 113.2 (Ar*C*), 100.5 (Ar*C*H=C); HRMS (APPI, pos.): *m/z* 204.0168 (204.0171 calc. for $C_9H_4N_2O_4$, $(M)^+$)

(*Z*)-5-(Cyclopentylmethylene)-3-diazofuran-2,4(3*H*,5*H*)-dione (11o): To a solution of **10** (150 mg, 1.19 mmol) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (0.39 mL, 3.57 mmol) at -78 °C and the solution was stirred for 20 min. To the mixture was added 2,4,6-collidine (0.47 mL, 3.6 mmol) followed by dropwise addition of cyclopentanecarboxaldehyde (127 µL, 1.19 mmol) in CH_2Cl (2 mL) over 5 min. The mixture was stirred at -78 °C for 20 min and then at 0 °C for 1 h. Saturated aqueous NH_4Cl (~3 mL) was added followed by cold water (~2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 19:1) to provide 97 mg (40%) of **11o** as a brown gum.

R_f = 0.73 (hexanes/EtOAc, 7:3); IR (neat): 2953, 2868, 2145, 1777, 1709, 1663, 1347, 1273, 1125, 1072, 1058, 1020, 960 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (d, 1H, *J* = 9.9 Hz, C_5H_9CH=C), 3.03-2.87 (m, 1H, CH_2CHCH_2), 2.00-7.86 (m, 2H, CH_2), 1.80-1.56 (m, 4H, CH_2), 1.47-1.32 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (*C*=O), 160.3 (O*C*=O), 143.2 (O-*C*=CHC_5H_9), 121.2 (C_5H_9*C*H=C), 36.8 (CH_2CHCH_2), 33.1 (2 × CH_2), 25.4 (2 × CH_2); HRMS (ESI, neg.): *m/z* 178.0628 (178.0630 calc. for $C_{10}H_{10}O_3$, $(M-N_2)^-$) and 223.0613 (223.0606 calc. for $C_{11}H_{11}O_5$, $(M+HCOO-N_2)^-$).

(*Z*)-3-Diazo-5-(2,2-dimethylpropylidene)furan-2,4(3H,5H)-dione (11p): The reaction of **10** (75 mg, 0.59 mmol), pivalaldehyde (64 µL, 0.59 mmol), $TiCl_4$ (0.2 mL, 1.78 mmol) and 2,4,6-collidine (0.23 mL, 1.78 mmol) in CH_2Cl_2 (5 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9.5:0.5), 49 mg (43%) of **11p** as a colourless gum. R_f = 0.19 (hexanes/EtOAc, 9.5:0.5); IR (neat): 2963, 2907, 2870, 2148, 1780, 1712, 1622, 1356, 1241, 1083, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (s, 1H, $((CH_3)_3C)$-C*H*), 1.23 (s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, (*C*=O), 160.3 (O-*C*=O), 142.3 (O-*C*=CH($C(CH_3)_3$)), 124.8 ($C(CH_3)_3$*C*H=C), 33.0 ($C(CH_3)_3$), 29.7 (CH_3)$_3$; HRMS (APPI, pos.): *m/z* 194.0699 (194.0691 calc. for $C_9H_{10}N_2O_3$ $(M)^+$), 195.0769 (195.0770 calc. for $C_9H_{11}N_2O_3$ $(M+H)^+$).

3-Diazo-5-(hydroxy(*p*-tolyl)methyl)furan-2,4(3*H*,5*H*)-dione (12): The reaction of **10** (126 mg, 1.00 mmol), tolualdehyde (0.14 mL, 1.20 mmol), $BF_3.OEt_2$ (0.37 mL, 3.0 mmol) and Et_3N (0.43 mL, 3.0 mmol) in CH_2Cl_2 (3 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1), 83 mg (38%) of **12** (dr = 1.2/1) as a white gum. R_f = 0.23 (hexanes/EtOAc, 4:1); IR: 3461, 2923, 2146, 1768, 1698, 1515, 1353, 1215, 1110, 1084, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 7.26 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.18 (d, 2H, *J* = 8.0 Hz, Ar*H*), 5.14 (d, 1H, *J* = 8.0 Hz, *CH*CO), 4.99 (d, 1H, *J* = 3.8 Hz, C*H*OH), 2.67 (br s, 1H, O*H*), 2.35 (s, 3H, CH_3); Minor diastereomer: δ 7.33 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.20 (d, 2H, *J* = 8.0 Hz, Ar*H*), 5.18 (br s, 1H, C*H*CO), 4.84 (d, 1H, *J* = 2 Hz, *CH*OH), 2.36 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$), Major diastereomer: δ 186.0 (*C*=O), 163.0 (O-*C*=O), 139.0 (Ar*C*ipso), 135.5 (Ar*C*ipso), 129.6 (2 × Ar*C*), 126.9 (2 × Ar*C*), 86.6 (*C*HCO), 73.6 (*C*HOH), 21.3 (CH_3); minor diastereomer: δ 186.8 (*C*=O), 163.5 (O-*C*=O), 138.9 (Ar*C*ipso), 133.5 (Ar*C*ipso), 129.5 (2 × Ar*C*), 126.6 (2 × Ar*C*), 86.7 (*C*HCO), 72.5 (*C*HOH), 21.3 (CH_3); HRMS (APPI, pos.): *m/z* 228.0543 (228.0535 calc. for $C_{12}H_8N_2O_3$ $((M-H_2O)^+)$, 229.0611 (229.0613 calc. for $C_{12}H_9N_2O_3$ $(((M-H_2O)+H)^+)$.

General procedures for the insertion reactions of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-diones and arenes:

Method A: To a solution of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (1 equiv) in the aromatic compound was added the Rh(II) catalyst (1 mol%) at room temperature. The reaction mixture was then placed in a pre-heated oil bath at 100 °C. The mixture was heated until complete consumption of the diazo compound (TLC), then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel.

Method B: To a suspension of (*Z*)-5-arylidene/alkylidene-3-diazofuran-2,4(3*H*,5*H*)-dione (1 equiv) in α,α,α-trifluorotoluene or DCE was added the aromatic compound (4 equiv) followed by the Rh(II) catalyst (1 mol%) at room temperature and the reaction mixture was placed in an oil bath that was pre-heated to 50 °C or to 100 °C. The mixture was heated until complete consumption of the diazo compound (TLC), then cooled to room temperature and concentrated. The residue was purified by flash chromatography on silica gel.

(*Z*)-5-Benzylidene-4-hydroxy-3-phenylfuran-2(5*H*)-one (Pulvinone (1)):[15,30] The reaction of **11b** (40 mg, 0.19 mmol), and benzene in the presence of $Rh_2(OAc)_4$ (0.80 mg, 1.9 x 10^{-3} mmol) in benzene (1.5 mL) at reflux for 42 h according to Method A provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3 to 1:1), 38 mg (78%, 81% based on recovery of **11b**) of **1** as a yellow solid.

R_f = 0.17 (hexanes/EtOAc, 7:3); mp: 247-251 °C (Lit.[24] 250-251 °C); IR (neat): 3007 (br), 2920, 2851, 2632 (br), 1698, 1621, 1595, 1406, 1332, 1303, 1210, 1150, 1122, 1001 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.98-7.91 (m, 2H, Ar*H*), 7.80-7.72 (m, 2H, Ar*H*), 7.53-7.27 (m, 6H, Ar*H*), 6.75 (s, 1H, PhC*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9 (*C*=O or C=*C*OH), 163.8 (*C*=O or C=*C*OH), 142.4 (O-*C*=CHPh), 132.7 (ArC_{ipso}), 130.1 (2 × Ar*C*), 129.8 (ArC_{ipso}), 129.0 (2 × Ar*C*), 128.8 (Ar*C*),

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128.3 (2 × Ar*C*), 127.2 (2 × Ar*C*), 127.1 (Ar*C*), 107.6 (Ph*C*H=C), 100.1 (*C*=COH); HRMS (APPI, pos.): *m/z* 264.0796 (264.0786 calc. for $C_{17}H_{12}O_3$, $(M)^+$) and 265.0868 (265.0865 calc. for $C_{17}H_{13}O_3$, $(M+H)^+$).

