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Convergent synthesis of 2*H*-chromenes—a formal [3+3] cycloaddition by a one-pot, three-step cascade

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ABSTRACT

In cases in which the palladium-catalyzed coupling of a bromoquinone with a vinyl stannane affords a vinyl quinone that enolizes, the resulting *ortho*-quinone methide undergoes an oxa-6π electrocyclization. Enolization is promoted by the presence of a polar additive. The net conversion is a formal [3+3] cycloaddition that gives 2*H*-chromenes. Because the first two steps of the cascade are catalyzed, the overall conversion is an example of multicatalysis. Yields for the optimized, one-pot protocol are dramatically improved over the conventional stepwise process.

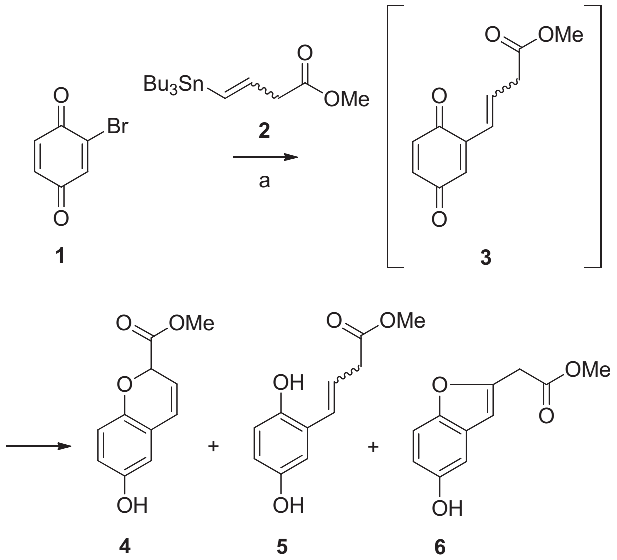
1. Introduction

In the course of our research directed toward the synthesis of aryl *C*-glycoside natural products,[1] we discovered that the coupling reaction of bromobenzoquinone (**1**) with vinyl stannane **2**[2] did not provide the desired vinyl quinone **3**. Instead, 2*H*-chromene **4** and hydroquinone **5** were isolated, each in modest yield (20–30%), along with small amounts of benzofuran **6** (approx. 5%, Scheme 1).[3]

We had not originally set out to prepare chromene compounds;[4,5] nonetheless, we were aware of the incidence of this structural feature among biologically active natural products.[6] Therefore we set out to elucidate the mechanism of the chromene synthesis and to examine its generality and practicality.

We soon discovered that vinyl quinone **3**, prepared by an independent route (see below), underwent conversion to chromene along with previously observed by-products when exposed to the $Pd(PPh_3)_4$ coupling conditions We concluded that quinone **3** was, as expected, the initial product of the Pd(0) catalyzed reaction and that the conversion of quinone **1** to 2*H*-chromene **4** took place by transformations of this intermediate under the coupling conditions.

In further experiments with quinone **3**, we took the precaution of excluding light from the reaction vessel. Both overhead fluorescent fixtures and sunlight can initiate photochemistry with quinones.[7] In fact, the photochemical isomerization of vinyl quinones to benzofurans is known.[8] We ourselves have seen efficient



Scheme 1. Unexpected products from Stille coupling. (a) 5 mol % $(Ph_3P)_4Pd$, toluene (10 mM), reflux.

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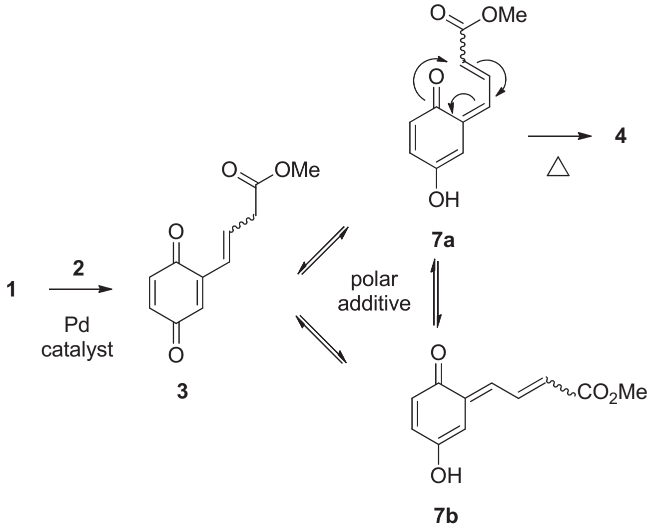
isomerization of a vinyl quinone imine to the isomeric indole in a sunlight induced reaction.[9]

Although the presence of catalytic amounts of $Pd(PPh_3)_4$ converted quinone **3** to chromene **4**, heating the substrate in toluene alone or in the presence of $Pd_2(dba)_3$ did not effect this change. Further experimentation revealed that the presence of 0.2–5 equiv of a phosphine or a phosphine oxide in the reaction medium was sufficient to lead to the formation of product mixtures. (It is likely that the phosphines are being converted to phosphine oxides in the reaction medium). We also found that DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) had the same effect. All of this indicated that a polar additive or Lewis base was essential for effecting the observed transformation (**3**→**4**).

A particularly convenient protocol involved the addition of traces of hexamethylphosphoramide (HMPA) to a toluene solution of vinyl quinone **3** before heating. In these experiments, we observed the appearance of a dark red color immediately upon the mixing of the HMPA with the solution of substrate. This color was maintained during the course of the reflux, gradually being replaced by a brown color as the reaction went to completion. Under these conditions,[10] the reaction was complete in a matter of hours. These improvements, when applied to quinone **3** gave chromene **4** as a single clean product.

