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Total synthesis of artochamins F, H, I, and J through cascade reactions

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Abstract

A concise and efficient cascade-based total synthesis of artochamins F, H, I, and J is described. The potential biogenetic connection between artochamin F, or a derivative thereof, and artochamins H, I, and J, through an unusual formal [2+2] cycloaddition process, was shown to be feasible. An alternative mechanism for this transformation is also proposed.

1. Introduction

The design and development of cascade reactions is a rapidly expanding area of research within the realm of chemical synthesis.[1] The virtues of such synthetic sequences are brilliantly reflected by some of the early developments in the field such as Sir Robert Robinson's total synthesis of tropinone (1917)[2] and Johnson's total synthesis of progesterone (1971).[3] During our own endeavors in total synthesis, we have demonstrated the power of cascade reactions beginning with the total synthesis of endiandric acids (1982)[4] and followed by numerous other examples, including bisorbicillinoids (1999),[5] CP molecules (1999),[6] colombiasin A (2001),[7] hybocarpone (2001),[8] diazonamide A (2003),[9,10] 1-*O*-methyl lateriflorone (2003),[11] thiostrepton (2004),[12] azaspiracid-1,[13] -2,[14a] and -3[14b] (2006), bisanthraquinones (2006),[15] and biyouyanagin (2007).[16] Cascade reactions are not only attractive due to their aesthetically pleasing nature, but also because of their capacity to rapidly increase molecular complexity, often efficiently and economically, from relatively simple starting materials. Furthermore, they frequently do so with savings in reagents and solvents, not to mention energy and time. As such they constitute part of the campaign of green chemistry to save and sustain the environment. In this article, we describe a detailed account of the synthesis of artochamins F, H, I, and J through cascade reactions involving a formal [2+2] cycloaddition process that proceeds thermally under a variety of conditions.

The *Artocarpus* genus encompasses approximately 60 species of trees that are thriving throughout the tropical lands of Asia. Belonging to the mulberry family Moraceae, several members of the species are cultivated for their fruit, edible seeds, and timber. A number of these trees are historically reputed to possess medicinal properties and are utilized as folk medicines in Taiwan, Thailand, and Indonesia.[17–21] Studies directed at the elucidation of the active ingredients of *Artocarpus chama* led to the isolation of several prenylated flavonoid compounds exhibiting cytotoxic, antiplatelet, and antibacterial activities.[20] More recent investigations with the stems of the same plant revealed a series of weakly cytotoxic prenylated stilbenes and derivatives thereof.[22] Artochamins, F, H, I, and J (**1**–**4**, Scheme 1) are amongst the most prominent and structurally interesting members of this class of compounds.

Inspection of the structures of artochamins F (**1**) and H–J (**2**–**4**) reveals a possible biogenetic relationship between them, whereby the stilbene-like structure **1**, or a derivative thereof, may serve as a precursor to the cyclobutane-containing structures **2**–**4** through a formal [2+2] cycloaddition reaction.[23] The occurrence of artochamins H–J (**2**–**4**) as racemates is suggestive of a non-enzymatic process, but does not necessarily preclude enzymatic intervention in the formation of the bicyclo[3.2.0]heptane ring system, as will be discussed in greater detail below. Herein, we describe our studies in this area that culminated in the total syntheses of several of the artochamins and shed some light on

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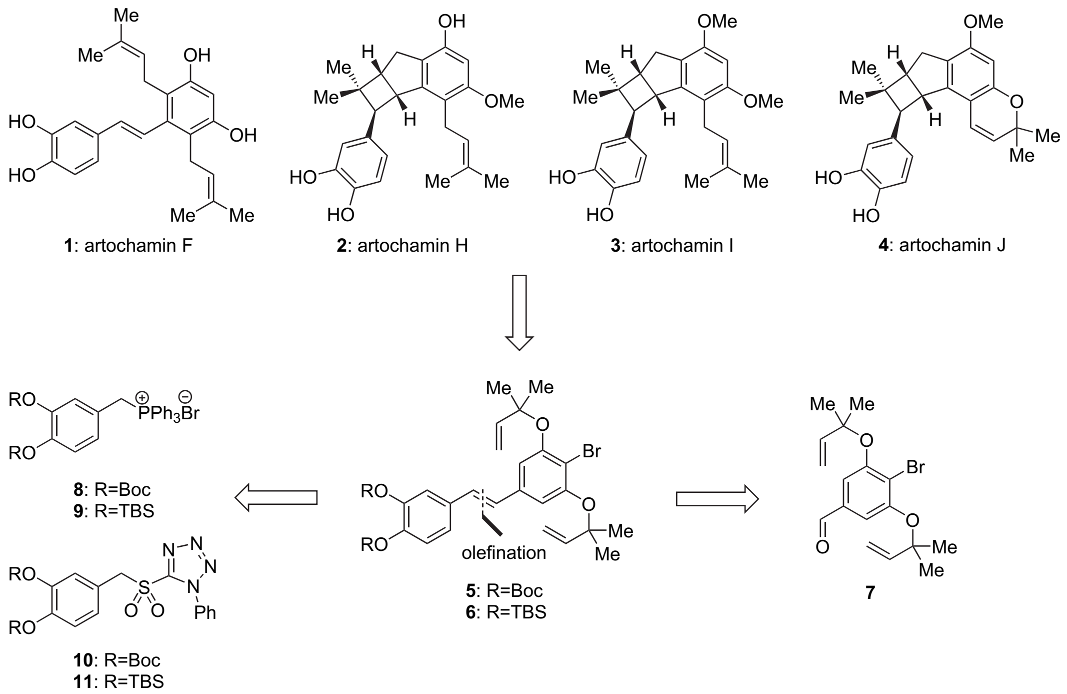


Scheme 1. Structures and retrosynthetic analysis of artochamins F, H, I, and J (**1**–**4**).

the mechanistic aspects of the proposed formal [2+2] thermal cycloaddition reaction.[24]

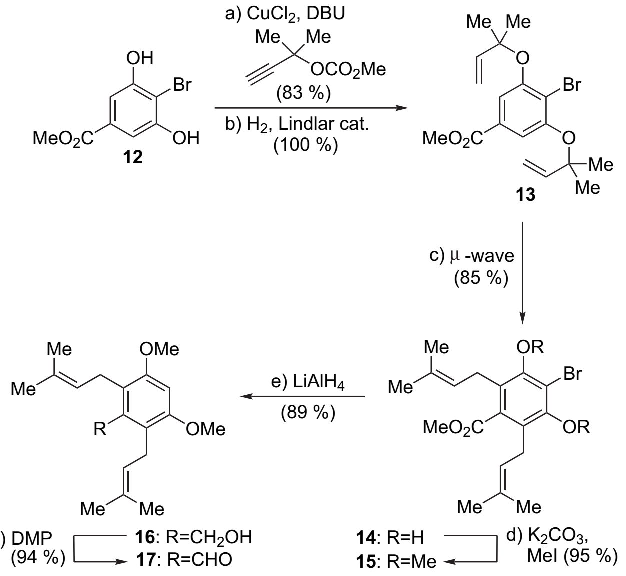
2. Results and discussion

2.1. Retrosynthetic analysis

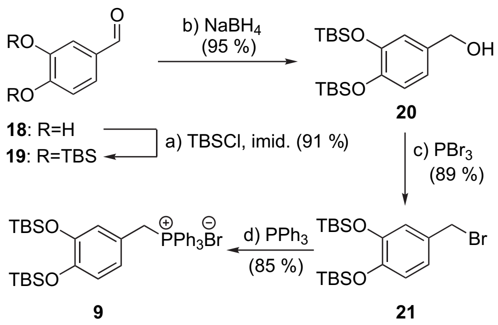
The architecture of the artochamins (Scheme 1) makes them amenable to a cascade sequence, which could potentially deliver them sequentially and/or selectively by fine-tuning the structure of the starting substrate. It was envisioned that a precursor such as **5** or **6** (Scheme 1), with or without protecting groups, equipped with the necessary functionality, could enter into a cascade sequence involving Claisen rearrangements to install the two prenyl groups, followed by a formal intramolecular [2+2] cycloaddition to forge the cyclobutane ring. The nature of the hydroxyl protecting groups could potentially favor or disfavor the formal [2+2] cycloaddition reaction,[23a] thus providing access to either artochamin F (**1**) or the skeletal framework of artochamins H–J (**2**–**4**). The stilbene precursors of **5** and **6** were traced back to phosphonium salts **8** and **9**, or sulfones **10** and **11**, respectively, and aldehyde **7** with the stereoselectivity of the relevant coupling reactions to be addressed experimentally.