(*Z*)-4-Hydroxy-5-(4-methoxybenzylidene)-3-(4-methoxyphenyl)furan-2(5*H*)-one (13a):[27] The reaction of **11d** (60 mg, 0.25 mmol) and anisole (107 µL, 0.980 mmol) in the presence of $Rh_2(CF_3CO_2)_4$ (1.6 mg, 2.5 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 100 °C for 6 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 3:7), 56 mg (71%) of **13a** as a brown solid and 16 mg (20%) of **13b** as a yellow solid.
R_f = 0.21 (hexanes/EtOAc, 1:1); mp: 241-244 °C (Lit.[15] 250-253 ºC); IR (neat): 3003, 2954, 2833, 2601 (br), 1685, 1595, 1507, 1426, 1398, 1247, 1175, 1156, 1130, 1098, 1027, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/one drop DMSO-d_6): δ 7.90 (d, 2H, *J* = 8.9 Hz, Ar*H*), 7.71 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.91 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 2H, *J* = 8.9 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*=C), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$/one drop DMSO-d_6): δ 169.0 (*C*=O or C=*C*OH), 162.3 (*C*=O or C=*C*OH), 159.7 (ArC_{ipso}), 158.4 (ArC_{ipso}), 141.1 (O-*C*=CHAr), 131.8 (2 × Ar*C*), 128.9 (2 × Ar*C*), 125.8 (ArC_{ipso}), 122.6 (ArC_{ipso}), 114.1 (2 × Ar*C*), 113.5 (2 × Ar*C*), 107.3 (Ar*C*H=C), 100.6 (*C*=COH), 55.2 (O*C*H_3), 55.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 324.0992 (324.0998 calc. for $C_{19}H_{16}O_5$, $(M)^+$) and 325.1064 (325.1076 calc. for $C_{19}H_{17}O_5$, $(M+H)^+$).

(*Z*)-4-Hydroxy-5-(4-methoxybenzylidene)-3-(2-methoxyphenyl)furan-2(5*H*)-one (13b):
R_f = 0.40 (hexanes/EtOAc, 7:3); mp: 109-115 R °C; IR (neat): 2922 (br), 2838 (br), 1708, 1593, 1511, 1451, 1428, 1302, 1244, 1175, 1145, 1125, 1098, 1024, 983, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.12 (s, 1H, O*H*), 8.09 (dd, 1H, *J* = 7.8, 1.1 Hz, Ar*H*), 7.78 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.35 (ddd, 1H, *J* = 7.8, 7.5, 1.2 Hz, Ar*H*), 7.18 (br td, 1H, *J* = 7.8, 1.1 Hz, Ar*H*), 7.06 (dd, 1H, *J* = 8.2, 1.1 Hz, Ar*H*), 6.93 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.37 (s, 1H, ArC*H*=C), 4.03 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4 (*C*=O or C=*C*OH), 162.8 (*C*=O or C=*C*OH or ArC_{ipso}), 160.3 (*C*=O or C=*C*OH or ArC_{ipso}), 154.7 (ArC_{ipso}), 140.3 (O-*C*=CHAr), 132.4 (2 × Ar*C*), 130.2 (Ar*C*), 129.3 (Ar*C*), 125.7 (ArC_{ipso}), 123.3 (Ar*C*), 119.4 (ArC_{ipso}), 114.4 (2 × Ar*C*), 113.0 (Ar*C*), 108.3 (Ar*C*H=C), 99.2 (*C*=COH), 57.7 (O*C*H_3), 55.5 (O*C*H_3); HRMS (APPI, pos.): *m/z* 324.0986 (324.0998 calc. for $C_{19}H_{16}O_5$, $(M)^+$) and 325.1058 (325.1076 calc. for $C_{19}H_{17}O_5$, $(M+H)^+$).

(*Z*)-5-(3,4-Dimethoxybenzylidene)-4-hydroxy-3-(4-methoxyphenyl)furan-2(5*H*)-one (14a):[27] The reaction of **11f** (90 mg, 0.33 mmol) and anisole (142 µL, 1.31 mmol) in the presence of $Rh_2(CF_3CO_2)_4$ (1.2 mg, 3.3 x 10^{-3} mmol) in α,α,α-trifluorotoluene (3 mL) at 100 °C for 22 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3 to 3:7), 61 mg (53%) of **14a** as a brown solid and 16 mg (14%) of **14b** as a yellow solid.
R_f = 0.22 (hexanes/EtOAc, 1:1); mp: 215-219 °C (Lit.[2] 219-222 °C); IR (neat): 3216 (br), 2959, 2921, 2851, 1693, 1657, 1625, 1595, 1510, 1464, 1443, 1425, 1401, 1242, 1139, 1096, 1018, 987 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/CD_3OD, 97:3): δ 7.81 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.45 (d, 1H, *J* = 1.7 Hz, Ar*H*), 7.30 (dd superimposed on $CHCl_3$ s, 1H, *J* = 8.2, 1.7 Hz, Ar*H*), 6.96 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.34 (s, 1H, ArC*H*=C), 3.95 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.7 (*C*=O or C=*C*OH), 158.1 (ArC_{ipso}), 149.6 (ArC_{ipso}), 148.7 (ArC_{ipso}), 141.0 (O-*C*=CHAr), 128.4 (2 × Ar*C*), 125.6 (ArC_{ipso}), 123.8 (Ar*C*), 122.4 (ArC_{ipso}), 113.8 (2 × Ar*C*), 113.0 (Ar*C*), 112.0 (Ar*C*), 107.3 (*C*=COH), 99.4 (Ar*C*H=C), 55.6 (O*C*H_3), 55.5 (O*C*H_3), 55.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1116 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1189 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

(*Z*)-5-(3,4-Dimethoxybenzylidene)-4-hydroxy-3-(2-methoxyphenyl)furan-2(5*H*)-one (14b):
R_f = 0.43 (hexanes/EtOAc, 1:1); mp: 104-108 °C; IR (neat): 3075 (br), 2954, 2923 (br), 2839, 1748, 1596, 1515, 1451, 1328, 1272, 1237, 1142, 1121, 1012, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar*H*), 7.45 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.40-7.32 (m, 2H, Ar*H*), 7.19 (td, 1H, *J* = 7.7, 1.1 Hz, Ar*H*), 7.07 (dd, 1H, *J* = 8.3, 1.1 Hz, Ar*H*), 6.89 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.35 (s, 1H, ArC*H*=C), 4.04 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3 (*C*=O or C=*C*OH), 162.8 (*C*=O or C=*C*OH), 154.7 (ArC_{ipso}), 150.1 (ArC_{ipso}), 149.2 (ArC_{ipso}), 140.5 (O-*C*=CHAr), 130.2 (Ar*C*), 129.4 (Ar*C*), 126.1 (ArC_{ipso}), 124.6 (Ar*C*), 123.3 (Ar*C*), 119.4 (ArC_{ipso}), 113.0 (2 × Ar*C*), 111.2 (Ar*C or* Ar*C*H=), 108.4 (Ar*C* or Ar*C*H=C), 99.2 (*C*=COH), 57.7 (O*C*H_3), 56.2 (O*C*H_3), 56.1 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1100 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1173 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

(*Z*)-3-(2,4-Dimethoxyphenyl)-4-hydroxy-5-(4-methoxybenzylidene)furan-2(5*H*)-one (15):[27] The reaction of **11d** (65 mg, 0.27 mmol) and 1,3-dimethoxybenzene (139 µL, 1.06 mmol) in the presence of $Rh_2(CF_3CO_2)_4$ (1.7 mg, 2.7 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 100 °C for 22 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7:3), 72 mg (76%) of **15** as a yellow solid.
R_f = 0.19 (hexanes/EtOAc, 7:3); mp: 176-178 °C (Lit.[2] 180-183 °C); IR (neat): 3258 (br), 2926 (br), 2841, 1751, 1603, 1577, 1508, 1327, 1299, 1253, 1210, 1160, 1096, 1023, 963, 932 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, O*H*), 8.01 (d, 1H, *J* = 8.7 Hz, Ar*H*), 7.76 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.92 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.70 (dd, 1H, *J* = 8.7, 2.4 Hz, Ar*H*), 6.59 (d, 1H, *J* = 2.4 Hz, Ar*H*), 6.31 (s, 1H, ArC*H*=C), 4.00 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (*C*=O or C=*C*OH), 161.3 (*C*=O or C=*C*OH or ArC_{ipso}), 160.7 (*C*=O or C=*C*OH or ArC_{ipso}), 160.1 (*C*=O or C=*C*OH or ArC_{ipso}), 155.8 (ArC_{ipso}), 140.3 (O-*C*=CHAr), 132.1 (2 × Ar*C*), 130.8 (Ar*C*), 125.7 (ArC_{ipso}), 114.3 (2 × Ar*C*), 111.7 (ArC_{ipso}), 107.5 (Ar*C*), 107.1 (Ar*C*), 100.3 (Ar*C*H=C), 99.0 (*C*=COH), 57.3 (O*C*H_3), 55.6 (O*C*H_3), 55.3 (O*C*H_3); HRMS (APPI, pos.): *m/z* 354.1108 (354.1103 calc. for $C_{20}H_{18}O_6$, $(M)^+$) and 355.1181 (355.1182 calc. for $C_{20}H_{19}O_6$, $(M+H)^+$).