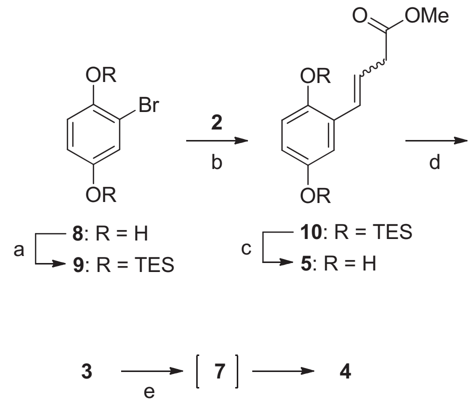
We suspected that the red color represented quinone methide **7** (presumably both **7a** and **7b**), the enol form of the vinyl quinone. In fact, we could observe the appearance of a new species corresponding to approximately 80% of the substrate in solution in the NMR spectrum of quinone **3** in THF-d_8 as soon as traces of hexamethylphosphoramide (HMPA) were added. This intermediate was stable in the NMR solution at 10 °C for several hours. An oxa-6π electrocyclization would convert enol **7a** to the observed product **4**. Enol **7b**, if present, must undergo isomerization to enol **7a** before the electrocyclization; it is reasonable to believe that low energy proton transfers, facilitated by HMPA, effect this change.[11] The oxa-6π electrocyclization then would complete the two-step transformation of vinyl quinone **3** or the three-step transformation of bromoquinone **1** to chromene **4** (Scheme 2).[12,13]



Scheme 2. Mechanism of the formation of 2*H*-chromene from vinyl quinone.

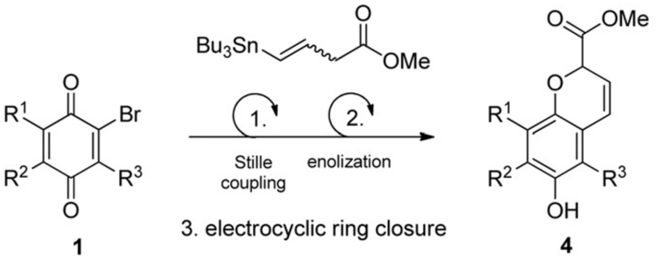
It is clear that the conversion of quinone **3** to a reactive intermediate requires the presence of a polar organic additive that promotes the enolization step by changing the polarity of the reaction medium, by acting as a Lewis base, or by both mechanisms. The additive accelerates the conversion to chromene and is not, itself, changed in the process. Therefore, it fits the classical definition of a catalyst.

The approach to chromenes in which the Stille coupling and enolization/electrocyclization conversions are effected in separate steps can be considered relatively efficient by today's standards. We applied this strategy (Scheme 3) to the synthesis of five additional chromenes and utilized one of these in a short synthesis of the purported structure of the juvenile hormone from *Ageratum conyzoides*. This preliminary work has been reported.[3]



Scheme 3. Multistep synthesis of 2*H*-chromenes. (a) triethylsilyl triflate (TESOTf), imidazole, DMF, rt; (b) 10 mol % $(Ph_3P)_4Pd$, toluene, cat. amounts of 2,6-di-*tert*-butyl-4-methylphenol (radical scavenger), reflux; (c) THF, 50% aq AcOH, rt; (d) Ag_2O, O_2, $MgSO_4$, THF, rt; (e) toluene, HMPA (0.5% v/v), reflux in the dark.

Nevertheless, we recognized the potential advantages of a one-pot transformation as suggested by the original observation of the direct production of chromene **4** from bromoquinone **1**. Multicatalysis and other cascade procedures[14] offer opportunities to optimize yields and to minimize the time, effort, and waste incurred in multistep transformations. Here we complete the survey of the stepwise convergent chromene synthesis and we also describe the development of a three-step cascade sequence that effects the equivalent conversion in a single reaction vessel (Scheme 4). This formal [3+3] cycloaddition has three steps, the Pd(0) catalyzed coupling, the HMPA-promoted enolization, and the thermal electrocyclization. However, no change in reaction conditions is required from one step to the next. We suggest that this is a case of 'tandem catalysis' or, more generally, multicatalysis and we utilize the relevant notation for the first two steps in Scheme 4.[15] Finally, we demonstrate the superiority of this protocol to the stepwise approach for the preparation of selected annulated chromene products.



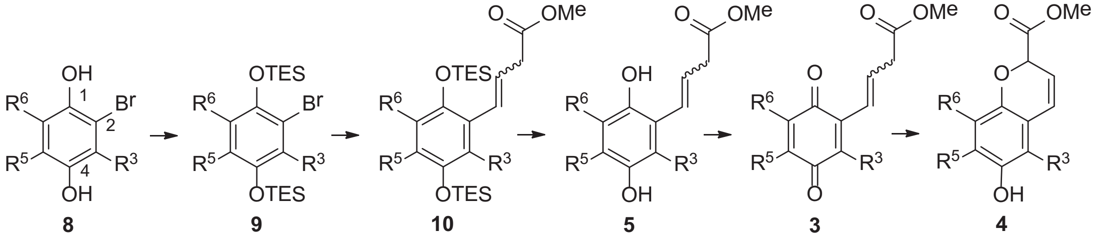
Scheme 4. One-pot synthesis of 2*H*-chromenes by a tandem catalysis cascade.

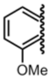
2. Results and discussions

2.1. Scope of the stepwise synthesis

We tested the generality of the stepwise procedure (Scheme 3) by extending it to a series of bromohydroquinone substrates that bear one or more methyl or methoxy substituents, structural features frequently found in naturally occurring benzo- and naphthopyrans (Table 1).[16] Thus each of the hydroquinones **8**, **8a**, and **8c**–**e** was converted to its bis TES ether **9**. Coupling with the known tin reagent **2** was followed by deprotection and oxidation of intermediates **10** to the corresponding quinones **3**. Quinone **3b** was most conveniently prepared by the AgO oxidation of the 1,3,4-trimethoxyphenyl butenoate **12** derived from the known 2-bromo-1,3,4-trimethoxybenzene (**11**; Scheme 5).[32] Heating vinyl quinone substrate **3**–**3e** in toluene in the presence of small amounts of HMPA gave, as expected, the corresponding chromene in each case. Yields for each step and the overall yields for the stepwise preparative sequence are shown in Table 1.