2.2. Synthesis of artochamin I

As a prelude to the development of a cascade-based sequence toward the artochamins, a stepwise approach to artochamin I (**3**) was designed in order to explore separately the Claisen rearrangements and, in particular, the feasibility of the thermal [2+2] cycloaddition reaction. To this end, the required aldehyde **17** and phosphonium salt **9** for a Wittig-based coupling were prepared as follows. As shown in Scheme 2, copper-catalyzed etherification[25] of bis-phenol **12**[26] with dimethylpropynyl carbonate followed by catalytic hydrogenation under Lindlar conditions led to bis-allyl ether **13** in 83% overall yield.



Scheme 2. Construction of aldehyde **17**. Reagents and conditions: (a) methyl 1,1-dimethyl-2-propynyl carbonate (3.0 equiv), $CuCl_2$ (0.01 equiv), DBU (3.0 equiv), CH_3CN, 0 °C, 14 h; (b) H_2 (balloon), Lindlar catalyst (10% w/w), quinoline (0.5 equiv), EtOAc, 23 °C, 3 h; (c) µ-wave, DMF, 180 °C, 5 min; (d) K_2CO_3 (5.0 equiv), MeI (6.0 equiv), DMF, 100 °C, 1 h; (e) $LiAlH_4$ (10 equiv), THF, 50 °C, 14 h; (f) DMP (1.5 equiv), CH_2Cl_2, 23 °C, 30 min; DMF=*N*,*N*-dimethylformamide; TBS=*tert*-butyldimethylsilyl; DMP=Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one).

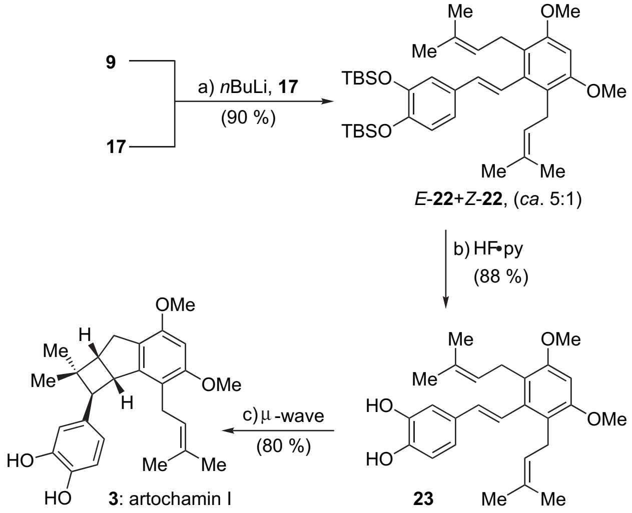


Scheme 3. Construction of phosphonium salt **9**. Reagents and conditions: (a) TBSCl (2.0 equiv), imidazole (3.0 equiv), DMF, 23 °C, 12 h; b) $NaBH_4$ (1.0 equiv), EtOH, 0→23 °C, 10 min; (c) PBr_3 (0.5 equiv), CH_2Cl_2, 0 °C, 30 min; (d) PPh_3 (1.0 equiv), toluene, 110 °C, 3 h.

Microwave-promoted (180 °C) Claisen rearrangements[27] then afforded the bis-prenylated ester **14** in good yield (85%). Subsequent methylation of **14** (K_2CO_3, MeI) afforded bis-methyl ether **15**, which was subjected to the action of $LiAlH_4$ to effect reduction of both the bromine substituent and the ester functionality, affording benzylic alcohol **16**. Dess–Martin oxidation of the latter compound then furnished the desired aldehyde **17** in 90% overall yield for the two steps.

The required phosphonium salt **9** was obtained in a straightforward manner from commercially available aromatic aldehyde **18** through a four-step sequence as shown in Scheme 3. Thus, protection of aldehyde **18** as the corresponding bis-TBS ether (TBSCl, imidazole, 91%) followed by $NaBH_4$ reduction afforded benzylic alcohol **20** (95%). Subsequent bromination of **20** with PBr_3 and reaction of the resulting benzylic bromide **21** with PPh_3 resulted in the formation of phosphonium salt **9** in 85% yield.

The Wittig coupling between the ylide derived from phosphonium salt **9** and aldehyde **17** (Scheme 4) proceeded in excellent yield (90%) and acceptable selectivity (*E*/*Z* ca. 5:1) providing *trans*-stilbene *E*-**22** as the major product. Removal of the TBS groups from *E*-**22** (HF·Py, 88%) afforded the protected artochamin F derivative **23**, setting the stage for the projected formal [2+2] cycloaddition reaction. We were pleased to observe that microwave heating of **23** in DMF at 180 °C resulted in the formation of artochamin I (**3**) as a single diastereoisomer in 80% yield. Significantly, attempts to cyclize the corresponding TBS ethers (*E*- or *Z*-**22**) under identical conditions failed, with only trace amounts of desilylated material visible (by TLC) after prolonged microwave heating (>45 min). Besides constituting an efficient synthesis of artochamin I (**3**), this study demonstrated the feasibility of both the double Claisen rearrangement and the formal [2+2] cycloaddition reaction under essentially identical reaction conditions. The study also demonstrated the expected dependence of the formal thermal cycloaddition reaction on the free hydroxyl groups of the stilbene substrate.[23c]

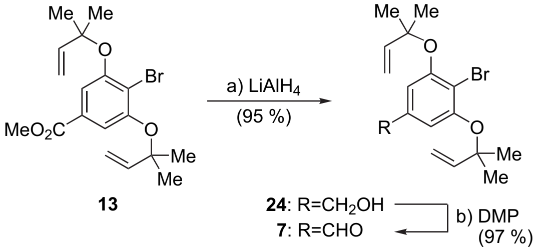


Scheme 4. Wittig reaction-based construction of stilbene **23** and synthesis of artochamin I (**3**). Reagents and conditions: (a) **9** (1.2 equiv), *n*-BuLi (1.2 equiv), −78 °C, 30 min; then **17**, −78→23 °C, 30 min; (b) HF·Py (excess), THF, 0→23 °C, 2 h; (c) μ-wave, DMF, 180 °C, 20 min; Py=pyridine.

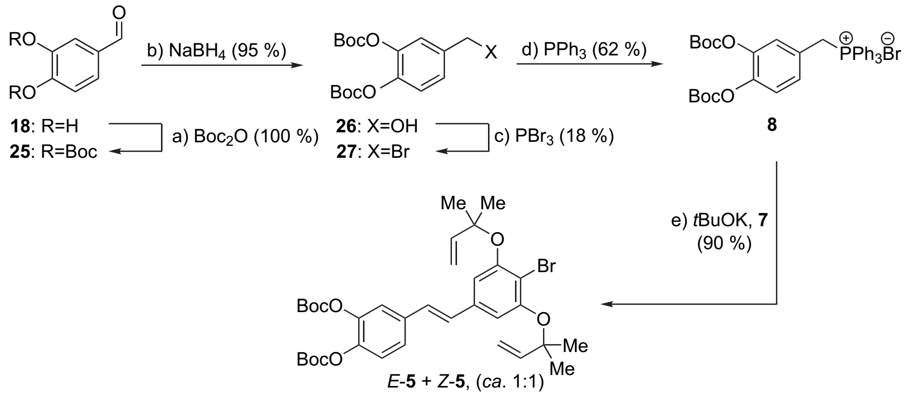
2.3. Development of the Julia–Kocieński approach to stilbenes and the cascade strategy for the total synthesis of artochamins F, H, I, and J

Having established appropriate conditions for the synthesis of the artochamins, we then proceeded to incorporate them within a cascade sequence toward an advanced common intermediate from which several of the natural products were expected to emerge. The bromine-containing bis-Boc protected stilbene derivative **5** (Scheme 1) was designed with the expectation that under thermal conditions it would undergo cleavage of the Boc groups, Claisen rearrangement of the two allylic ether moieties, and a formal [2+2] cycloaddition reaction to afford the tetracyclic core structure of artochamins H–J (**2**–**4**). Our initial route to precursor **5** involved a Wittig coupling that required aldehyde **7** (Scheme 1) and phosphonium salt **8** (Scheme 1). To this end, chemoselective reduction of methyl ester **13** with $LiAlH_4$ provided alcohol **24**, which was oxidized to aldehyde **7** in 91% yield over the two steps as shown in Scheme 5.

Next, the bis-Boc protected phosphonium salt **8** was prepared from commercially available aldehyde **18** by the same sequence as that employed to construct its bis-TBS-protected counterpart (**9**, Scheme 3), as shown in Scheme 6. The two fragments, the ylide derived from **8** and aldehyde **7**, were then combined using the Wittig reaction to afford stilbene **5** in 90% yield as a ca. 1:1 mixture of geometric isomers (Scheme 6). This stereoselectivity setback in combination with the low-yielding bromination (**26**→**27**, 18%) prompted us to search for an alternative route to the targeted stilbene substrate.