(*Z*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzylidene)-3-(4-(*tert*-butyldimethylsilyloxy)phenyl)-4-hydroxyfuran-2(5H)-one (16): The reaction of **11f** (150 mg, 0.40 mmol) and *tert*-butyldimethyl(phenoxy)silane (334 mg, 1.60 mmol) in the presence of $Rh_2(esp)_2$ (3 mg, 0.004 mmol) in DCE at reflux for 3 h according to Method B provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9.2:0.8), 29 mg (40%) of **16** as a yellow solid.
R_f = 0.19 (hexanes/EtOAc, 9.2:0.8); mp: 201-203 °C; IR (neat): 3012, 2950, 2927, 2884, 2855, 1693, 1658, 1627, 1597, 1510, 1468, 1426, 1399, 1360, 1292, 1264, 1248, 1149, 1130, 967, 911 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.88-7.82 (m, 2H, Ar*H*), 7.34 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.25 (dd, 1H, *J* = 8.4, 2.0 Hz, Ar*H*), 6.95-6.89 (m, 3H, Ar*H*), 6.63 (s, 1H, ArC*H*), 3.82 (s, 3H, OCH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 0.96 (s, 9H, Si-C(CH_3)$_3$), 0.21 (s, 6H, Si(CH_3)$_2$), 0.16 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0 (*C*=O or *C*=*C*OH), 162.6 (*C*=O or *C*=*C*OH), 154.1 (ArC_{ipso}), 150.6 (ArC_{ipso}), 145.3 (O-*C*=CHAr), 141.0 (ArC_{ipso}), 128.5 (2 × Ar*C*), 126.8 (ArC_{ipso}), 123.7 (Ar*C*), 123.2 (ArC_{ipso}), 120.9 (Ar*C*), 119.7 (2 × Ar*C*), 113.7 (Ar*C*), 107.4 (Ar-*C*H), 99.6 (*C*=COH), 55.4

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(OCH_3), 25.6 ($C(CH_3)_3$), 25.5 ($C(CH_3)_3$), 18.2 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$), -4.5 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$); HRMS (ESI, pos.): *m/z* 554.2508 (554.2520 calc. for $C_{30}H_{42}O_6Si_2$ $(M)^+$), 555.2581 (555.2598 calc. for $C_{30}H_{43}O_6Si_2$ $(M+H)^+$), 577.2400 (577.2418 calc. for $C_{30}H_{42}NaO_6Si_2$ $(M+Na)^+$).

(*Z*)-5-((2,2-Dimethylchroman-6-yl)methylene)-4-hydroxy-3-(7-methoxy-2,2-dimethylchroman-6-yl)furan-2(5*H*)-one (19): The reaction of **11i** (60 mg, 0.20 mmol) and **18**[39] (155 mg, 0.800 mmol) in the presence of $Rh_2(esp)_2$ (1.30 mg, 2.01 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 50 °C for 2 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 8.5:1.5), 79 mg (85%) of **19** as a yellow solid.

R_f = 0.26 (hexanes/EtOAc, 9.5:0.5); mp: 200-204 °C; IR (neat): 3277 (br), 2976, 2933 (br), 2848, 1742, 1605, 1578, 1492, 1451, 1309, 1260, 1151, 1117, 1089, 1017, 976, 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.98 (s, 1H, O*H*), 7.78 (s, 1H, Ar*H*), 7.60 (br d, 1H, *J* = 1.8 Hz, Ar*H*), 7.51 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.49 (s, 1H, Ar*H*), 6.27 (s, 1H, ArC*H*=C), 3.96 (s, 3H, OCH_3), 2.82 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 2.80 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$) (overlapping triplets), 1.83 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.82 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.35 (s, 12H, 4 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8 (*C*=O or C=*C*OH), 161.3 (*C*=O or C=*C*OH), 155.0 (ArC_{ipso}), 154.9 (ArC_{ipso}), 154.2 (ArC_{ipso}), 139.9 (O-*C*=CHAr), 131.9 (Ar*C*), 130.5 (Ar*C*), 130.2 (Ar*C*), 124.8 (ArC_{ipso}), 121.3 (ArC_{ipso}), 117.7 (Ar*C*), 115.5 (ArC_{ipso}), 110.7 (ArC_{ipso}), 107.8 (Ar*C*), 101.6 (Ar*C*H=C), 99.0 (*C*=COH), 75.2 (Ar-O-$C(CH_3)_2$), 75.0 (Ar-O-$C(CH_3)_2$), 57.3 (OCH_3), 32.8 ($ArCH_2CH_2$), 32.7 ($ArCH_2CH_2$), 26.94 (2 × CH_3), 26.86 (2 × CH_3), 22.5 ($ArCH_2CH_2$), 21.8 ($ArCH_2CH_2$); HRMS (APPI, pos.): *m/z* 462.2042 (462.2042 calc. for $C_{28}H_{30}O_6$, $(M)^+$) and 463.2114 (463.2121 calc. for $C_{28}H_{31}O_6$, $(M+H)^+$).

(*Z*)-5-(4-(*tert*-Butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-3-(2,2-dimethylchroman-6-yl)-4-hydroxyfuran-2(5H)-one (20): The reaction of **11h** (50 mg, 0.12 mmol) and **17** (78 mg, 0.48 mmol) in the presence of $Rh_2(esp)_2$ (0.9 mg, 0.001 mmol) in DCE at reflux for 2 h according to Method B provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9:1), 39 mg (59%) of **20** as a yellow solid.

R_f = 0.19 (hexanes/EtOAc, 9:1); mp: 116-118 °C; IR (neat): 2929, 2856, 1711, 1599, 1495, 1258, 1223, 1156, 1117, 991, 935, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar*H*), 7.46 (d, 1H, *J* = 2.0 Hz, Ar*H*) 7.39 (br s, 1H, Ar*H*), 7.34 (br dd, 1H, *J* = 8.4, 1.8 Hz, Ar*H*), 6.84 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.79 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.71-6.54 (bs, 1H, O*H*), 6.26 (s, 1H, ArC*H*), 5.34-5.25 (m, 1H, $(CH_3)_2C=CH$), 3.32 (d, 2H, *J* = 7.0 Hz, $CH_2CH=(CH_3)_2$), 2.80 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.80 (t, 2H, *J* = 6.7 Hz, $ArCH_2CH_2$), 1.76 (s, 3H, CH=C(CH_3)$_2$), 1.71 (s, 3H, CH=C(CH_3)$_2$), 1.33 (s, 6H, O-C(CH_3)$_2$), 1.02 (s, 9H, C(CH_3)$_3$), 0.26 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1 (*C*=O or *C*=*C*OH), 160.6 (*C*=O or C=*C*OH), 154.8 (ArC_{ipso}), 154.3 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 133.1 (ArC_{ipso} or $(CH_3)_2C$=C), 132.9 (ArC_{ipso} or $(CH_3)_2C$=C), 132.7 (Ar*C*), 129.6 (Ar*C*), 129.2 (ArC_{ipso}), 126.9 (Ar*C*), 125.8 (Ar*C*), 122.4 (ArC_{ipso}), 122.0 (ArC_{ipso}), 119.9 ($(CH_3)_2C=CH$), 119.0 (Ar*C*), 118.1 (Ar*C*), 108.7 (Ar-*C*H), 103.1 (*C*=COH), 74.9 (O-$C(CH_3)_2$), 32.8 (CH_2), 28.7 (CH_2), 27.0 ((O-C(CH_3)$_2$), 25.9 ((Si-C(CH_3)$_3$) and 1 × C=C(CH_3)$_2$), 22.6 (CH_3), 18.5 ((Si-$C(CH_3)_3$), 18.0 (1 × C=C(CH_3)$_2$), -4.0 ($Si(CH_3)_2$); HRMS (ESI, pos.): *m/z* 546.2799 (546.2802 calc. for $C_{33}H_{42}O_5Si$ $(M)^+$) and 547.2872 (547.2880 calc. for $C_{33}H_{43}O_5Si$ $(M+H)^+$) and 569.2690 (569.2699 calc. for $C_{33}H_{42}NaO_5Si$ $(M+Na)^+$).