Table 1
Multistep synthesis of chromenes via protected hydroquinones



Example	Yield **9** [%]	Yield **10** [%]	Yield **5** [%]	Yield **3** [%]	Yield **4** [%]	Overall yield [%]
8R^3=R^5=R^6=H	**9**: 98	**10**: 70	**5**: 92[a]	**3**: quant. (*trans*) **3**: quant. (*cis*)	**4**: 76 **4**: 86	**4**: 48[b] **4**: 54[b]
8a[c] R^3=H, R^5=R^6=CH_3	**9a**: 98	**10a**: 69	**5a**: 80	**3a**: quant.	**4a**: 70	**4a**: 38
8b R^3=OMe, R^5=H, R^6=H	—	—	—	**3b**: 98	**4b**: 58	**4b**: 30[d]
8c[e] R^3=H, R^5=OMe, R^6=H	**9c**: 99	**10c**: 53	**5c**: 81	**3c**: 97	**4c**: 70	**4c**: 29[b]
8d[f] R^3=R^5=H, R^6=OMe	**9d**: 85	**10d**: 42	**5d**: 75	**3d**: 98	**4d**: 63	**4d**: 17
8e[g] R^3=H, R^5=R^6=  OMe	**9e**: 89	**10e**: 83	**5e**: 86	**3e**: 94	**4e**: 59	**4e**: 35[b]

[a] 65% *trans* compound and 25% *cis* compound isolated by chromatography.

[b] Experimental procedures and compound characterization data for this entry are reported in the Supplementary data for Ref. 3.

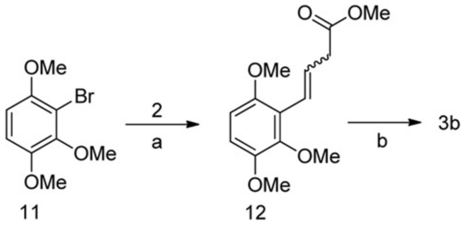
[c] Hydroquinone **8a** was prepared by bromination of 2,3-dimethyl-1,4-hydroquinone according to Takanashi and Mori, Ref. 17.

[d] 30% yield from 2-bromo-1,3,4-trimethoxybenzene; see text.

[e] Hydroqinone **8c** was prepared by bromination of methoxyhydroquinone according to Guzikowski et al., Ref. 18.

[f] Hydroquinone **8d** was prepared according to Zhu et al., Ref. 19.

[g] Hydroquinone **8e** was prepared by reduction of the corresponding quinone and used immediately; see the Supplementary data for Ref. 3.



Scheme 5. (a) 10 mol % $(Ph_3P)_4Pd$, toluene, cat. amounts of 2,6-di-*tert*-butyl-4-methylphenol (radical scavenger), reflux; (b) AgO, HNO_3, THF, rt.

The low to modest overall yields of the multistep syntheses of 2*H*-chromenes reflect, in part, the losses affiliated with the manipulation and the isolation procedures of up-to five sequential reactions. The yields of the coupling reactions of TES-protected bromohydroquinones with stannane **2** and, in some cases, the enolization/electrocyclization steps are especially unsatisfying. In an effort to improve the efficiency of the chromene synthesis, we therefore focused attention again on the original one-pot protocol. In this approach, enolization/electrocyclization occurs in-situ, offering the possibility that vinyl quinones **3** could be converted to chromene products **4** as soon as they are formed.[20] The one-pot protocol avoids the Stille coupling of the relatively unreactive,[21] electron rich benzene derivative **9** entirely.

2.2. Development of the one-pot synthesis

The development of one-pot multi-reaction cascades requires not only the careful optimization of each step but also the establishment of conditions under, which the reagents and intermediates do not interfere with each other in counterproductive phenomena. For the transformation discussed herein, particular attention had to be paid to eliminating photochemical transformations of the quinone intermediates. Thus, light was excluded from the reaction mixtures in all attempts to develop the one-pot procedure. Also, we needed to minimize the redox chemistry of the bromoquinones and vinyl quinones along the reaction pathway and promote the conversion of the delicate *ortho*-quinone methide intermediates to stable chromene products.

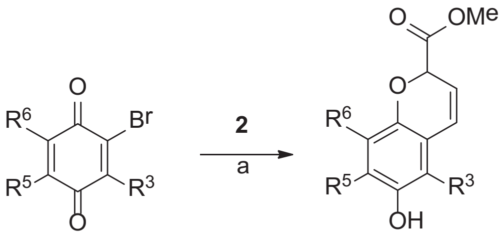
Optimization studies were performed with the parent bromobenzoquinone system. Reaction of substrate **1** with stannane **2** in toluene (10 mM) containing traces of HMPA (0.5% v/v) and $(Ph_3P)_4Pd$ (10–20 mol %) at reflux in the dark gave a 1:1 mixture of desired 2*H*-chromene **4** and vinyl hydroquinone **5** in combined yields of approximately 70%. Thus, the formation of benzofuran **6** was prevented.

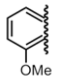
Vinyl hydroquinone **5**, arises from a redox reaction, most likely between the phosphine ligand of the palladium catalysts and the quinone starting material and/or vinyl quinone intermediate.[22] Since vinyl hydroquinone **5** does not undergo the enolization/electrocyclic ring closure transformation, its formation helps to explain the moderate yield of 2*H*-chromene **4**. To overcome the problems encountered with phosphine ligands of the palladium catalyst we attempted to make use of 'ligand-free' (or phosphine-free) conditions[23] reported for the successful Stille coupling of delicate substrates.[24] However, employment of $Pd(OAc)_2$, $Pd_2(dba)_3$ or $(CH_3CN)_2PdCl_2$ in the absence of phosphine ligands gave complex product mixtures, in some cases even at rt. Experiments in which the quantity of catalyst was reduced 1–2 mol % instead of 10–20 mol % $(Ph_3P)_4Pd$ were slow; complete conversion to chromene products could not be achieved within reasonable times.

Although only traces (0.5% v/v) of HMPA are adequate for catalyzing the conversion of quinone **3** to dihydrochromene **4**,[3] increasing the amount of HMPA in the reaction medium of the one-pot reaction (**1**→**4**) was advantageous. When only 1–2% of $(Ph_3P)_4Pd$ was used, concentrations of 2–5% v/v, HMPA accelerated the overall conversion so that it was complete within a convenient timeframe. Furthermore, we found that more dilute reaction solutions (3 mM instead of 10 mM) gave cleaner products. Presumably, the presence of HMPA increases the rate of enolization, if not the rates of coupling and electrocyclization, and lowering the concentration of substrate decelerates bimolecular redox reactions.