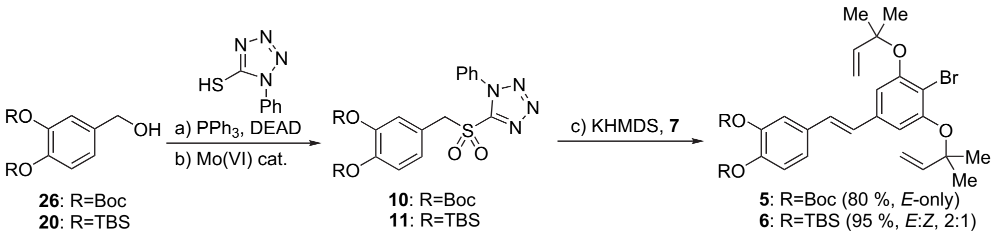
Scheme 5. Construction of aldehyde **7**. Reagents and conditions: (a) $LiAlH_4$ (1.2 equiv), THF, 0 °C, 10 min; (b) DMP (1.2 equiv), CH_2Cl_2, 23 °C, 30 min.



Scheme 6. Wittig reaction-based construction of stilbene **5**. Reagents and conditions: (a) Boc_2O (2.0 equiv), 4-DMAP (0.05 equiv), *i*-Pr_2NEt (0.1 equiv), THF, 23 °C, 2 h; (b) $NaBH_4$, (1.0 equiv), EtOH, 0→23 °C, 10 min; (c) PBr_3 (2.0 equiv), CH_2Cl_2, 0 °C, 1 h; (d) PPh_3 (1.5 equiv), toluene, 60 °C, 14 h; (e) **8** (1.2 equiv), *t*-BuOK (1.2 equiv), −78 °C, 30 min; then **7**, −78→23 °C, 30 min; DMAP=4-dimethylaminopyridine.

Whilst numerous examples of the Wittig reaction to prepare stilbenes can be found in the literature,[28] precedent for the corresponding Julia–Kocieński olefination was lacking.[29] Nevertheless, we decided to explore this alternative in the hope that we could improve upon the selectivity of the coupling reaction. Toward this end, stilbenes **5** and **6** were targeted for synthesis according to Scheme 7. Thus, the previously prepared benzylic alcohols **20** and **26** were subjected to thioetherification under Mitsunobu conditions to afford the corresponding sulfides, which were converted through molybdenum-catalyzed oxidation to the desired sulfone coupling partners **10** and **11** in 79 and 82% yield, respectively, over the two steps. In the main event of this sequence, employing sulfone **10** as a starting material, we were pleased to observe that the Julia–Kocieński olefination[30] with aldehyde **7** using KHMDS in THF afforded the bis-Boc protected stilbene **5** in 86% yield as a single *E*-stereoisomer (vide infra). The bis-TBS-protected stilbene **6** was obtained in a similar fashion from the corresponding sulfone (**11**) in 95% yield, but as a ca. 2:1 mixture of *E*/*Z* isomers. In contrast to the TBS-protected stilbenes, whose stereochemistry could be determined by NMR spectroscopy, the geometry of the bis-Boc protected stilbene **5** could not be comfortably assigned from its ^{1}H NMR spectrum. Fortunately, this compound yielded to X-ray crystallographic analysis, which confirmed the suspected *E*-geometry (see ORTEP drawing, Fig. 1).[31]

With ample quantities of stilbene **5** available through the Julia–Kocieński route, we were in a position to test our hypothesis regarding the proposed cascade sequence to the bicyclo[3.2.0] ring system of artochamins H–J (**2**–**4**). After considerable experimentation, it was discovered that the desired cascade could be realized under microwave conditions[32] in *o*-xylene at 180 °C (20 min.) in the presence of trace amounts of Ph_3PO as shown in Scheme 8. The beneficial effect



Scheme 7. Julia–Kocieński reaction-based construction of stilbenes **5** and **6**. Reagents and conditions: (a) 1-phenyl-1*H*-tetrazole-5-thiol (1.0 equiv), DEAD (1.2 equiv), PPh_3 (1.1 equiv), THF, 0 °C, 30 min; (b) ammonium molybdate tetrahydrate (0.1 equiv), 30% aqueous H_2O_2 (20 equiv), EtOH, 0→23 °C, 14 h; (c) **10** or **11** (1.5 equiv), KHMDS (1.5 equiv), −78 °C, 30 min; then **7** (1.0 equiv), THF, −78→23 °C; Boc=*tert*-butylcarbonate; KHMDS=potassium bis(trimethylsilyl)amide; TBS=*tert*-butyldimethylsilyl.

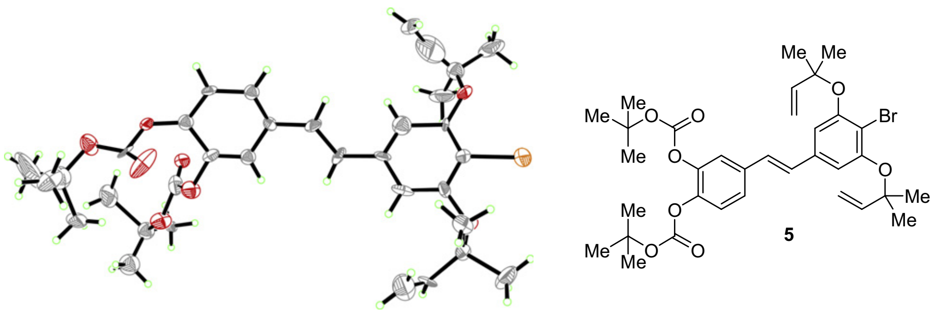
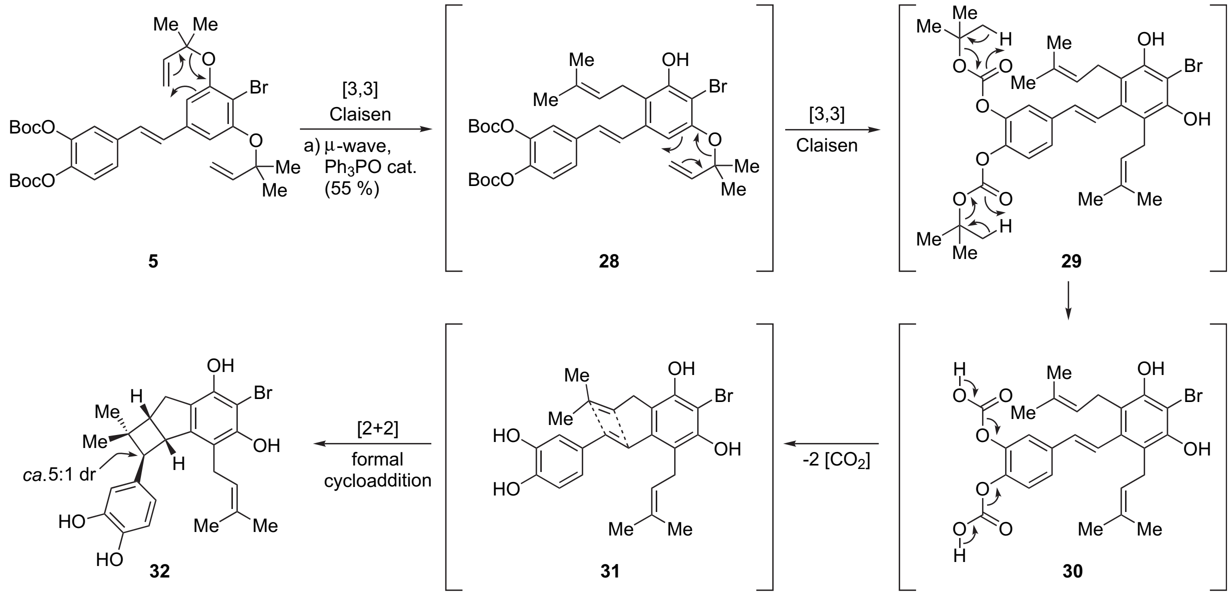