***tert*-Butyl(2,2-dimethylchroman-7-yloxy)dimethylsilane (21):** To a solution of 2,2-dimethylchroman-7-ol[41] (650 mg, 3.65 mmol) in DMF (8 mL) at ambient temperature was added imidazole (348 mg, 5.11 mmol) followed by TBSCl (715 mg, 4.74 mmol) and the mixture was stirred for 2 h. Cold water (8 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (1 × 10 mL), brine, dried (Na_2SO_4) and concentrated under reduced pressure to provide 850 mg (80%) of **21** as a colourless liquid.

R_f = 0.6 (hexanes/EtOAc, 9:1); IR (neat): 2974, 2929, 2895, 2857, 1617, 1576, 1501, 1472, 1344, 1307, 1281, 1253, 1168, 1149, 1120, 1106, 999, 836, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, 1H, *J* = 8.2 Hz), 6.33 (dd, 1H, *J* = 8.2, 2.4 Hz, Ar*H*), 6.29 (d, 1H, *J* = 2.4 Hz, Ar*H*), 2.69 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$), 1.77 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$) 1.31 (s, 6H, 2 × CH_3), 0.97 (s, 9H, C(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2 (Ar*C*ipso), 155.0 (Ar*C*ipso), 130.0 (Ar*C*), 114.2 (Ar*C*ipso), 112.4 (Ar*C*), 108.9 (Ar*C*), 74.5 (Ar-O-$C(CH_3)_2$), 33.4 ($ArCH_2CH_2$), 27.3 (2 × CH_3), 26.1 (C(CH_3)$_3$), 22.3 (Si-$C(CH_3)_3$), 18.6 ($ArCH_2CH_2$), -4.0 ($Si(CH_3)_2$); HRMS (APPI, pos.): *m/z* 292.1865 (292.1858 calc. for $C_{17}H_{28}O_2Si$ $(M)^+$) and 293.1944 (239.1937 calc. for $C_{17}H_{29}O_2Si$ $(M+H)^+$).

(*Z*)-3-(7-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylchroman-6-yl)-5-(4-(*tert*-butyldimethylsilyloxy)-3-(3-methylbut-2-enyl)benzylidene)-4-hydroxyfuran-2(5H)-one (22): The reaction of **11h** (47 mg, 0.11 mmol) and **21** (133 mg, 0.45 mmol), $Rh_2(esp)_2$ (0.8 mg, 0.001 mmol) in DCE at reflux for 6 h according to Method B provided, after purification of by flash column chromatography on silica gel (hexanes/EtOAc, 9.7:0.3), 29 mg (38%, 43% based on recovered SM) of **22** as a yellow solid.

R_f = 0.18 (hexanes/EtOAc, 9.7:0.3); mp: 67-69 °C; IR (neat): 2955, 2929, 2857, 1753, 1611, 1600, 1495, 1471, 1325, 1276, 1254, 1119, 1091, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H, OH), 7.68 (dd, *J* = 8.5, 2.4 Hz, Ar*H*), 7.60 (br s, 1H, Ar*H*), 7.49 (d, 1H, *J* = 2.4 Hz, Ar*H*), 6.83 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.39 (s, 1H, Ar*H*), 6.27 (s, 1H, ArC*H*), 5.36-5.28 (m, 1H, $(CH_3)_2C=CH$), 3.33 (d, 2H, *J* = 7.2 Hz, $CH_2CH=(CH_3)_2$), 2.78 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$), 1.80 (t, 2H, *J* = 6.8 Hz, $ArCH_2CH_2$), 1.77 (s, 3H, CH=C(CH_3)$_2$), 1.73 (s, 3H, CH=C(CH_3)$_2$), 1.33 (s, 6H, C(CH_3)$_2$) 1.02 (s, 9H, C(CH_3)$_3$), 0.96 (s, 9H, C(CH_3)$_3$), 0.26 (s, 6H, Si(CH_3)$_2$), 0.20 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7 (*C*=O or *C*=*C*OH), 161.6 (*C*=O or *C*=*C*OH), 154.9 (ArC_{ipso}), 154.5 (ArC_{ipso}), 150.4 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 133.1 (ArC_{ipso} or $(CH_3)_2C$=C) , 132.8 (ArC_{ipso} or $(CH_3)_2C$=C), 132.5 (Ar*C*), 130.4 (Ar*C*), 129.5 (Ar*C*), 126.2 (ArC_{ipso}), 122.4 (($(CH_3)_2C=C$), 119.0 (Ar*C*), 116.7 (ArC_{ipso}), 113.3 (ArC_{ipso}), 109.2 (Ar-*C*H) , 107.8 (Ar*C*) , 100.3 (*C*=COH), 75.1 ($C(CH_3)_2$), 32.9 (CH_2), 28.7 (CH_2), 27.0 ((O-C(CH_3)$_2$), 25.9 (2 × (Si-C(CH_3)$_3$), 1 × C=C(CH_3)$_2$), 22.0 (CH_2). 18.53 (Si-$C(CH_3)_2$), 18.48 (Si-$C(CH_3)_2$), 18.1 (1× C=C(CH_3)$_2$), -3.9 ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$); HRMS (APPI, pos.): *m/z* 676.3616 (676.3615 calc. for $C_{39}H_{56}O_6Si_2$ $(M)^+$) and 677.3686 (677.3694 calc. for $C_{39}H_{57}O_6Si_2$ $(M+H)^+$).

General procedure for the demethylation of aryl methyl ethers 13a, 14a and 15: To a solution of methoxypulvinones in CH_2Cl_2 was added BBr_3 (1M in CH_2Cl_2) at 0 °C. The mixture was warmed to room temperature, stirred for 20 min and then heated to reflux until consumption of the starting material (TLC). The mixture was then cooled to 0 °C and water (3 mL) was added. The resulting suspension was extracted with ethyl acetate (5 x 4 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was dissolved in dichloromethane with the aid of methanol and a few drops of hexanes were added. The

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mixture was left for a day at room temperature and the precipitated product (yellow solid) was isolated by filtration. This material was pure by ^{1}H NMR.

(*Z*)-4-Hydroxy-5-(4-hydroxybenzylidene)-3-(4-hydroxyphenyl)furan-2(5*H*)-one (Aspulvinone E (2)):[27,43] The reaction of **13a** (80 mg, 0.25 mmol), BBr_3 (1.5 mL 1.5 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (3 mL) for 3 h, according to the general procedure, provided 61 mg (84%) of **2** as a brown solid.
R_f = 0.27 (EtOAc/hexanes, 3:2); mp: 261-266 °C (Lit.[2] >250 °C); IR (neat): 3202 (br), 2923, 2853, 1695, 1602, 1509, 1443, 1408, 1340, 1248, 1194, 1158 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 7.74 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.65 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.82 (d, 4H, *J* = 8.7 Hz, Ar*H*), 6.40 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.2 (*C*=O or C=*C*OH), 163.3 (*C*=O or C=*C*OH), 159.7 (ArC_{ipso}), 157.9 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 133.3 (2 × Ar*C*), 130.3 (2 × Ar*C*), 125.9 (ArC_{ipso}), 122.3 (ArC_{ipso}), 116.8 (2 × Ar*C*), 116.1 (2 × Ar*C*), 108.9 (Ar*C*H=C), 102.5 (*C*=COH); HRMS (APPI, pos.): *m/z* 296.0690 (296.0685 calc. for $C_{17}H_{12}O_5$, $(M)^+$) and 297.0763 (297.0763 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