Thus we developed suitable conditions for the one-pot, three-step procedure. Heating of a dilute toluene solution (3 mM) of equimolar amounts of bromobenzoquinone (**1**) and vinyl stannane **2** in the dark, in the presence 2–5% v/v HMPA and 1–2 mol % catalyst ($(Ph_3P)_4Pd$) for 30 min provided 2*H*-chromene **4** cleanly and in good yields (Table 2; entry 1).

Table 2
Synthesis of substituted benzo- and naphthopyrans by multicatalysis



Entry	Bromoquinone substrates		Product (yield)[b]
1	**1**: $R^3=R^5=R^6=H$		**4** (66%)
2	**1a**: $R^3=H$, $R^5=R^6=CH_3$		**4a** (71%)
3	**1b**: $R^3=OMe$, $R^5=R^6=H$		**4b** (70%)
4	**1c**: $R^3=H$, $R^5=OMe$, $R^6=H$		**4c** (64%)
5	**1d**: $R^3=R^5=H$, $R^6=OMe$		**4d** (66%)
6	**1e**: [c] $R^3=H$ $R^5=R^6=$		**4e** (70%)

[a] Stoichiometric amounts of the bromoquinones and vinyl stannane **2** (scale: 0.1–0.15 mmol) in toluene (30–45 mL; approx. 3 mM), 2–5% v/v HMPA, 1–2 mol % $(Ph_3P)_4Pd$, 1–5 h reflux in the dark.

[b] Yields of isolated products.

[c] Compound **1e**=2-bromo-5-methoxynaphthoquinone (2-bromojuglone methylether).

With these optimized reaction conditions, we set out to investigate the general utility of the one-pot procedure and compare it to the stepwise synthesis. Except for the known **1b**,[25] each of the bromoquinone starting materials was prepared according to the literature. 2-Bromo-5,6-dimethylbenzoquinone (**1a**)[26] was prepared by oxidation of the known hydroquinone.[17] 2-Bromo-5-methoxybenzoquinone (**1c**) and 2-bromo-6-methoxybenzoquinone (**1d**), were prepared according to Blatchly et al.[25] and 2-bromojuglone methylether **1e** was prepared according to Jung.[27] Quinone **1b** was prepared by AgO oxidation of known compound **11**. Each was subjected to reaction with vinyl stannane **2** under the optimized multicatalysis conditions (Table 2). The yields of isolated products **4**–**4e** were uniformly good and in all cases superior to the overall yields achieved by the alternative multistep procedure (Table 1). It can therefore be concluded that neither methyl (entry 2) nor methoxy (entries 3–5) substituents on the bromoquinone substrate interfere with the reaction cascade. In addition, the methodology can be applied to extended aromatic systems (e.g., naphthopyrans; entry 6). It is noteworthy that the multicatalysis method provides crude materials uncontaminated with by-products; only extractive removal of the polar additive and filtration through a short pad of silica gel is required for purification.

3. Conclusions

A one-pot, three-step cascade that consists of a Stille-coupling/enolization/oxa-6π electrocyclization cascade effects the conversion of bromoquinones and vinyl stannanes to annulated 2*H*-chromenes. Although the yields for these transformations (**1**→**4**) could be termed modest, each represents three individual reactions and compares favorably with the corresponding stepwise sequences. This suggests—as is sometimes the case with cascade reactions—that unstable intermediates may be forwarded in the direction of the desired product before they can partition along undesired pathways.

A key feature of the method is the use of HMPA to promote the formation of the quinone methide that undergoes the oxa-6π electrocyclization. It is reasonable to believe that HMPA acts catalytically as a proton shuttle.[28] Similar enolizations of *allyl* quinones that preface oxa-6π electrocyclizations are promoted by basic alumina,[29] pyridine,[30] and triethyl amine.[31] In any case, the conversion of vinyl quinone to chromene requires the presence of a polar additive, leading us to apply the term 'multicatalytic' to the three-step cascade. Furthermore, we suggest that, as the field of multicatalysis develops, there will be additional examples of sequences in which an additive, such as HMPA plays a critical role in one of the steps.

This new synthetic methodology enhances the portfolio of synthetic approaches by which structurally diverse benzo- and naphthopyrans can be prepared. Because it tolerates structural variants of the bromoquinone substrate, this attractive approach appears well suited for general applications in natural product total synthesis and compound library design.

4. Experimental section

4.1. General information

Reagents and solvents from Sigma–Aldrich, and TCI and catalysts from Strem Chemicals were used as supplied. Flash chromatography was performed with Fisher brand silica gel (170–400 mesh) and preparative TLC on Analtech precoated silica gel GF, 1000-microns glass plates (20×20 cm). All experiments were monitored by thin layer chromatography performed on EM Science precoated silica gel 60 F_{254} glass supported plates.

Reactions in the dark were performed by covering the reaction flask in aluminum foil.

Nuclear magnetic resonance spectra were recorded with a Bruker 300 or 400 MHz spectrometer with the corresponding solvent signal as an internal standard. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). Values of coupling constants, J, are given in hertz (Hz). The following abbreviations are used in the Experimental section for the description of ^{1}H NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublets of triplets (dt), and broad singlet (br s). Low-resolution mass spectra were measured with a Kratos MS80RFA (LRFAB, NBA/NaI) or with an HPGCD (LRGC-MS). Infrared spectra were recorded with a Perkin–Elmer 1600 Series FT-IR. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

4.2. General synthetic procedures

4.2.1. General procedure 1: synthesis of TES-protected hydroquinones. Bromohydroquinones (1.5–3.2 mmol) were dissolved in DMF (1 mL/mmol) and imidazole (5 equiv) and TESOTf (3 equiv) were added at 0 °C. The resulting solution was warmed to rt, stirred for 30–60 min and poured into water (10–20 mL). The mixture was extracted three times with ether. The organic phases were combined and the resulting solution was washed twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel with hexane to afford the TES-protected product.

*4.2.2. General procedure 2: Stille coupling of protected bromohydroquinones with vinyl stannane **2**.* Protected bromohydroquinones (0.6–2 mmol) and vinyl stannane **2** (1.2 equiv) were dissolved in toluene (10–100 mL/mmol) and $(Ph_3P)_4Pd$ (10 mol %) and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol (radical scavenger) were added. The mixture was stirred at reflux until TLC indicated complete conversion of the bromohydroquinone substrate (7–20 h). The reaction mixture was filtered through Celite® and concentrated under reduced pressure. The crude product was purified by flash chromatography or preparative TLC on silica gel with mixtures of ethyl acetate and hexane to afford the final product.