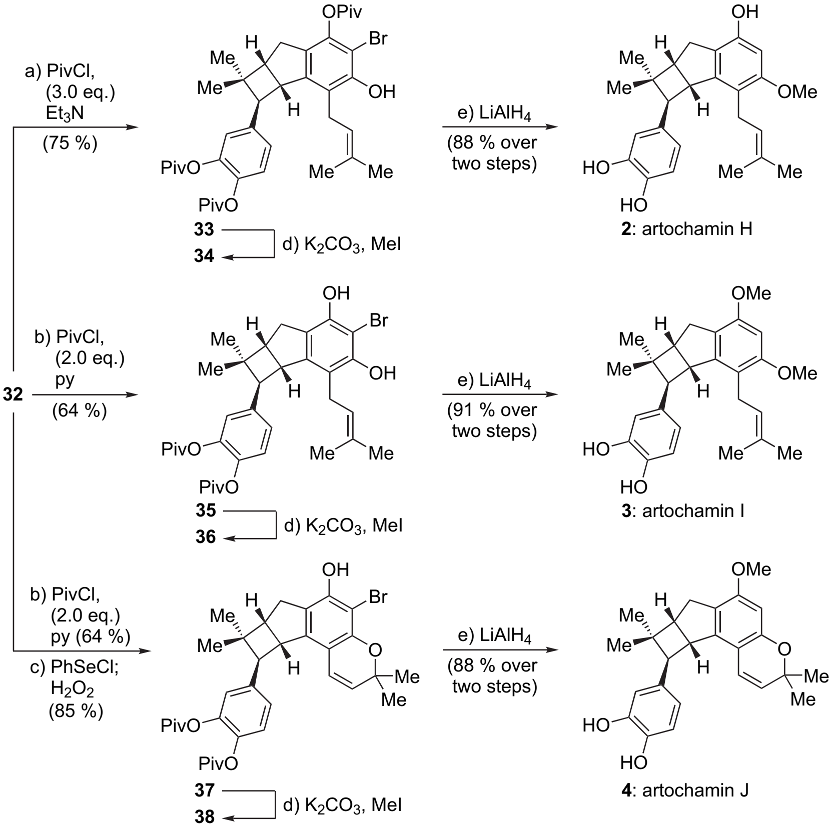
Figure 1. X-ray derived ORTEP drawing of stilbene **5**. Thermal ellipsoids at the 30% probability level.



Scheme 8. Cascade-based synthesis of artochamin ring framework **32**. Reagents and conditions: (a) µ-wave, Ph_3PO (5 wt %), *o*-xylene, 180 °C, 20 min.

of Ph_3PO was discovered serendipitously when a sample of precursor **5** that had been obtained through the Wittig route was used for the reaction (vide infra). The tetracyclic product **32** was obtained in 55% yield as a ca. 5:1 mixture of diastereoisomers with respect to the benzylic stereocenter adjacent to the all-carbon quaternary center (see Scheme 8).

With common intermediate **32** available through the cascade sequence, the total synthesis of artochamins H–J (**2**–**4**) was completed as shown in Scheme 9. Thus, treatment of **32** with PivCl (2.0 equiv) and pyridine (6.0 equiv) in CH_2Cl_2 furnished the bis-pivalate **35** in 64% yield, with recyclable monopivalates accounting for the remainder of the mass balance. As



Scheme 9. Total synthesis of artochamins H–J (**2**–**4**). Reagents and conditions: (a) PivCl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, 23 °C, 30 min; (b) PivCl (2.0 equiv), Py (6.0 equiv), CH_2Cl_2, 23 °C, 14 h; (c) PhSeCl (1.0 equiv), CH_2Cl_2, −78→23 °C, 30 min; then H_2O_2 (20 equiv), CH_2Cl_2, 0→23 °C, 3 h; (d) K_2CO_3 (5.0 equiv), MeI (6.0 equiv), DMF, 100 °C, 1 h; (e) $LiAlH_4$ (6.0 equiv), THF, 0→23 °C, 24 h; Piv=trimethylacetyl; Py=pyridine.

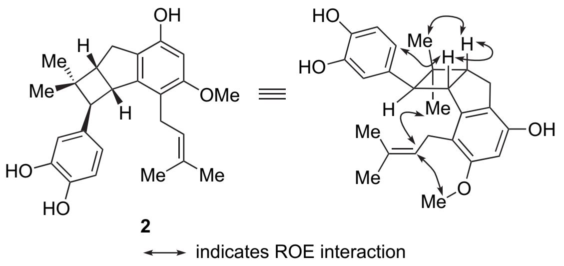


Figure 2. Principal ROE interactions in synthetic artochamin H (**2**).

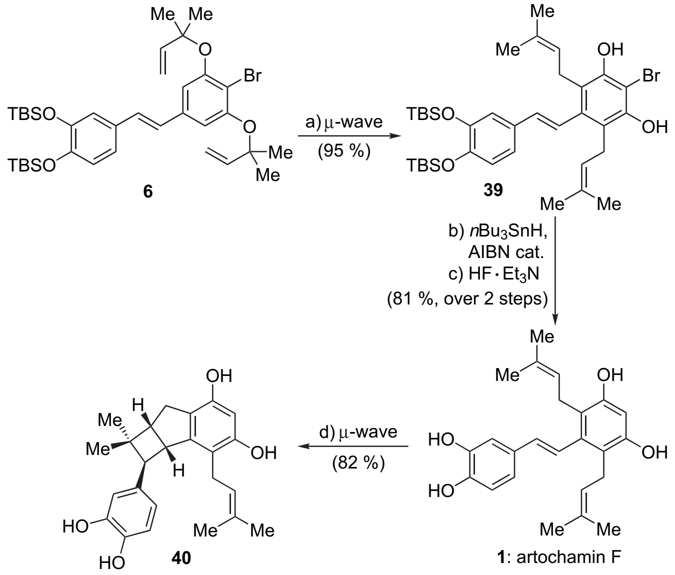
anticipated, steric shielding from the adjacent bromine atom disfavored acylation of the two remaining hydroxyl groups under these conditions. Subsequent methylation of the remaining hydroxyl groups (K_2CO_3, MeI) and simultaneous cleavage of the bromine and pivalate moieties ($LiAlH_4$) then furnished artochamin I (**3**) in 91% overall yield for the two steps. The total synthesis of artochamin J (**4**) was completed from common intermediate **32** via pivalate **35** by selenoetherification[33] (PhSeCl) and oxidative elimination (H_2O_2) to afford benzopyran **37** (85% overall yield), which was converted to artochamin J (**4**) by methylation and exhaustive $LiAlH_4$ reduction as described above for artochamin I (**3**). Finally, artochamin H (**2**) was secured from common intermediate **32** through tri-pivalate **33**, obtained in 75% yield under somewhat more forcing acylation conditions (3.0 equiv PivCl, 6.0 equiv Et_3N). Methylation and deprotection as above provided artochamin H (**2**) in 88% overall yield (see Scheme 9).

The spectroscopic data of synthetic artochamins H–J (**2**–**4**) matched those reported for the natural products.[34] Furthermore, in the case of artochamin H (**2**), a ROESY NMR experiment provided unequivocal support of its regiochemistry and relative stereochemistry through the observation of the appropriate ROE interactions, as shown in Figure 2.

Finally, based on the results obtained during the first-generation synthesis of artochamin I (**3**) (see Scheme 4), the total synthesis of artochamin F (**1**) was completed as shown in Scheme 10. Thus, the Julia–Kocieński derived stilbene **6** (see Scheme 7) was subjected to microwave heating resulting in the formation of bis-prenyl phenol **39** in excellent yield (95%). As expected, no cyclobutane-containing product was obtained from this microwave-promoted reaction. Reductive cleavage of the bromide followed by desilylation afforded synthetic artochamin F (**1**) in 81% yield over the two steps. Subjection of artochamin F (**1**) to microwave heating, both in the presence and in the absence of Ph_3PO provided, in 82% yield, derivative **40** containing the [3.2.0] ring system of artochamins H–J (**2**–**4**), thereby demonstrating that neither the bromine atom nor the Ph_3PO is necessary for the formal [2+2] cycloaddition reaction to take place, at least in this instance.