(*Z*)-3-(2,4-Dihydroxyphenyl)-4-hydroxy-5-(4-hydroxybenzylidene)furan-2(5*H*)-one (Aspulvinone G (3)):[27] The reaction of **14a** (60 mg, 0.17 mmol), BBr_3 (1.5 mL, 1.5 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (3 mL) for 2 h, according to the general procedure, provided 43 mg (81%) of **3** as a yellow solid.
R_f = 0.25 (EtOAc/hexanes, 3:2); mp: 243-248 °C (Lit.[2] >250 °C); IR (neat): 3151 (br), 1729, 1603, 1513, 1464, 1443, 1376, 1343, 1307, 1256, 1226, 1174, 1118, 1093, 983 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 7.64 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.60 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.82 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.43 (dd, 1H, *J* = 8.2, 2.1 Hz, Ar*H*), 6.42 (s, 1H, Ar*H*), 6.32 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.4 (*C*=O or C=*C*OH), 163.6 (*C*=O or C=*C*OH), 159.9 (ArC_{ipso}), 159.7 (ArC_{ipso}), 155.7 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 133.3 (2 × Ar*C*), 131.7 (Ar*C*), 126.1 (ArC_{ipso}), 116.8 (2 × Ar*C*), 109.6 (ArC_{ipso}), 109.1 (Ar*C*), 108.5 (Ar*C*), 103.9 (Ar*C*H=C), 100.1 (*C*=COH); HRMS (APPI, pos.): *m/z* 312.0635 (312.0634 calc. for $C_{17}H_{12}O_6$, $(M)^+$) and 313.0708 (313.0712 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

(*Z*)-5-(3,4-Dihydroxybenzylidene)-4-hydroxy-3-(4-hydroxyphenyl)furan-2(5*H*)-one (3',4,'4-Trihydroxypulvinone (4)):[27] The reaction of **15** (55 mg, 0.16 mmol), BBr_3 (1.6 mL, 1.6 mmol, 1.0 M in CH_2Cl_2) in dichloromethane (2 mL) for 4 h, according to general procedure, provided 41 mg (85%) of **4** as a brown solid.
R_f = 0.31 (EtOAc/hexanes, 3:2); mp: 277-283 °C (Lit.[7] 289-291 °C); IR (neat): 3304 (br), 2921, 2628 (br), 1693, 1597, 1509, 1443, 1407, 1326, 1241, 1156, 1129, 1098, 1015, 964 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 10.43 (br s, 1H, O*H*), 8.51 (s, 1H, O*H*), 8.36 (s, 1H, O*H*), 8.24 (s, 1H, O*H*), 7.83 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.47 (d, 1H, *J* = 2.0 Hz, Ar*H*), 7.09 (dd, 1H, *J* = 8.2, 2.0 Hz, Ar*H*), 6.89 (d, 1H, *J* = 8.8 Hz, Ar*H*), 6.87 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.44 (s, 1H, ArC*H*=C); ^{13}C NMR (75 MHz, CD_3OD): δ 171.4 (*C*=O or C=*C*OH), 163.4 (*C*=O or C=*C*OH), 158.0 (ArC_{ipso}), 148.2 (ArC_{ipso}), 146.7 (ArC_{ipso}), 141.8 (O-*C*=CHAr), 130.3 (2 × Ar*C*), 126.4 (ArC_{ipso}), 124.9 (Ar*C*), 122.4 (ArC_{ipso}), 118.0 (Ar*C*), 116.5 (Ar*C*), 116.1 (2 × Ar*C*), 109.4 (Ar*C*H=C), 102.5 (*C*=COH); HRMS (APPI, pos.): *m/z* 312.0628 (312.0634 calc. for $C_{17}H_{12}O_6$, $(M)^+$) and 313.0704 (313.0712 calc. for $C_{17}H_{13}O_6$, $(M+H)^+$).

(*Z*)-3-(2,2-Dimethylchroman-6-yl)-5-((2,2-dimethylchroman-6-yl)methylene)-4-hydroxyfuran-2(5*H*)-one (Aspulvinone A (6)):[27,43] The reaction of **11i** (60 mg, 0.21 mmol) and **17** (134 mg, 0.830 mmol) in the presence of $Rh_2(esp)_2$ (1.6 mg, 2.1 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 50 °C for 6 h according to Method B provided, after purification by flash column chromatography on silica gel (CH_2Cl_2/EtOAc, 9.8:0.2 to 9:1), 63 mg (60%) of **6** as a yellow solid.
R_f = 0.12 (hexanes/EtOAc, 7:3); mp: 244-247 °C (Lit.[2] 241-243 °C); IR (neat): 2973 (br), 2928 (br), 1690, 1624, 1605, 1572, 1495, 1390, 1300, 1259, 1234, 1154, 1121, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6, 95:5): δ 10.99 (br, 1H, O*H*), 7.70 (s, 1H, Ar*H*), 7.68 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 7.56 (br d, 1H, *J* = 2.0 Hz, Ar*H*), 7.48 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 6.79 (dd, 1H, *J* = 8.6. 2.0 Hz, Ar*H*), 6.76 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*=C), 2.83 (br t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 2.82 (br t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.83 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.82 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.35 (s, 6H, 2 × CH_3), 1.34 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.0 (*C*=O or C=*C*OH), 154.5 (ArC_{ipso}), 152.8 (ArC_{ipso}), 140.4 (O-*C*=CHAr), 131.6 (Ar*C*), 129.6 (Ar*C*), 128.4 (Ar*C*), 126.4 (Ar*C*), 124.4 (ArC_{ipso}), 121.5 (ArC_{ipso}), 121.3 (ArC_{ipso}), 120.6 (ArC_{ipso}), 117.5 (Ar*C*), 116.6 (Ar*C*), 107.3 (O-C=*C*HAr), 99.7 (*C*=COH), 74.9 (Ar-O-*C*$(CH_3)_2$), 74.3 (Ar-O-*C*$(CH_3)_2$), 32.1 (ArCH_2CH_2), 31.9 (ArCH_2CH_2), 26.6 (4 × CH_3), 22.0 (ArCH_2CH_2), 21.8 (ArCH_2CH_2); HRMS (APPI, pos.): *m/z* 432.1921 (432.1937 calc for $C_{27}H_{28}O_5$ $(M)^+$) and 433.1993 (433.2015 calc for $C_{27}H_{29}O_5$ $(M+H)^+$).

(*Z*)-5-((2,2-Dimethylchroman-6-yl)methylene)-4-hydroxy-3-(7-hydroxy-2,2-dimethylchroman-6-yl)furan-2(5*H*)-one (Aspulvinone C (7)):[5,43] To a solution of compound **19** (50 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (0.32 mL, 0.32 mmol, 1.0 M in CH_2Cl_2) at -78 °C and the mixture was stirred for 40 min. The reaction mixture was then warmed to 0 °C and stirred for 20 min. Water (2 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 4 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was dissolved in dichloromethane (3 mL), a few drops of hexanes were added, and the mixture was allowed to stand at room temperature for 22 h to provide 36 mg (75%) of **6** (Aspulvinone C) as a yellow solid that was isolated by filtration. This was pure by ^{1}H NMR.
R_f = 0.61 (EtOAc/hexanes, 7:3); mp: 224-230 °C; IR (neat): 3065 (br), 2973, 2924 (br), 1709, 1602, 1494, 1428, 1343, 1284, 1263, 1229, 1154, 1109, 1088 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (s, 1H, Ar*H*), 7.48 (dd, 1H, *J* = 8.9, 2.1 Hz, Ar*H*), 7.11 (s, 1H, Ar*H*), 6.77 (d, 1H, *J* = 8.9 Hz, Ar*H*), 6.28 (s, 1H, Ar*H* or ArC*H*=C), 6.24 (s, 1H, Ar*H* or ArC*H*=C), 2.78 (t, 2H, *J* = 6.6 Hz, ArCH_2CH_2), 2.64 (t, 2H, *J* = 6.6 Hz, ArCH_2CH_2), 1.79 (t, 2H, *J* = 6.6 Hz, ArCH_2CH_2), 1.73 (t, 2H, *J* = 6.6 Hz, ArCH_2CH_2), 1.30 (s, 6H, 2 × CH_3), 1.27 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or C=*C*OH), 163.6 (*C*=O or C=*C*OH), 154.20 (ArC_{ipso}), 154.19 (ArC_{ipso}), 154.1 (ArC_{ipso}), 141.3 (O-*C*=CHAr), 131.4 (Ar*C*), 130.6 (Ar*C*), 129.4 (Ar*C*), 124.7 (ArC_{ipso}), 121.3 (ArC_{ipso}), 117.3 (Ar*C*), 111.5 (ArC_{ipso}), 108.8 (ArC_{ipso}), 105.5 (Ar*C or* Ar*C*H=C), 103.4 (Ar*C or* Ar*C*H=C), 97.9 (*C*=COH), 74.8 (Ar-O-*C*$(CH_3)_2$), 74.1 (Ar-O-*C*$(CH_3)_2$), 32.4 (ArCH_2CH_2), 32.0 (ArCH_2CH_2), 26.62 (2 × CH_3), 26.59 (2 × CH_3), 21.8 (ArCH_2CH_2), 21.2 (ArCH_2CH_2); HRMS (ESI, pos.): *m/z* 448.1866 (448.1886 calc for $C_{27}H_{28}O_6$ $(M)^+$) and 471.1755 (471.1784 calc for $C_{27}H_{28}NaO_6$ $(M+Na)^+$).