4.2.3. General procedure 3: removal of TES-protective groups from vinyl hydroquinones. Protected vinyl hydroquinones (0.1–1 mmol) were dissolved in THF (12 mL/mmol) and 50% aq AcOH (12 mL/mmol) was added. The mixture was stirred at rt until TLC indicated complete conversion of the protected vinyl hydroquinone substrate (18–48 h). The reaction mixture was poured into 5% aq $NaHCO_3$ and extracted with ether (three times). The organic phases were combined and the resulting solution was washed twice with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography or preparative TLC on silica gel with mixtures of ethyl acetate and hexane to afford the final product.

4.2.4. General procedure 4: oxidation of vinyl hydroquinones. Vinyl hydroquinones (0.05–0.2 mmol) were dissolved in THF (20–200 mL/mmol) and Ag_2O (5–10 equiv) and $MgSO_4$ (ca. 50–100 mg, ca. 10 equiv) were added. The suspension was stirred at rt under an oxygen atmosphere (O_2-balloon) until TLC indicated complete conversion of the vinyl hydroquinone substrate (30–45 min). The reaction mixture was filtered through Celite® and concentrated under reduced pressure to afford the final product.

4.2.5. General procedure 5: synthesis of 2H-chromenes from vinyl quinones. Vinyl quinones (0.05–0.1 mmol) were dissolved in toluene (5 mM) and HMPA (0.5% v/v) was added. The mixture was stirred at reflux in the dark until TLC indicated complete conversion of the vinyl quinone substrate (0.25–36 h). The reaction mixture was diluted with toluene and washed with water (twice). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography or preparative TLC on silica gel with mixtures of ethyl acetate and hexane to afford the final product.

4.2.6. General procedure 6: one-pot synthesis of 2H-chromenes. - Bromoquinone substrates and vinyl stannane **2** were dissolved in equimolar amounts (0.1–0.25 mmol) in toluene (30–80 mL; approx. 3 mM) and HMPA (2–5 %v/v) and $(Ph_3P)_4Pd$ (1–2 mol %) were added. The solution was stirred at reflux in the dark for 0.5–1.5 h after which time TLC indicated complete conversion of the substrates. The reaction mixture was diluted with toluene and washed twice with water. The water phases were extracted two more times with toluene. The organic phases were then combined and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified either by flash chromatography on silica gel or by filtration through a short pad of silica gel using mixtures of ethyl acetate and hexane.

4.3. Synthesis and characterization of compounds

For additional characterization of compounds **4**, **4c**, and **4e** and their respective precursors, see the Supplementary data for Ref. 3.

*4.3.1. Synthesis of bromoquinone **1a**[26].* From 5-bromo-2,3-dimethylbenzene-1,4-diol[17] (44 mg, 0.2 mmol) according to general procedure 4; reaction time: 15 min. Orange crystals (42 mg, 98%); mp 47–49 °C.

*4.3.2. Synthesis of vinyl quinone **3a**.* From vinyl hydroquinone **5a** (cis/trans 1:7; 12 mg, 0.05 mmol) according to the general procedure 3; reaction time: 30 min. Brown oil (12 mg, quant.; mixture of trans/cis isomers 7:1): IR (neat) ν 2954, 1739, 1650, 1252, 1165 cm^{-1}; ^{1}H NMR (THF-d_8) δ 6.79–6.65 (m, 1.87H, trans-isomer), 6.57–6.46 (m, 1H), 6.20 (dt, 0.13H, ^3J=12.0, 7.2 Hz, cis-isomer), 3.65 and 3.64 (each s, total 3H, cis/trans 1:7 in the order given), 3.33 and 3.26 (each dd, total 2H, ^3J=7.2 Hz, ^4J=1.9 Hz and ^3J=7.1 Hz, ^4J=1.2 Hz, respectively, cis/trans 1:7 in the order given), 2.00, 1.99, 1.98, and 1.97 (each s, total 6H) ppm; ^{13}C NMR (THF-d_8) (dominant signals of the major trans-isomer) δ 187.8, 187.2, 171.3, 142.2, 141.5, 141.3, 132.6, 129.3, 125.9, 52.0, 39.1, 12.4, 12.1 ppm; LRFAB-MS: $[M+Na]^+$=257 (calcd for $C_{13}H_{14}O_4Na$: 257).

*4.3.3. Synthesis of vinyl quinone **3b**.* 1,3,4-Trimethoxy butenoate **12** (cis/trans 1:3, 19 mg, 0.07 mmol) was dissolved THF (1.5 mL) and AgO (69 mg, 0.28 mmol) was added. The suspension was sonicated for 1 min and 6 N HNO_3 (71 μL, 0.43 mmol) was added to the homogenous suspension. The reaction mixture was stirred at rt for 10 min during which the precipitate was dissolved. The solution was poured into water (5 mL) and the resulting mixture was extracted with ether (3×5 mL). The organic layers were washed with water (2×5 mL) and then combined, dried over $MgSO_4$ and concentrated under reduced pressure affording a cis/trans-mixture (1:3) of pure quinone **3b** as a brown oil (16 mg, 98%): IR (neat) ν 2953, 1737, 1658, 1572, 1443, 1323, 1208, 1165, 1057, 847 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 6.97 (dt, 0.75H, ^3J=16.2, 7.3 Hz, trans-isomer), 6.68–6.59 (m, 2H), 6.49 (dt, 0.75H, ^3J=16.2 Hz, ^4J=1.5 Hz, trans-isomer), 6.20 (d, 0.25H, ^3J=11.7 Hz, cis-isomer), 6.11 (dt, 0.25H, ^3J=11.7, 5.9 Hz, cis-isomer), 4.06 and 3.96 (each s, total 3H, trans/cis 3:1 in the order given), 3.68 and 3.66 (each s, total 3H, trans/cis 3:1 in the order given), 3.26 (dd, 1.5H, ^3J=7.3 Hz, ^4J=1.5 Hz, trans-isomer), 2.98 (br d, 0.5H, ^3J=5.9 Hz, cis-isomer) ppm; ^{13}C NMR (CD_2Cl_2) δ 188.0, 187.8, 184.0, 183.8, 171.94, 171.85, 155.1, 155.0, 137.04, 137.02, 135.5, 135.4, 134.1, 130.7, 125.6, 125.5, 122.2, 121.1, 61.5, 61.4, 52.4, 52.2, 40.3, 36.0 ppm; LRFAB-MS: $[M+Na]^+$=259 (calcd for $C_{12}H_{12}O_5Na$: 259).