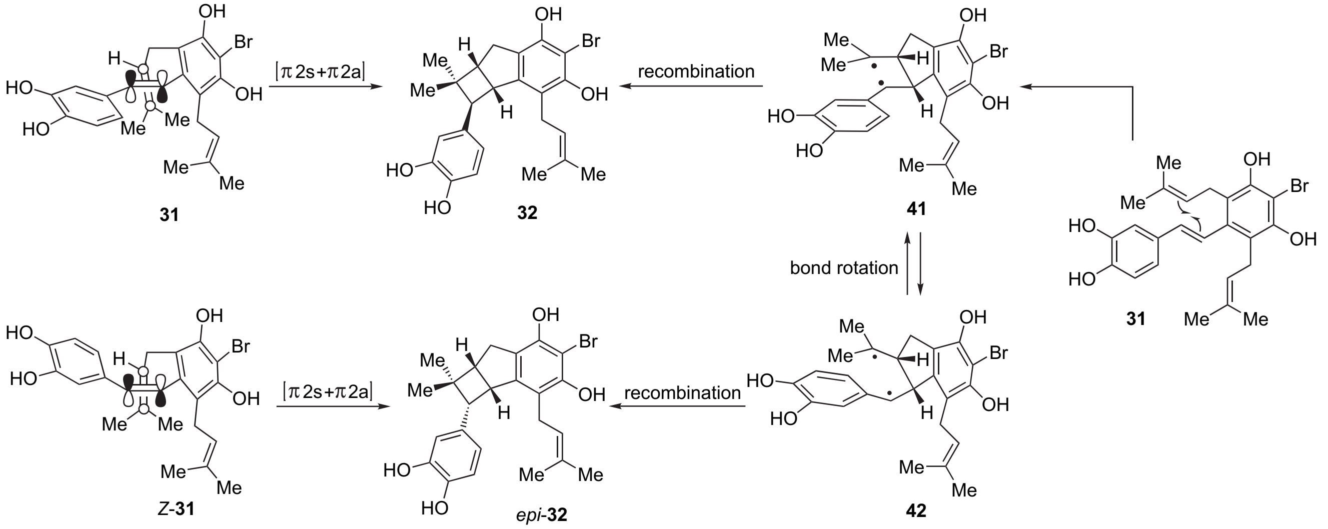
2.4. Mechanistic studies

The cascade sequence described above could also be conducted successfully by conventional heating (*o*-xylene, 165 °C, sealed tube, PH_3PO 5%, w/w), although 1 h was required for the reaction to reach completion. TLC analysis of the reaction mixture indicated that the Claisen rearrangements proceed faster than the Boc cleavage or the formal [2+2] cycloaddition reaction. Given the fact that the free hydroxyl groups are necessary for the formal cycloaddition reaction to occur, we surmise the sequence shown in Scheme 8 as the most reasonable order of events in this cascade sequence. Thus, it is thought that rapid Claisen rearrangements are followed by slower deprotections and ring closures (**5**→**28**→**29**→**30**→**31**→**32**, Scheme 8).



Scheme 10. Total synthesis of artochamin F (**1**). Reagents and conditions: (a) *o*-xylene, μ-wave, 180 °C, 5 min; (b) AIBN (0.1 equiv), *n*-Bu_3SnH (2.0 equiv), benzene, reflux, 1 h; (c) HF·Et_3N (5.0 equiv), THF, 23 °C, 1 h; (d) *o*-xylene, μ-wave, 180 °C, 10 min; AIBN=azobis*iso*butylonitrile.

The precise mechanism of the formal [2+2] cycloaddition reaction is quite fascinating, but not fully illuminated as yet. At present, we can outline three potential alternatives for this interesting transformation, the first two of which are described in Scheme 11. The first scenario involves a concerted [π2s+π2a] cycloaddition[35] between the stilbene alkene and one of the prenyl groups (**31**→**32**, Scheme 11). Such a process ought to be stereospecific with respect to the geometry of the stilbene alkene. We view this first possibility to be highly unlikely due to the difficulty in obtaining the necessary orbital overlap, especially when the conformational constraints imposed by the tether are taken into account. The second, and more reasonable scenario, may involve a stepwise radical mechanism in which an initial 5-*exo* cyclization is followed by rapid recombination of the biradical so-obtained (**31**→**41**→**32**, Scheme 11).[23c] The stereochemical outcome of this process with respect to the benzylic stereocenter adjacent to the *gem*-dimethyl group should be governed by the relative rates of the indicated bond rotation and radical coupling processes. If the radical recombination occurs faster than the bond rotation, then the stereochemistry of the starting olefin will be retained in the product, whereas, in the reverse scenario, the formation of *epi*-**32** will be competitive with that of **32**.

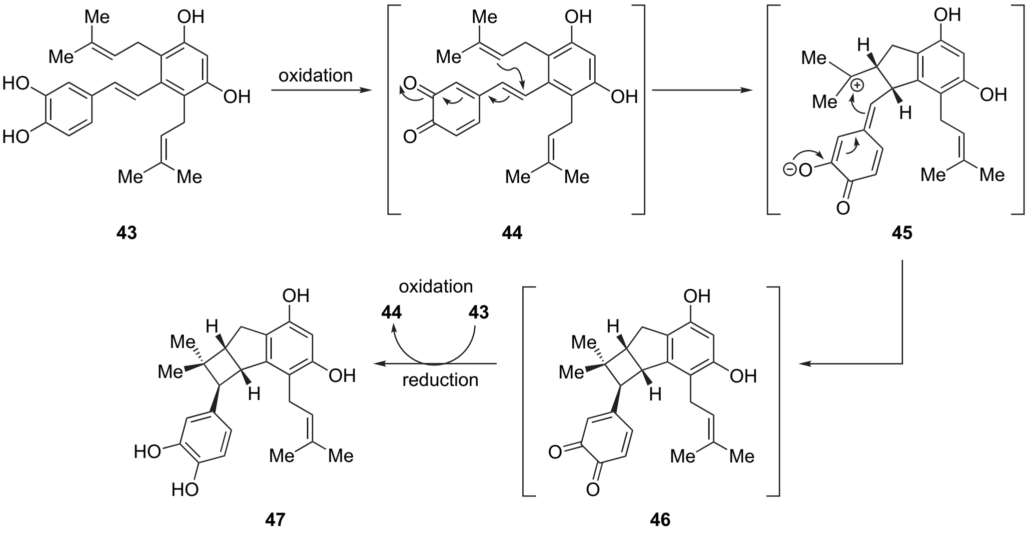


Scheme 11. Potential mechanistic pathways for the formal [2+2] cycloaddition reaction.

In an initial experiment with Wittig-derived stilbenes *E*- and *Z*-**5**, it was discovered that the reaction was not stereospecific with respect to the geometry of the alkene, although possible *E*/*Z* isomerization of the stilbene under the reaction conditions in the case of the *Z*-isomer could undermine this conclusion. These observations corroborate the stepwise biradical mechanism in which bond rotation occurs at a rate competitive with radical recombination.

The third, and most attractive, alternative is the ionic mechanism depicted in Scheme 12. This mechanism may be particularly relevant to the formation of artochamins H–J (**2**–**4**) in nature due to the ease of enzymatic generation of *o*-quinones from catechols.[36] This alternative biosynthetic pathway appears to be more attractive than the one originally proposed based on a [2+2] cycloaddition mechanism since the conditions typically required to bring about such transformations are rather forcing.[23] According to this newly proposed process, initial enzymatic[36] or chemical[37] oxidation of the electron-rich catechol moiety of generic stilbene **43** (Scheme 12) would furnish *o*-quinone **44**, which could readily undergo intramolecular conjugate addition as shown, affording the intermediate **45**, whose facile ring closure to tetracyclic quinone **46** would be expected. Finally, redox reaction between quinone **46** and dihydroquinone **43** (starting material) may be responsible for the completion of the cascade, leading to product **47** with concomitant re-generation of *o*-quinone **44**, thus necessitating only a trace amount of the initial oxidant. This could be an enzyme,[36] trace amounts of O_2,[38] or other oxidants such as DDQ or even Ph_3PO, as will be discussed further below.

The intriguing effect of Ph_3PO on the cascade reaction was first noticed when stilbene **5** derived from the Julia–Kocieński olefination failed to reproducibly undergo the cascade reaction observed previously with the Wittig-derived material. Suspecting that a trace impurity arising from the Julia–Kocieński olefination was causing the problem, we proceeded to further purify our substrate by crystallization only to observe the same



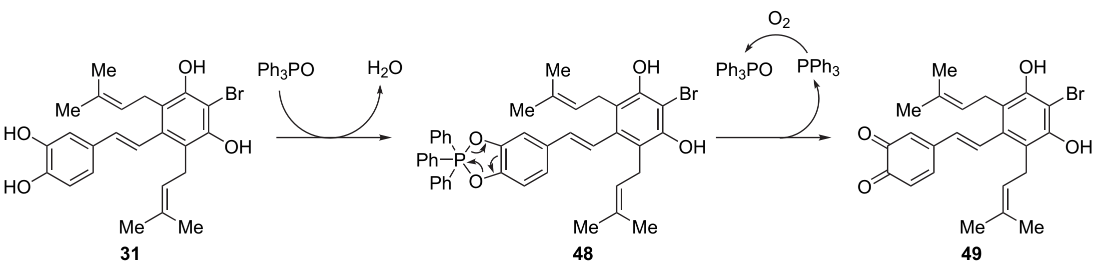
Scheme 12. Postulated redox-based mechanistic pathway for the biogenesis of artochamins H–J from stilbene precursors.

unsuccessful results in inducing the desired cascade reaction. On turning our attention to possible contaminants in the Wittig-derived stilbene, we begun experimentation with Ph_3PO as an additive to the Julia–Kocieński derived stilbene. These experiments led us to the discovery that 3–5% w/w of Ph_3PO was required for the desired cascade reaction to take place smoothly. Although we cannot at present define precisely the exact role played by the phosphine oxide, some speculations are possible. To recap our observations, we know that Ph_3PO is neither absolutely essential in every instance for the [2+2] cycloaddition reaction nor is it required for the Claisen rearrangements or Boc cleavages. However that it is not essential does not preclude a role in which it facilitates one or more of the events in the cascade sequence. We suspect that this additive could potentially facilitate the cycloaddition step based on the following considerations. Proton transfer from phenols to phosphine oxides both in solution and in solid state has been observed to vary degrees spectroscopically.[39] In such events, it is typical to observe a downfield shift of the ^1H NMR signal of the hydroxyl group in the phenol–Ph_3PO complex as the pK_a of the phenol decreases. These results, together with a recent report[23a] describing a base-promoted intramolecular [2+2] cycloaddition reaction between a prenyl group and a benzopyran moiety, suggest that Ph_3PO may be acting as a Lewis base providing formal HOMO activation of the stilbene system toward cycloaddition. Additionally, it is noteworthy to mention the distinct color differences of the reaction mixtures of these cascade reactions in the presence and absence of Ph_3PO. The latter becomes significantly darker in color, suggesting that decomposition does not occur to the same extent in the presence of the additive.