General procedure for the deprotection of TBS ethers 16, 19, 20, 22: To a solution of the TBS protected substrate in THF was added TBAF (1M in THF) at 0 °C. The mixture was warmed to room temperature and stirred until consumption of the starting material (TLC). The solvent was removed under educed pressure, the residue suspended in water and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulphate and concentrated. The residue was purified by flash chromatography on silica gel.

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(*Z*)-4-Hydroxy-5-(4-hydroxy-3-methoxybenzylidene)-3-(4-hydroxyphenyl)furan-2(5H)-one (Aspulvinone Q (5)):[11] The reaction **16** (75 mg, 0.135 mmol) and TBAF (0.40 ml, 0.40 mmol) in THF (2 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 3:2 1% AcOH), 38 mg (86%) of **5** as a yellow solid.

R_f = 0.23 (hexanes/EtOAc, 3:2, 1% vol AcOH); mp: 223-225 °C; IR (neat): 3300 (br), 3129, 2931, 1692, 1624, 1592, 1512, 1432, 1406, 1277, 1234, 1148, 1130, 1095 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.49 (bs, 2H, O*H*), 7.80 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.30 (s, 1H, Ar*H*), 7.18 (dd, 1H, *J* = 8.1, 2.0 Hz,), 6.86 (d, 1H, *J* = 8.1 Hz, Ar*H*), 6.80 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.53 (br s, 1H, ArC*H*), 3.80 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 163.6 (*C*=O or *C*=*C*OH), 156.1 (ArC_{ipso}), 147.7 (ArC_{ipso}), 147.6 (ArC_{ipso}), 141.0 (O-*C*=CHAr), 128.1 (2 × Ar*C*), 124.6 (ArC_{ipso}), 124.0 (Ar*C*), 121.5 (ArC_{ipso}), 115.9 (Ar*C*), 115.0 (2 × Ar*C*), 113.7 (Ar*C*), 106.7 (Ar-*C*H), 98.5 (*C*=COH), 55.6 (OCH_3); HRMS (APPI, pos.): *m/z* 326.0781 (326.0790 calc. for $C_{18}H_{14}O_6$ $(M)^+$), 327.0853 (327.0869 calc. for $C_{18}H_{15}O_6$ $(M+H)^+$).

(*Z*)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-(4-hydroxy-3-(3-methylbut-2-enyl)benzylidene)furan-2(5H)-one (Aspulvinone B (8)):[27] The reaction of **20** (50 mg, 0.091 mmol) and TBAF (0.18 ml, 0.18 mmol) in THF (2 mL) according to the general procedure for 1 h. provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 7.5:2.5, 1% AcOH), 22 mg (56%) of **8** as a yellow solid.

R_f = 0.23 (hexanes/EtOAc, 7.5:2.5, 1% vol AcOH); mp: 146-149 °C; IR (neat): 3310 (br), 2973, 2927, 1704, 1598, 1496, 1434, 1261, 1221, 1156, 1116, 989 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.87 (s, 1H, O*H*), 7.70-7.63 (m, 2H, Ar*H*), 7.47-7.41 (m, 2H, Ar*H*), 6.87 (d, 1H, *J* = 8.2, Ar*H*), 6.75 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.54 (s, 1H, ArC*H*) 5.29 (br t, 1H, *J* = 7.4 Hz, CH_2CH=$(CH_3)_2$), 3.24 (d, 2H, *J* = 7.4 Hz, CH_2CH=$(CH_3)_2$), 2.76 (br t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.78 (br t, 2H, *J* = 6.7 Hz, ArCH_2CH_2) 1.72 (s, 3H, CH=$(CH_3)_2$), 1.70 (s, 3H, CH=$(CH_3)_2$), 1.29 (s, 6H, C$(CH_3)_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3 (*C*=O or *C*=*C*OH), 162.6 (*C*=O or C=*C*OH), 156.0 (ArC_{ipso}), 152.6 (ArC_{ipso}), 140.1 (O-*C*=CHAr), 131.9 (ArC_{ipso} or $(CH_3)_2C$=C), 131.6 (Ar*C*), 129.3 (Ar*C*), 128.2 (Ar*C*), 128.0 (ArC_{ipso} or $(CH_3)_2C$=C), 126.2 (Ar*C*), 123.9 (ArC_{ipso}), 122.4 ($(CH_3)_2$C=*C*), 121.6 (ArC_{ipso}), 120.5 (ArC_{ipso}), 116.5 (Ar*C*), 115.4 (Ar*C*), 107.5 (Ar*C*H), 99.1 (*C*=COH), 74.3 (O-*C*$(CH_3)_2$), 32.2 (*C*H_2), 27.8 (*CH*$_2$), 26.6 ((O-C(*CH*$_3)_2$), 25.5 (C=C(*CH*$_3)_2$), 22.0 (*CH*$_2$), 17.7 (C=C(*CH*$_3)_2$); HRMS (APPI, pos.): *m/z* 432.1929 (432.1937 calc. for $C_{27}H_{28}O_5$ $(M)^+$), 433.2001 (433.2015 calc. for $C_{27}H_{29}O_5$ $(M+H)^+$).

(*Z*)-4-Hydroxy-3-(7-hydroxy-2,2-dimethylchroman-6-yl)-5-(4-hydroxy-3-(3-methylbut-2-enyl)benzylidene)furan-2(5H)-one (Aspulvinone D (9)):[5,43] The reaction of **22** (165 mg, 0.243 mmol) and TBAF (0.70 ml, 0.73 mmol) in THF (3 mL) according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 8.0:2.0, 1% AcOH), 90 mg (83%) of **9** as a yellow solid.

R_f = 0.20 (hexanes/EtOAc, 8.0:2.0, 1% vol AcOH); mp: 199-201 °C (decomp.); IR (neat): 3300 (br), 2973, 2925, 1696, 1662, 1589, 1505, 1425, 1344, 1276, 1229, 1157, 1090, 990 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 9.81 (bs, 1H, O*H*), 7.47 (br d, 1H, *J* = 1.9 Hz, Ar*H*), 7.45 (br dd, 1H, *J* = 8.3, 1.9 Hz, Ar*H*), 7.10 (s, 1H, Ar*H*), 6.86 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.27 (s, 1H, Ar*H* or ArC*H*), 6.24 (s, 1H, ArC*H* or Ar*H*), 5.29 (br t, 1H, *J* = 6.7 Hz, CH_2CH=$(CH_3)_2$), 3.24 (d, 2H, *J* = 6.7 Hz, CH_2CH=$(CH_3)_2$), 2.64 (br t, 2H, *J* = 6.5 Hz, ArCH_2CH_2), 1.73 (t, 2H, *J* = 6.5 Hz, ArCH_2CH_2), 1.72 (s, 3H, CH=C(*CH*$_3)_2$), 1.70 (s, 3H, CH=C(*CH*$_3)_2$), 1.27 (s, 6H, *C*$(CH_3)_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 163.3 (*C*=O or *C*=*C*OH), 155.8 (ArC_{ipso}), 154.1 (2 × ArC_{ipso}), 140.6 (O-*C*=CHAr), 131.8 (ArC_{ipso} or $(CH_3)_2C$=C), 131.6 (Ar*C*), 130.7 (Ar*C*), 129.2 (Ar*C*), 128.0 (ArC_{ipso} or $(CH_3)_2C$=C), 124.0 (ArC_{ipso}), 122.5 ($(CH_3)_2$C=*C*), 115.3 (Ar*C*), 111.6 (ArC_{ipso}), 108.7 (ArC_{ipso}), 106.1 (Ar-*C*H), 103.4 (Ar*C*), 98.0 (*C*=COH), 74.1 (O-*C*$(CH_3)_2$), 32.4 (*CH*$_2$), 27.9 (*CH*$_2$), 26.6 (C(*CH*$_3)_2$), 25.5 (C=C(*CH*$_3)_2$), 21.2 (*CH*$_2$), 17.7 (C=C(*CH*$_3)_2$); HRMS (ESI, pos.): *m/z* 448.1890 (448.1886 calc. for $C_{27}H_{28}O_6$ $(M)^+$), 449.1963 (449.1964 calc. for $C_{27}H_{29}O_6$ $(M+H)^+$), 471.1778 (471.1784 calc. for $C_{27}H_{28}NaO_6$ $(M+Na)^+$).