*4.3.4. Synthesis of vinyl quinone **3d**.* From hydroquinone **5d** (trans-isomer; 24 mg, 0.10 mmol) according to the general procedure 4; reaction time: 30 min. Yellow solid (23 mg, 98%; trans-isomer): mp 113–116 °C; IR (KBr) ν 2953, 1733, 1676, 1635, 1603, 1239, 1176 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.71–6.59 (m, 2H), 6.47 (br d, 1H, ^3J=16.1 Hz), 5.90 (d, 1H, ^4J=2.2 Hz), 3.80 and 3.69 (each s, each 3H), 3.28 (dd, 2H, ^3J=7.1 Hz, ^4J=1.2 Hz) ppm; ^{13}C NMR (CD_2Cl_2) δ 187.8, 181.7, 171.4, 159.2, 140.4, 132.1, 130.1, 124.9, 108.0, 57.0, 52.5, 39.0 ppm; LRFAB-MS: $[M+Na]^+$=259 (calcd for $C_{12}H_{12}O_5Na$: 259).

*4.3.5. Chromene **4**[3]. Multistep procedure*: From vinyl quinone **3** (12.4 mg, 0.06 mmol; trans- or cis-isomer) according to procedure 5 (in the case of the trans-isomer in the presence of 3.5 equiv of $FeCl_3$); reaction time: 45 min (trans-isomer) and 2 h (cis-isomer): yields: 10 mg, 76% (trans-isomer) and 11 mg, 86% (cis-isomer). *One-pot procedure*: From the reaction of bromobenzoquinone (**1**, 19 mg, 0.10 mmol) and vinyl stannane **2** (40 mg, 0.10 mmol) according to general procedure 6; reaction time 30 min. Yellow solid (13.5 mg, 66%).

*4.3.6. Chromene **4a**. Multistep procedure*: From vinyl quinone **3a** (24 mg, 0.10 mmol) according to the general procedure 5; reaction time: 10 h (16.5 mg, 70%). *One-Pot procedure*: From 2-bromo-5,6-dimethylquinone **3a** (24 mg, 0.10 mmol)[26] and vinyl stannane **2** (40 mg, 0.10 mmol) by general procedure 6; reaction time: 1 h (16.6 mg, 71%). Beige solid: mp 130–133 °C (decomposition); IR (KBr) ν 3468, 2928, 1738, 1434, 1206, 1086 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.40 (dd, 1H, ^3J=9.6 Hz, ^4J=1.7 Hz), 6.32 (s, 1H), 5.82 (dd, ^3J=9.6 Hz, 4.6 Hz), 5.34 (dd, 1H, ^3J=4.6 Hz, ^4J=1.7 Hz), 3.71 (s, 3H), 2.17 and 2.14 (each s, each 3H) ppm; ^{13}C NMR (CD_2Cl_2) δ 170.9, 148.40, 148.37, 145.1, 126.0, 125.1, 120.0, 118.8, 110.7, 73.7, 52.7, 12.4, 12.0 ppm; LRFAB-MS: $[M+Na]^+$=257 (calcd for $C_{13}H_{14}O_4Na$: 257).

*4.3.7. Chromene **4b**. Multistep procedure*: From vinyl quinone **3b** (cis/trans isomer 1:3, 12 mg, 0.05 mmol) according to the general procedure 5; reaction time: 36 h (7 mg, 58%). *One-Pot procedure*: From 2-bromo-3-methoxyquinone (**3b**,[25] 32.5 mg, 0.15 mmol) and vinyl stannane **2** (59 mg, 0.15 mmol) by the one-pot procedure by general procedure 6; reaction time: 1 h (24.8 mg, 70%). Yellow oil: IR (neat) ν 3436, 2953, 1739, 1479, 1437, 1240, 1097, 1042, 800 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.78 (br s, 1H), 6.71 (dd, 1H, ^3J=9.9 Hz, ^4J=1.8 Hz), 6.78 and 6.49 (each d, each 1H, ^3J=8.7 Hz), 5.91 (dd, 1H, ^3J=9.9, 4.6 Hz), 5.36 (dd, 1H, ^3J=4.6 Hz, ^4J=1.8 Hz) 3.78 and 3.70 (each s, each 3H) ppm; ^{13}C NMR (acetone-d_6) δ 170.6, 147.0, 145.2, 144.4, 121.0, 120.9, 117.4, 115.8, 112.0, 73.5, 61.7, 52.5 ppm; LRFAB-MS: $[M+Na]^+$=259 (calcd for $C_{12}H_{12}O_5Na$: 259).

*4.3.8. Chromene **4c**[3]. Multistep procedure*: From vinyl quinone **3c** (cis/trans isomer 1:3, 40 mg, 0.17 mmol) according to the general procedure 5; reaction time: 8h (28 mg, 70%). *One-pot procedure*: From the reaction of 2-bromo-5-methoxybenzoquinone (**1c**,[25] 32.5 mg, 0.15 mmol) and vinyl stannane **2** (59 mg, 0.15 mmol) according to general procedure 6; reaction time: 1.5 h. Yellow oil (22.5 mg, 64%).

*4.3.9. Chromene **4d**. Multistep procedure*: From vinyl quinone **3d** (14 mg, 0.06 mmol; trans-isomer) according to the general procedure 5; reaction time: 15 min (9 mg, 63%). *One-pot procedure*: From the reaction of 2-bromo-6-methoxybenzoquinone (**1d**,[25] 24 mg, 0.10 mmol) and vinyl stannane **2** (40 mg, 0.10 mmol) by general procedure 6; reaction time: 1 h (15.6 mg, 66%). Brown oil: IR (neat) ν 3413, 2923, 1739, 1591, 1475, 1200, 1066, 995 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.41 (dd, 1H, ^3J=9.7 Hz, ^4J=1.9 Hz), 6.38 and 6.12 (each d, each 1H, ^4J=2.8 Hz), 5.88 (dd, 1H, ^3J=9.7, 4.4 Hz), 5.35 (dd, 1H, ^3J=4.4 Hz, ^4J=1.9 Hz), 4.79 (br s, 1H), 3.83 and 3.73 (each s, each 3H) ppm; ^{13}C NMR (CD_2Cl_2) δ 170.6, 151.8, 148.9, 148.8, 126.0, 122.0, 121.0, 105.3, 102.1, 73.8, 56.7, and 52.8 ppm; LRFAB-MS: $[M+Na]^+$=259 (calcd for $C_{12}H_{12}O_5Na$: 259).