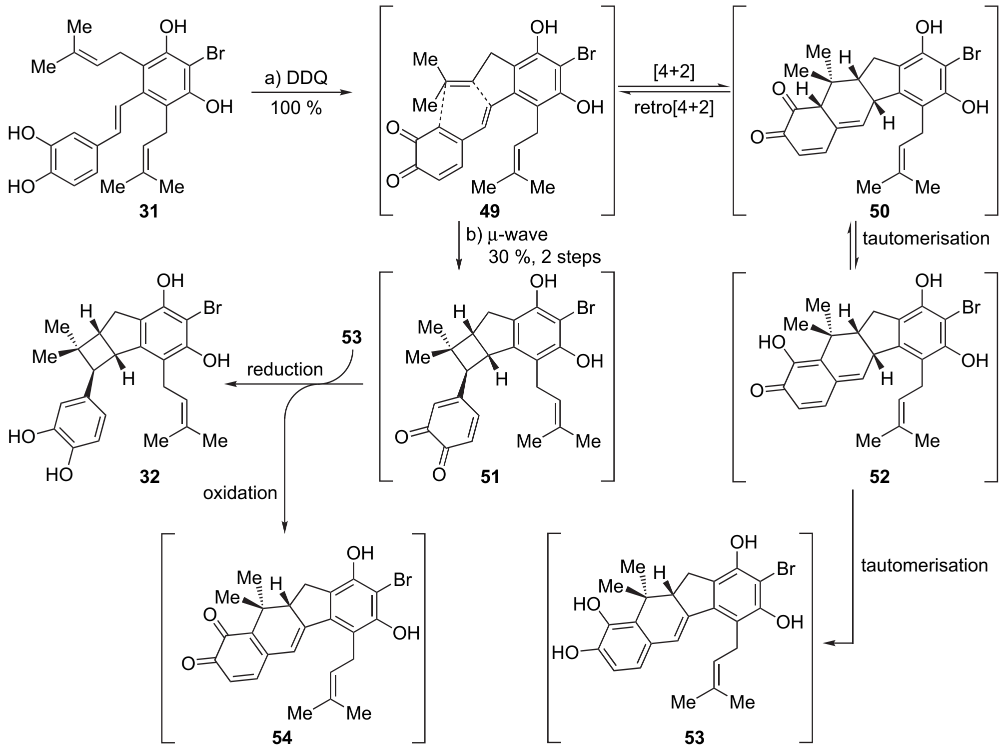
An intriguing possibility for the role of the Ph_3PO in the described cascade reactions and in the context of the redox/ionic mechanism proposed above (Scheme 12) for the biogenesis of artochamins H–J is outlined in Scheme 13.

Given that the redox-based sequence described above is dependent on the initial generation of small amounts of *o*-quinone stilbene, in order to initiate we contemplated the possible role that Ph_3PO might play in this oxidation process. The somewhat counterintuitive process, outlined in Scheme 13, hinges upon combining the dehydration reaction known to take place between Ph_3PO and catechols[40] and the chelotropic elimination of Ph_3P from the so-derived phospholene.[38] Thus, formation of phospholene **48** from stilbene **31** (Scheme 13) may occur under the reaction conditions; its conversion to Ph_3P and *o*-quinone **49** (which may be reversible) could be driven by re-oxidation of the former to Ph_3PO with molecular oxygen present in trace amounts in the reaction mixture. It should be reiterated that only a trace amount of the *o*-quinone stilbene intermediate is necessary for the cascade sequence described in Scheme 12 to become operative. The direct oxidation of stilbene **31** by molecular oxygen is another possibility[38] that could account for the generation of quinone stilbene intermediate **49**. This process is potentially more relevant in the conversion of stilbene **23** to artochamin I (**3**) (Scheme 4) or the conversion of artochamin F (**1**) to **40** (Scheme 10), where the stilbenes could, in principle, already contain traces of the corresponding *o*-quinones arising from aerial oxidation before entering into the formal cycloaddition reaction. Given that deprotection of the catechol moiety of stilbene **5** occurs during the cascade process, the Ph_3PO oxidation cycle described above may also be relevant in the cascade sequence described in Scheme 8.

In order to gain further insight into these mechanistic proposals, we considered the following experiments to be relevant. The addition of a more conventional oxidant to the cascade reaction of Scheme 8 should also have a similar effect as Ph_3PO, but obviously will not provide any information with respect to the differentiation of the diradical and redox/ionic mechanisms. The inclusion of 1 wt % DDQ in this cascade gave similar results to those obtained with Ph_3PO. Interestingly, the initial deep red color of the reaction mixture was slowly bleached after heating for a few minutes at 180 °C in *o*-xylene. Presumably, this color change signals the fact that the DDQ persists in solution until the cleavage of both Boc groups from one or more of the cascade intermediates has occurred, after which time it is reduced by the free catechol moiety. In an attempt to observe this process spectroscopically, stilbene **31** possessing a free catechol moiety was prepared and reacted with DDQ (1.5 equiv) in $CDCl_3$ at ambient temperature and the reaction mixture was analyzed by ^1H and ^{13}C NMR spectroscopy (Scheme 14). Exclusive formation of tetracycle **50** was observed in minutes. Formed through initial oxidation of **31** to *o*-quinone **49** followed by an intramolecular [4+2] cycloaddition as shown in Scheme 14, this conjugated *o*-quinone proved too labile for isolation. However, upon removal of the solvent ($CDCl_3$), dissolution of the residue in *o*-xylene, and microwave irradiation at 180 °C for 30 min, cyclobutane **32** was formed (30% overall yield from **31**). A most likely pathway for the conversion of **50** to **32** involves thermally induced reversal of the [4+2] cycloaddition followed by conversion of the so-obtained *o*-quinone **49** to **32**, via o-quinone **51**, by the redox/ionic mechanism described above (Scheme 12). We suspect that under the acidic reaction conditions and high temperatures, Diels–Alder adduct **50** undergoes rapid tautomerisation to



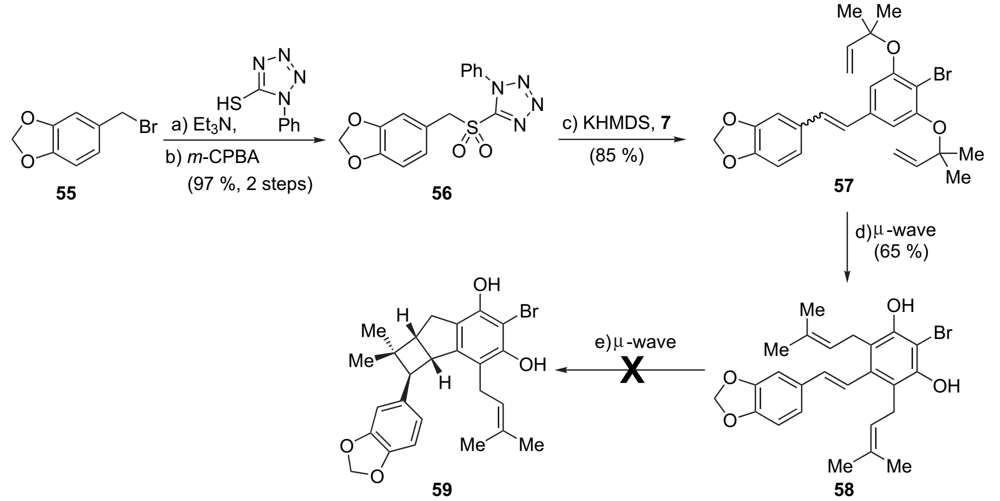
Scheme 13. Potential role of Ph_3PO in the generation of *o*-quinone intermediate **49**.