(*Z*)-5-(Cyclopentylmethylene)-3-(2,2-dimethylchroman-6-yl)-4-hydroxyfuran-2(5*H*)-one (23): The reaction of **11o** (56 mg, 0.27 mmol) and **17** (176 mg, 1.08 mmol) in the presence of $Rh_2(esp)_2$ (1.8 mg, 2.7 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 50 °C for 22 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 9:1 to 7:3), 54 mg (58%) of **23** as a white solid.

R_f = 0.21 (hexanes/EtOAc, 7:3); mp: 176-179 °C; IR (neat): 2942 (br), 2865 (br), 1697, 1670, 1627, 1613, 1576, 1497, 1438, 1395, 1370, 1253, 1223, 1155, 1120, 1099, 1003 cm^{-1}; ^1H NMR NMR (300 MHz, $CDCl_3/CD_3OD$, 95:5): δ 7.60 (br s, 1H, Ar*H*), 7.57 (dd, 1H, *J* = 8.3, 2.2 Hz, Ar*H*), 6.78 (d, 1H, *J* = 8.3, Hz, Ar*H*), 5.56 (d, 1H, *J* = 9.7 Hz, C_5H_9CH=C), 3.16-3.00 (m, 1H, CH_2CHCH_2), 2.81 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 2.02-1.87 (m, 2H, CH_2), 1.81 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.77-1.56 (m, 4H, CH_2), 1.48-1.24 (m, 2H, CH_2), 1.34 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$, 95:5): δ 169.9 (*C*=O or C=*C*OH), 160.8 (*C*=O or C=*C*OH), 153.4 (ArC_{ipso}), 142.9 (O-*C*=CHAr), 129.1 (Ar*C*), 127.2 (Ar*C*), 121.2 (ArC_{ipso}), 121.0 (ArC_{ipso}), 117.1 (Ar*C* or O-C=*C*HAr), 115.6 (Ar*C* or O-C=*C*HAr), 102.6 (*C*=COH), 74.7 (Ar-O-*C*$(CH_3)_2$), 37.1 (*CH*$(CH_2)_2$), 33.7 (2 × *CH*$_2$), 32.9 (*CH*$_2$), 26.9 (2 × *CH*$_3$), 25.4 (2 × *CH*$_2$), 22.5 (*CH*$_2$); HRMS (APPI, pos.): *m/z* 340.1667 (340.1675 calc. for $C_{21}H_{24}O_4$, $(M)^+$) and 341.1739 (341.1753 calc. for $C_{21}H_{25}O_4$, $(M+H)^+$).

(*Z*)-3-(2,2-Dimethylchroman-6-yl)-4-hydroxy-5-(naphthalen-2-ylmethylene)furan-2(5*H*)-one (24): The reaction of **11j** (70 mg, 0.27 mmol) and **17** (175 mg, 1.08 mmol) in the presence of $Rh_2(esp)_2$ (1.8 mg, 2.7 x 10^{-3} mmol) in α,α,α-trifluorotoluene (2 mL) at 70 °C for 5 h according to Method B provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 4:1 to 1:1), 44 mg (42%) of **24** as a yellow solid.

R_f = 0.15 (hexanes/EtOAc, 3:2); mp: 164-169 °C; IR (neat): 3053 (br), 2974 (br), 2929 (br) 2849, 1695, 1621, 1495, 1386, 1314, 1267, 1222, 1156, 1118, 1020, 943 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.20 (s, 1H, Ar*H*), 8.04-7.88 (m, 4H, Ar*H*), 7.70 (s, 1H, Ar*H*), 7.70-7.65 (br s, 1H, Ar*H*), 7.60-7.57 (m, 2H, Ar*H*), 6.83 (s, 1H, ArC*H*=C), 6.78 (d, 1H, *J* = 8.3 Hz, Ar*H*), 2.78 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.79 (t, 2H, *J* = 6.7 Hz, ArCH_2CH_2), 1.30 (s, 6H, 2 × CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1 (*C*=O or C=*C*OH), 162.2 (*C*=O or C=*C*OH), 152.9 (ArC_{ipso}), 142.9 (O-*C*=CHAr), 133.0 (ArC_{ipso}), 132.6 (ArC_{ipso}), 130.6 (ArC_{ipso}), 129.7 (Ar*C*), 128.5 (2 × Ar*C*), 128.3 (Ar*C*), 127.6 (Ar*C*), 127.0 (Ar*C*), 126.9 (Ar*C*), 126.7 (Ar*C*), 126.5 (Ar*C*), 121.2 (ArC_{ipso}), 120.6 (ArC_{ipso}), 116.7 (Ar*C*), 106.8 (O-C=*C*HAr), 100.3 (*C*=COH), 74.4 (Ar-O-*C*$(CH_3)_2$), 32.1 (ArCH_2CH_2), 26.6 (2 × CH_3), 22.0 (ArCH_2CH_2); HRMS (APPI, pos.): *m/z* 398.1509 (398.1518 calc. for $C_{26}H_{22}O_4$, $(M)^+$) and 399.1580 (399.1596 calc. for $C_{26}H_{23}O_4$, $(M+H)^+$).

(*Z*)-3-(5-Bromo-1H-indol-3-yl)-5-((2,2-dimethylchroman-6-yl)methylene)-4-hydroxyfuran-2(5H)-one (25): The reaction of **11i** (50 mg, 0.16 mmol) and 5-bromoindole (131 mg, 0.67 mmol) in the presence of $Rh_2(esp)_2$ (1.2 mg, 0.001 mmol) in $PhCF_3$ at 50 °C for 24 h according to the general procedure provided, after purification by flash column chromatography on silica gel (hexanes/EtOAc, 1:1), 70 mg (90 %) of **25** as a green solid.

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R_f = 0.2 (hexanes/EtOAc, 3:2); mp: 243-245 °C; IR (neat): 3427, 2972, 2926, 1711, 1605, 1574, 1531, 1496, 1453, 1295, 1264, 1254, 1153, 1116 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 11.57 (s, 1H, O*H*), 8.22 (s, 1H, Ar*H*), 7.78 (s, 1H, Ar*H*), 7.50-7.42 (m, 2H, Ar*H*), 7.39 (d, 1H, *J* = 8.5 Hz, Ar*H*), 7.24 (d, 1H, *J* = 8.5 Hz, Ar*H*), 6.80 (s, 1H, *J* = 8.5 Hz, Ar*H*), 6.47 (s, 1H, ArC*H*), 2.79 (br t, 2H, *J* = 6.8 Hz, CH_2), 1.80 (br t, 2H, *J* = 6.8 Hz, CH_2), 1.30 (s, 6H, (CH_3)$_2$); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6 (*C*=O or *C*=*C*OH), 161.5 (*C*=O or *C*=*C*OH), 154.2 (ArC_{ipso}), 141.5 (O-*C*=CHAr), 134.7 (ArC_{ipso}), 131.4 (Ar*C*), 129.4 (Ar*C*), 127.2 (ArC_{ipso}), 126.5 (Ar*C*), 124.7 (ArC_{ipso}), 124.0 (Ar*C*), 123.8 (Ar*C*), 121.4 (ArC_{ipso}), 117.4 (Ar*C*), 113.6 (Ar*C*), 111.4 (ArC_{ipso}), 106.2 (Ar*C*H), 104.2 (*C*=COH), 96.7 (ArC_{ipso}), 74.9 (O-*C*(CH$_3$)$_2$), 32.0 (*C*H$_2$), 26.6 (*C*H$_3$)$_2$, 21.8 (*C*H$_2$); HRMS (ESI, pos.): *m/z* 465.0589 (465.0576 calc. for $C_{24}H_{20}Br^{79}NO_4$ $(M)^+$), 466.0662 (467.0654 calc. for $C_{24}H_{21}Br^{79}NO_4$ $(M+H)^+$), 468.0646 (469.0633 calc. for $C_{24}H_{21}Br^{81}NO_4$ $(M+H)^+$), 488.0482 (488.0473 calc. for $C_{24}H_{20}Br^{79}NNaO_4$ $(M+Na)^+$), 490.0465 (491.0452 calc. for $C_{24}H_{20}Br^{81}NNaO_4$ $(M+Na)^+$).