*4.3.10. Chromene **4e**[3]. Multistep procedure*: From vinyl naphthoquinone **3e** (cis/trans isomer 1:2, 23 mg, 0.08 mmol) according to procedure 5; reaction time: 8 h (13.5 mg, 59%). *One-pot procedure*: From the reaction of 2-bromojuglone methylether **3e**[27] (27 mg, 0.10 mmol) and vinyl stannane **2** (40 mg, 0.1 mmol) by general procedure 6; reaction time: 1 h; pink solid (20 mg, 70%).

*4.3.11. Vinyl hydroquinone **5a**.* From protected hydroquinone **10a** (cis/trans 1:7; 240 mg, 0.52 mmol) according to the general procedure 3; reaction time: 48 h. Pale orange solid (97 mg, 80%): mp 66–71 °C; IR (KBr) ν 3405, 2953, 1715, 1438, 1213, 1079 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.66 and 6.41 (each s, total 1H, trans/cis 7:1 in the order given), 6.64 and 6.54 (each dt, total 1H, ^3J=15.9 Hz, ^4J=1.4 Hz and ^3J=11.1 Hz, ^4J=1.5 Hz, respectively, trans/cis 7:1 in the order given), 6.12 and 5.96 (each dt, total 1H, ^3J=15.9, 7.2 Hz and ^3J=11.1, 7.5 Hz, respectively, trans/cis 7:1 in the order given), 4.95 and 4.83 (each br s, total 2H), 3.70 and 3.68 (each s, total 3H, trans/cis 7:1 in the order given), 3.24 and 3.14 (each dd, total 2H, ^3J=7.2 Hz, ^4J=1.4 Hz and ^3J=7.5 Hz, ^4J=1.5 Hz, respectively, trans/cis 7:1 in the order given), 2.16 and 2.14 (each s, total 6H, cis/trans 1:7 in the order given) ppm; ^{13}C NMR (CD_2Cl_2) δ 173.1, 173.0, 148.1, 147.5, 145.4, 128.7, 128.1, 127.3, 125.1, 124.3, 123.4, 122.4, 113.0, 110.6, 52.6, 52.5, 38.8, 34.6, 12.64, 12.56, 12.4 ppm; LRFAB-MS: $[M+Na]^+$=259 (calcd for $C_{13}H_{16}O_4Na$: 259).

*4.3.12. Vinyl hydroquinone **5d**.* From protected hydroquinone **10d** (cis/trans 1:5; 131 mg, 0.28 mmol) according to the general procedure 3; reaction time: 36 h. Pale brown solid (50 mg, 75%; mixture of cis/trans isomers with the trans-isomer as the major product): mp 146–149 °C; IR (KBr) ν 3475, 3392, 2957, 1710, 1598, 1489, 1442, 1284, 1148, 966 cm^{-1}; ^1H NMR (acetone-d_6; dominant signals of the major trans-isomer) δ 7.71 and 7.01 (each br s, each 1H), 6.77 (dt, 1H, ^3J=16.0 Hz, ^4J=1.4 Hz), 6.52 and 6.41 (each d, each 1H, ^4J=2.7 Hz), 6.26 (dt, 1H, ^3J=16.0, 7.2 Hz), 3.79 and 3.65 (each s, each 3H), 3.25 (dd, 2H, ^3J=7.2 Hz, ^4J=1.4 Hz) ppm; ^{13}C NMR (acetone-d_6; dominant signals of the major trans-isomer) δ 172.5, 151.0, 149.0, 138.1, 128.8, 124.3, 122.8, 104.3, 100.3, 56.4, 51.9, 38.9 ppm; LRFAB-MS: $[M+Na]^+$=261 (calcd for $C_{12}H_{14}O_5Na$: 261).

*4.3.13. TES-protected bromohydroquinone **9a**.* Obtained from 2-bromo-5,6-dimethyl hydroquinone **8a**[17] (326 mg, 1.50 mmol) according to general procedure 1; reaction time: 1 h. Pale yellow oil (660 mg, 98%): IR (neat) ν 2956, 2879, 1460, 1410, 1231, 1095, 928, 735 cm^{-1}; ^1H NMR (CD_2Cl_2) δ 6.84 (s, 1H), 2.18 and 2.09 (each s, each 3H), 1.05–0.85 (m, 18H), 0.83–0.70 (m, 12H) ppm; ^{13}C NMR (CD_2Cl_2) δ 148.8, 146.6, 130.5, 128.5, 120.5, 111.6, 15.2, 13.6, 7.2, 7.0, 6.3, 5.7 ppm; LRFAB-MS: $[M]^+$=446 (calcd for $C_{20}H_{37}O_2BrSi_2$: 446).

*4.3.14. TES-protected bromohydroquinone **9d**.* Obtained from 2-bromo-6-methoxy hydroquinone **8d**19 (701 mg, 3.20 mmol) according to general procedure 1; reaction time: 30 min. Colorless oil (1.22 g, 85%): IR (neat) ν 2956, 2878, 1597, 1566, 1489, 1454, 1411, 1242, 1207, 1147, 998, 908, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64 (d, 1H, ^4J=2.8 Hz), 6.37 (d, 1H, ^4J=2.8 Hz), 3.76 (s, 3H), 1.10–0.93 (m, 18H), 0.83–0.69 (m, 12H) ppm; ^{13}C NMR ($CDCl_3$) δ 151.6, 150.0, 138.0, 115.3, 115.1, 104.0, 55.5, 6.9, 6.7, 5.7, 5.1 ppm; LRFAB-MS: $[M]^+$=448 (calcd for $C_{19}H_{35}O_3Si_2Br$: 448).