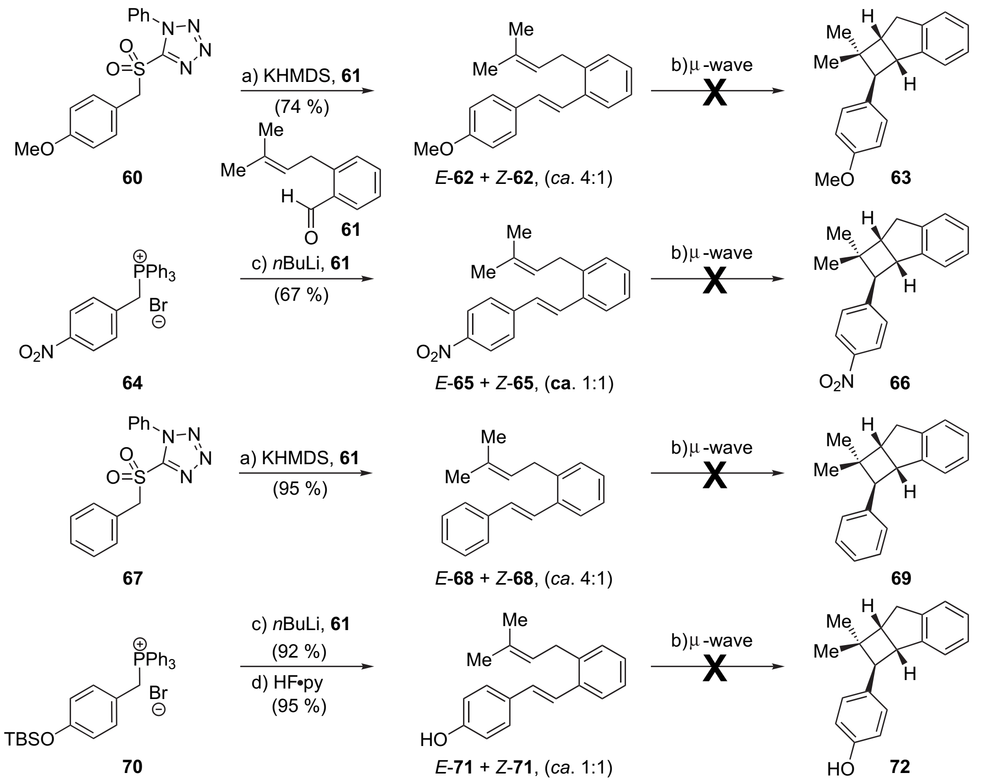
Scheme 14. Spectroscopic observation of Diels–Alder adduct **50** from direct oxidation of stilbene **31** and its conversion to cyclobutane **32**. Reagents and conditions: (a) DDQ (1.5 equiv), $CDCl_3$, 23 °C, 5 min; (b) μ-wave, *o*-xylene, 180 °C, 30 min; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

catechol **53**, via hydroquinone **52**, which may, in turn, be responsible for the reduction of *o*-quinone **51** to cyclobutane **32**, also leading to *o*-quinone **54**. This cycle reaches equilibrium, accounting for the loss of reactivity over longer periods of heating. Another scenario in which Diels–Alder adduct **50** would lead to **32** is by a formal [1,3]-alkyl shift giving *o*-quinone **51** directly. We believe this pathway to be highly unlikely given the formidable geometrical constraints to the required orbital overlap.[35]

An obvious corollary of the redox/ionic mechanism proposed in Scheme 12 is the availability of the catechol unit; given that the methylene acetal derivative of **58** (Scheme 15) ought to be inert with respect to oxidation, any formal cycloaddition product obtained from this substrate should be derived from the diradical pathway shown in Scheme 11, since we have already rejected the concerted pathway on the grounds of insufficient orbital overlap. Furthermore, the absence of product in this experiment would provide circumstantial evidence for the redox/ionic mechanism proposed. We therefore prepared the methylene acetal stilbene **58**, through intermediates **56** and **57** as depicted in Scheme 15, and subjected it to microwave heating.



Scheme 15. Construction and microwave irradiation of methylene acetal stilbene **58**. Reagents and conditions: (a) 1-phenyl-1*H*-tetrazole-5-thiol (1.0 equiv), Et_3N (1.25 equiv), THF, 23 °C; then **55** (1.25 equiv), reflux, 14 h; (b) thioether (1.0 equiv), *m*-CPBA (3.5 equiv), CH_2Cl_2, 0→23 °C, 24 h; (c) **56** (1.8 equiv), KHMDS (1.8 equiv), −78 °C, 30 min; then **7** (1.0 equiv), THF, −78→23 °C, 1 h, *E*/*Z* ca. 2:1; (d) *o*-xylene, μ-wave, 180 °C, 5 min; (e) *o*-xylene, μ-wave, 180 °C, >30 min; *m*-CPBA=3-chloroperbenzoic acid.



Scheme 16. Construction and microwave irradiation of stilbenes **62**, **65**, **68**, and **71**. Reagents and conditions: (a) **60** or **67** (1.8 equiv), KHMDS (1.8 equiv), −78 °C, 30 min; then **61** (1.0 equiv), THF, −78→23 °C, 1 h, *E*/*Z* ca. 4:1 for **62** and **68**; (b) *o*-xylene, μ-wave, 180 °C, >30 min; (c) **64** or **70** (1.2 equiv), *n*-BuLi (1.2 equiv), THF, 0→23 °C, 30 min; then **58** (1.0 equiv), THF, 0→23 °C, 14 h, *E*/*Z* ca. 1:1 for **65** and **71**; (d) HF·Py (excess), THF, 0→23 °C, 2 h.

Exposure of stilbene **58** to microwave heating failed to yield any cyclobutane-containing products; indeed, this substrate was recovered quantitatively even after prolonged heating (>30 min at 180 °C). This provides strong circumstantial evidence for the intervention of the *o*-quinone intermediate in the formation of the bicylco[3.2.0]heptane ring system.

In an attempt to further investigate the mechanism of the formal cycloaddition and to probe the generality of the reaction, four simplified stilbene substrates (**62**, **65**, **68**, and **71**) were prepared from known aldehyde **61** as shown in Scheme 16. After microwave heating at 180 °C (>30 min), stilbenes **62**, **65**, **68**, and **71** were recovered quantitatively, clearly demonstrating their failure to undergo the formal cycloaddition reaction (Scheme 16). These negative results provide further evidence that the redox/ionic mechanism shown in Scheme 12 is the most likely scenario operating in these reactions.

3. Conclusions

Described herein are a series of cascade-based strategies whose implementation resulted in expeditious and efficient total syntheses of artochamins H–J (**2**–**4**) as well as artochamin F (**1**). The mechanism for those cascade reactions was investigated and a number of proposals are put forward, including a redox-based mechanism involving *o*-quinone species that may be relevant to the biosynthesis of members of this class. These cascade-based total syntheses highlight, once again, the advantages of such synthetic sequences in rapidly building molecular complexity and diversity from relatively simple starting materials in efficient and environmentally benign ways.

4. Experimental

4.1. General experimental

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), dimethylformamide (DMF), triethylamine (Et_3N), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an ethanolic solution of anisaldehyde and sulfuric acid or an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. Preparative thin-layer chromatographic (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, or AMX-400 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to designate multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, quin=quintuplet, sext=sextet, sep=septet, br=broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometric (MS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

*4.2. First-generation synthesis of artochamin I (**3**)*

*4.2.1. 4-Bromo-3,5-bis-(1,1-dimethyl-allyloxy)-benzoic acid methyl ester (**13**)*

To a solution of methyl 4-bromo-3,5-dihydroxybenzoate (**12**) (3.0 g, 12.1 mmol) in CH_3CN (120 mL) at 0 °C was added $CuCl_2$ (30 mg, 0.12 mmol) followed by DBU (5.46 mL, 36.3 mmol). After stirring for 15 min, methyl 1,1-dimethyl-2-propynyl carbonate (5.19 g, 36.3 mmol) was added and the resulting mixture was stirred at 0 °C overnight. The reaction mixture was treated with H_2O (50 mL) and extracted with Et_2O (3×100 mL), and then the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc in hexanes) to give the bis-alkyne (3.32 g, 83%) as a clear oil. R_f=0.50 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 2982m, 1724m, 1576m, 1415m, 1382w, 1364w, 1331m, 1240m, 1134m, 1058s, 1033s, 1014m, 840w, 771w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=8.00 (s, 2H), 3.91 (s, 3H), 2.63 (s, 2H), 1.73 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=166.4, 154.0, 129.0, 117.9, 116.1, 85.4, 74.5, 74.5, 52.4, 29.5 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{19}BrO_4$ [M+H$^+$]: 379.0539, found: 379.0544.