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 L. Vieweg, S. Reichau, R. Schobert, P. F. Leadlay and R. D. Süssmuth, *Nat. Prod. Rep.,* 2014, **31**, 1554.
2 R. Schobert, R and A. Schlenk, *Bioorg. Med. Chem.*, 2008, **16**, 4203.
3 R. L. Edwards and M. Gill, *J. Chem. Soc. Perkin Trans.*, *1* 1973, 1921.
4 N. Ojima, S. Takenaka and S. Seto, *Phytochemistry*, 1973, **12**, 2527.
5 N. Ojima, S. Takenaka and S. Seto, *Phytochemistry*, 1975, **14,** 573.
6 M. J. Begley, D. R. Gedge, D. W. Knight and G. Pattenden, *J. Chem. Soc. Perkin Trans. 1*, 1979, 77.
7 L.-H. Zhang, B.-M. Feng, Y.-Q. Zhao, Y. Sun, B. Liu, F. Liu, G. Chen, J. Bai, H.-M. Hua, H.-F. Wang and Y.-H. Pei, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 346.
8 N. Ojima, I. Takahashi, K. Ogura, S. Seto, *Tetrahedron Lett.*, 1976, **17**, 1013.
9 P. G. Cruz, D. S. Auld, P. J. Schultz, S. Lovell, K. P. Battaile, R. MacArthur, M. Shen, G. Tamayo-Castillo, J. Inglese and D. H. Sherman, *Chem. Biol.*, 2011, **18**, 1442.
10 P. Zhang, X.-M. Li, J. N. Wang, X. Li and B.-G. Wang, *Phytochem. Lett.*, 2015, **11**, 85.
11 X. Pang, J.-Y. Zhao, X.-M. Fang, T. Zhang, D.-W. Zhang, H.-Y. Liu, J. Su, S. Cen and L.-Y. Yu, *J. Nat. Prod.*, 2017, **80**, 2595.
12 K. Rehse and J. Lehmke, *Arch. Pharm.*, 1985, **318**, 11 and references therein.
13 H.-W. Xu, C. Xu, Z.-Q. Fan, L. J. Zhao, and H.-M. Liu, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 737.
14 T. S. Mansour, C. E. Caufield, B. Rasmussen, R. Chopra, G. Krishnamurthy, K. M. Morris, K. Svenson, J. Bard, C. Smeltzer, S. Naughton, S. Antane, Y. Yang, A. Severin, D. Quagliato, P. J. Petersen and G. Singh, *ChemMedChem*, 2007, **2**, 1414 and references therein.
15 F. R. Foden, J. McCormick and D. M. O'Mant, *J. Med. Chem.*, 1975, **18**, 199.
16 D. Peter and R. Brückner, *Chem. Eur. J.*, 2017, **23**, 12104.
17 C. L. Zhang, S. S. Chatterjee, U. Stein and U. Heinemann, *N.-S. Arch. Pharmacol.*, 1992, **345**, 85.
18 K. Luk and S. A. Readshaw, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1641.
19 H. Gao, W. Guo, Q. Wang, L. Zhang, M. Zhu, T. Zhu, Q. Gu, W. Wang and D. Li, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1776.
20 R. T. Dewi, S. Tachibana, S. Fajriah and M. Hanafi, *Med. Chem. Res.*, 2015, **24**, 737.
21 D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1979, 70.
22 R. Ramage, G. J. Griffiths and F. E. Shutt, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1539.
23 N. Kaczybura and R. Brückner, *Synthesis*, 2007, 118.
24 A. C. Campbell, M. S. Maidment, J. H. Pick and D. F. M. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1567.
25 M. Gill, M. J. Kiefel, D. A. Lally and A. Ten, *Aust. J. Chem.*, 1990, **43**, 1497.
26 S. Antane, C. E. Caufield, W. Hu, D. Keeney, P. Labthavikul, K. Morris, S. M. Naughton, P. J. Petersen, B. A. Rasmussen, G. Singh and Y. Yang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 176.
27 D. Bernier and R. Brückner, *Synthesis*, 2007, 2249.
28 B. Nadal, J. Rouleau, H. Besnard, P. Thuéry, and T. Le Gall, *Tetrahedron* 2011, **67**, 2605.
29 D. Hermann, D. Arican and R. Brückner, *Synthesis*, 2017, 326.
30 Y. Sadamitsu, K. Komatsuki, K. Saito and T. Yamada, *Org. Lett.,* 2017, **19**, 3191.
31 (a) A. Manchoju and S. V. Pansare, *Org. Lett.*, 2016, **18**, 5952. For selected reports on arene C-H insertion reactions of diazocarbonyl compounds, see: (b) X. Hu, X. Chen, Y. Shao, H. Zhie, Y. Deng, Z. Ke, H. Jiang and W. Zheng, *ACS Catal.* 2018, **8**, 1308. (c) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert and F. Glorius, *Angew. Chem., Int. Ed.* 2015, **54**, 4508. (d) E. Tayama, T. Yanaki, H. Iwamoto and E. Hasegawa, *Eur. J. Org. Chem.* 2010, 6719. (e) J.-M. Yang, Y. Cai, S.-F. Zhu and Q.-L. Zhou, *Org. Biomol. Chem.* 2016, **14**, 5516.
32 (a) Studies on O-H bond insertion: H. D. Stachel, H. Poschenrieder, J. Redlin, J. Schachtner and K. Zeitler, *Liebigs Ann. Chem.*, 1994, 129. (b) P. V. Murphy, T. J. O'Sullivan, B. D. Kennedy and N. W. A. Geraghty, *J. Chem. Soc. Perkin Trans. 1*, 2000, **13**, 2121.
33 Review: M. Periasamy, *ARKIVOC*, 2002, (**vii**), 151.
34 The $TiCl_4$-Et_3N reagent system typically provides aldol addition products when used in reactions of α-diazo β-ketoesters and aromatic aldehydes; M. A. Calter and C. Zhu, *J. Org. Chem.*, 1999, **64**, 1415.
35 For *Z*-selective aldol condensations of glycolic acid derivatives and of azlactones with aromatic aldehydes, see: (a) Z. Cai, J. Feng, Y. Guo, P. Li, Z. Shen, F. Chu and Z. Guo, *Bioorg. Med. Chem.*, 2006, **14**, 866. (b) L. Shi, L. Wang, Z. Wang, H.-L. Zhu and Q. Song, *Eur. J. Med. Chem.*, 2012, **47**, 585.
36 M. Hoffmann, S. Miaskiewicz, J.-M. Weibel, P. Pale and A. Blanc, *RSC Adv.*, 2015, **5**, 37138.
37 K. W. Fiori and J. Du Bois, *J. Am. Chem. Soc.*, 2007, **129**, 562.
38 T. T. Dang, F. Boeck and L. Hintermann, *J. Org. Chem.*, 2011, **76**, 9353.
39 M. M. Naik, D. P. Kamat, S. G. Tilve and V. P. Kamat, *Tetrahedron*, 2014, **70**, 5221.
40 For a similar cyclization, see: H. E. Zaugg, J. E. Leonard, R. W. DeNet and D. L. Andersen, *J. Het. Chem.*, 1974, **11**, 797.
41 V. K. Ahluwalia, K. K. Arora and R. S. Jolly, *J. Chem. Soc. Perkin Trans. 1*, 1982, 335.
42 C. E. Caufield, S. A. Antane, K. M. Morris, S. M. Naughton, D. A. Quagliato, P. M. Andrae, A. Enos and J. F. Chiarello, US 20050054721 A1, March 10, 2005.
43 H. Sugiyaman, B. Ojima, M. Kobayashyi, S. Senda, J.-I. Ishiyama and S. Seto, *Agric. Biol. Chem.*, 1979, **43**, 403.

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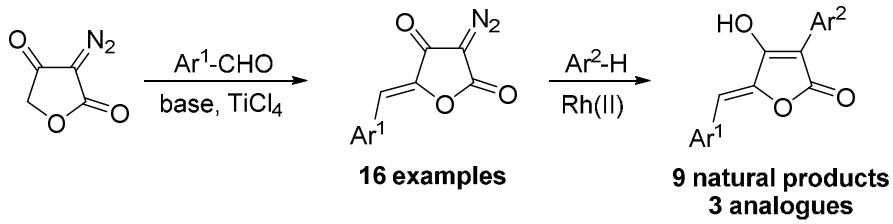

Diastereoselective aldol condensation of diazotetronic acid and a subsequent arene C-H insertion provides an efficient route to the aspulvinone motif.