*4.3.15. TES-protected vinyl hydroquinone **10a**.* From TES-protected 2-bromo-5,6-dimethyl hydroquinone **9a** (446 mg, 1.00 mmol) and vinyl stannane **2** (mixture of cis/trans isomers) according to the general procedure 2; reaction time: 7 h. Pale yellow oil (320 mg, 69%, mixture of 7:1 trans/cis isomers): IR (neat) ν 2955, 2877, 1745, 1469, 1415, 1223, 1092, 925, 741 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 6.75 and 6.52 (each s, total 1H, trans/cis 7:1 in the order given), 6.71 and 6.65 (each br d, total 1H, ^{3}J=15.9 and 11.8 Hz, respectively, trans/cis 7:1 in the order given), 6.05 and 5.81 (each dt, total 1H, ^{3}J=15.9, 7.1 and ^{3}J=11.8, 7.4 Hz, respectively, trans/cis 7:1 in the order given), 3.70 and 3.69 (each s, total 3H, trans/cis 7:1 in the order given), 3.28 and 3.24 (each dd, total 2H, ^{3}J=7.4 Hz, ^{4}J=1.8 Hz and ^{3}J=7.1 Hz, ^{4}J=1.3 Hz, respectively, cis/trans 1:7 in the order given), 2.14, 2.13 and 2.12 (each s, total 6H, trans/cis isomers), 1.07–0.88 (m, 18H), 0.84–0.65 (m, 12H) ppm; ^{13}C NMR (CD_2Cl_2) δ 172.6, 172.5, 148.6, 148.0, 147.0, 146.5, 140.5, 133.7, 130.4, 129.3, 128.8, 128.5, 126.4, 125.5, 123.3, 121.3, 117.1, 113.4, 52.2, 52.1, 39.0, 34.6, 14.4, 14.3, 14.1, 13.6, 7.09, 7.08 6.2, 6.0, 5.84, 5.78, ppm; LRFAB-MS: $[M]^{+}$=464 (calcd for $C_{25}H_{44}O_4Si_2$: 464).

4.3.16. TES-protected vinyl hydroquinone ***10d***. From TES-protected bromohydroquinone **9d** (448 mg, 1.00 mmol) and vinyl stannane **2** (mixture of cis/trans isomers) according to the general procedure 2; reaction time: 20 h. Pale yellow oil (195 mg, 42%; mixture of trans/cis isomers 5:1): IR (neat) ν 2956, 2878, 1743, 1477, 1227, 1192, 1160, 1007, 908, 732 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 6.79 and 6.67 (each dt, total 1H, ^{3}J=16.2 Hz, ^{4}J=1.4 Hz and ^{3}J=11.5 Hz, ^{4}J=1.5 Hz, respectively, trans/cis 5:1 in the order given), 6.56 and 6.40 (each d, total 1H, ^{4}J=2.7 Hz and ^{4}J=2.8 Hz, respectively, trans/cis 5:1 in the order given), 6.35 and 6.33 (each d, total 1H, ^{4}J=2.7 Hz and ^{4}J=2.8 Hz, respectively, trans/cis 5:1 in the order given), 6.17 and 5.85 (each dt, total 1H, ^{3}J=16.2, 7.1 Hz and ^{3}J=11.5, 7.4 Hz, trans/cis 5:1 in the order given), 3.77 and 3.76 (each s, total 3H, cis/trans 1:5 in the order given), 3.71 and 3.69 (each s, total 3H, trans/cis 5:1 in the order given), 3.28 and 3.26 (each dd, total 2H, ^{3}J=7.4 Hz, ^{4}J=1.5 Hz and ^{3}J=7.1 Hz, ^{4}J=1.4 Hz, respectively, cis/trans 1:5 in the order given), 1.09–0.91 (m, 18H), 0.83–0.65 (m, 12H) ppm; ^{13}C NMR (CD_2Cl_2) δ 172.6, 172.4, 151.8, 150.2, 149.8, 148.9, 138.2, 137.9, 129.3, 129.2, 129.1, 128.9, 124.0, 122.6, 112.3, 108.4, 104.5, 104.4, 56.5, 55.7, 52.2, 52.0, 39.0, 34.7, 7.2, 7.1, 6.1, 5.6 ppm; LRFAB-MS: $[M+Na]^{+}$=489 (calcd for $C_{24}H_{42}O_5Si_2Na$: 489).

4.3.17. 1,3,4-Trimethoxyphenyl butenoate ***12***. From 2-bromo-1,3,4-trimethoxybenzene (**11**)[32] (151 mg, 0.61 mmol) and vinyl stannane **2** (mixture of cis/trans isomers) according to general procedure 2; reaction time: 18 h. Pale yellow oil (84 mg, 52%, mixture of trans/cis isomers 3:1): IR (neat) ν 2951, 2837, 1738, 1483, 1257, 1164, 1100, 796 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 6.82 and 6.78 (each d, total 1H, ^{3}J=9.0 Hz, cis/trans 1:3 in the order given), 6.79–6.64 (m, 1.75H), 6.59 (d, 0.75H, ^{3}J=9.0 Hz, trans-isomer), 6.40 (dt, 0.25H, ^{3}J=11.3 Hz, ^{4}J=1.6 Hz, cis-isomer), 5.97 (dt, 0.25H, ^{3}J=11.3, 7.2 Hz, cis-isomer), 3.80, 3.79, 3.78, 3.76, 3.72, 3.69, 3.66 and 3.65 (each s, total 12H), 3.26 (d, 1.5H, ^{3}J=6.2 Hz, trans-isomer), 3.01 (dd, 0.5H, ^{3}J=7.2 Hz, ^{4}J=1.6 Hz, cis-isomer) ppm; ^{13}C NMR (CD_2Cl_2) δ 172.8, 172.7, 152.8, 151.9, 148.6, 148.1, 147.8, 147.7, 120.6, 127.5, 126.6, 124.6, 123.5, 120.4, 112.3, 111.9, 106.4, 106.1. 40.3, 35.5, 60.6, 56.72, 56.70, 56.4, 56.2, 52.2, 52.0 ppm; LRFAB-MS: $[M+Na]^{+}$=289 (calcd for $C_{14}H_{18}O_5Na$: 289).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.068.

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