To a solution of bis-alkyne (2.50 g, 6.59 mmol) in EtOAc (66 mL) under an atmosphere of argon at room temperature was added quinoline (389 μL, 3.30 mmol) followed by 5% Pd/$CaCO_3$ (poisoned with Pb) (250 mg, 10% w/w). The system was flushed with H_2 and then stirred under an atmosphere of H_2 (balloon) for 3 h. The system was flushed with argon, and the reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc in hexanes) to give the bis-alkene **13** (2.53 g, 100%) as a colorless oil. R_f=0.18 (silica gel, 15% EtOAc in hexanes); IR ν_{max} (film) 2982m, 1725s, 1571m, 1415s, 1379w, 1364w, 1334m, 1238s, 1128m, 1072m, 1005w, 927w, 772w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.46 (s, 2H), 6.17 (dd, J=17.6, 6.8 Hz, 2H), 5.24 (d, J=17.6 Hz, 2H), 5.18 (d, J=6.8 Hz, 2H), 3.86 (s, 3H), 1.53 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=166.6, 154.5, 143.6, 128.5, 118.4, 115.7, 114.1, 82.2, 52.3, 26.9 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{23}BrO_4$ [M+H$^+$]: 383.0852, found: 383.0862.

*4.2.2. 4-Bromo-3,5-dihydroxy-2,6-bis-(3-methyl-but-2-enyl)-benzoic acid methyl ester (**14**)*

A solution of bis-alkene **13** (900 mg, 0.24 mmol) in DMF (2.0 mL) was subjected to microwave heating for 5 min at 180 °C. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (2 mL) was added. The aqueous phase was acidified (pH 3) with HCl (1 M) and the layers were separated. The organic phase was further washed with H_2O (4×2 mL) and brine (2 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (60% CH_2Cl_2 in hexanes) to give bis-prenyl compound **14** (76.5 mg, 85%) as a clear oil. R_f=0.22 (silica gel, 60% CH_2Cl_2 in hexanes); IR ν_{max} (film) 3464br m, 2965w, 2914w, 2856w, 1717s, 1579m, 1431s, 1363s, 1320m, 1253s, 1206m, 1144s, 1092s, 1023m, 1002w, 927w, 901w, 799w, 775w, 735w, 604w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=5.68 (s, 2H), 5.16 (m, 2H), 3.86 (s, 3H), 3.28 (d, J=7.0 Hz, 4H), 1.73 (s, 6H), 1.70 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=169.4, 149.4, 134.3, 133.4, 121.8, 117.2, 101.4, 52.1, 27.3, 25.7, 17.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{18}H_{23}BrO_4$ [M+H$^+$]: 383.0852, found: 383.0850.

*4.2.3. 4-Bromo-3,5-dimethoxy-2,6-bis-(3-methyl-but-2-enyl)-benzoic acid methyl ester (**15**)*

To a solution of bis-phenol **14** (200 mg, 0.52 mmol) in DMF (10 mL) were added K_2CO_3 (361 mg, 2.61 mmol) and MeI (195 μL, 3.13 mmol), and the resulting mixture was heated at 100 °C for 1 h. Once cooled, the reaction mixture was diluted with EtOAc (30 mL) and washed with H_2O (5×5 mL) and brine (5 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (60% CH_2Cl_2 in hexanes) to give the bis-methyl ether **15** (204 g, 95%) as a clear oil. R_f=0.38 (silica gel, 60% CH_2Cl_2 in hexanes); IR ν_{max} (film) 2934w, 2859w, 1730s, 1561w, 1450m, 1434m, 1398s, 1375w, 1319s, 1248m, 1194m, 1144m, 1093s, 1031s, 984m, 950w, 925w, 895w, 833w, 802w, 764w, 732w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=5.09 (m, 2H), 3.81 (s, 3H), 3.78 (s, 6H), 3.35 (d, J=6.5 Hz, 4H), 1.70 (s, 6H), 1.67 (d, J=1.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=169.0, 154.6, 135.0, 132.2, 129.6, 122.4, 114.8, 60.9, 52.0, 27.0, 25.6, 17.9 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{20}H_{27}BrO_4$ [M+H$^+$]: 411.1165, found: 411.1164.

*4.2.4. [4-Bromo-3,5-dimethoxy-2,6-bis-(3-methyl-but-2-enyl)-phenyl]-methanol (**16**)*

To a solution of methyl ester **15** (180 mg, 0.44 mmol) in THF (4.0 mL) at 0 °C was added $LiAlH_4$ (4.4 mL, 4.4 mmol, 1 M solution in THF) and the resulting mixture was warmed to 50 °C and stirred for 14 h. Excess $LiAlH_4$ was quenched by the addition of EtOAc, and then H_2O (1 mL), NaOH (1 mL, 1 M aqueous solution), and H_2O (2 mL), and $MgSO_4$ were added successively and the mixture was filtered. The solvent was concentrated in vacuo and the residue was purified by column chromatography (CH_2Cl_2) to give alcohol **16** (119 mg; 89%) as a clear oil. R_f=0.39 (silica gel, CH_2Cl_2); IR ν_{max} (film) 3418br m, 2962m, 2913m, 2855m, 1592s, 1453m, 1437m, 1375m, 1311s, 1207m, 1158m, 1114m, 1084s, 1001m, 957w, 927w, 888w, 817m, 756w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=6.50 (s, 1H), 5.13 (m, 2H), 4.65 (s, 2H), 3.84 (s, 6H), 3.46 (d, J=7.0 Hz, 4H), 1.81 (s, 6H), 1.69 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=156.4, 138.7, 131.0, 124.5, 121.9, 95.8, 59.1, 55.8, 25.7, 24.4, 17.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{28}O_3$ [M+H$^+$]: 305.2111, found: 305.2102.

*4.2.5. 4-Bromo-3,5-dimethoxy-2,6-bis-(3-methyl-but-2-enyl)-benzaldehyde (**17**)*

To a solution of alcohol **16** (100 mg, 0.33 mmol) in CH_2Cl_2 (5.0 mL) at room temperature was added Dess–Martin periodinane (209 mg, 0.49 mmol). After 30 min, the reaction mixture was diluted with Et_2O (30 mL) and a solution of $Na_2S_2O_3$ (840 mg) in saturated aqueous $NaHCO_3$ (10 mL) was added, and stirring maintained until a clear biphase persisted. The aqueous phase was removed and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (30% CH_2Cl_2 in hexanes) to give aldehyde **7** (93 mg, 94%) as a clear oil. R_f=0.32 (silica gel, 30% CH_2Cl_2 in hexanes); IR ν_{max} (film) 2951m, 2925m, 2850m, 1697m, 1603m, 1588m, 1462m, 1437m, 1375w, 1311s, 1200m, 1163w, 1119w, 1097w, 1082w, 1027w, 965w, 827w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=10.44 (s, 1H), 6.64 (s, 1H), 5.10 (m, 2H), 3.85 (s, 6H), 3.54 (d, J=6.8 Hz, 4H), 1.74 (s, 6H), 1.66 (d, J=0.8 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=195.3, 156.4, 134.9, 131.4, 123.8, 123.5, 99.9, 56.1, 25.8, 23.8, 17.9 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{26}O_3$ $[M+H^+]$: 303.1955, found: 303.1943.

*4.2.6. 3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-benzaldehyde (**19**)*

Aldehyde **19** was prepared according to the literature and displayed identical physical properties to those reported.[41]

*4.2.7. [3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl]-methanol (**20**)*

To a solution of aldehyde **19** (3.28 g, 8.96 mmol) in EtOH (45 mL) was added $NaBH_4$ (339 mg, 8.96 mmol) portion wise at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 10 min. The reaction was quenched with water, extracted with EtOAc (2×50 mL), dried ($MgSO_4$), and concentrated in vacuo to yield benzyl alcohol **20** (3.23 g, 98%). R_f=0.22 (silica gel, 15% EtOAc in hexanes); IR (film) ν_{max} 3318br w, 2954m, 2930s, 2886w, 2858s, 1605w, 1578w, 1509s, 1472m, 1422m, 1295s, 1252s, 1158m, 1123m, 904s, 777s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=6.85 (s, 1H), 6.80 (s, 2H), 4.55 (d, J=6.0 Hz, 2H), 1.47 (t, J=6.0 Hz, 1H), 0.99 (s, 18H), 0.20 (s, 12H) ppm; ^{13}C NMR (500 MHz, $CDCl_3$) δ=146.9, 146.5, 134.2, 121.0, 120.2, 120.1, 65.2, 25.9, 18.5 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{36}O_3Si_2$ $[M+Na^+]$: 391.2095, found: 391.2111.

*4.2.8. 4-Bromomethyl-1,2-bis-(tert-butyl-dimethyl-silanyloxy)-benzene (**21**)*

To solution of benzyl alcohol **20** (430 mg, 1.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of PBr_3 (55 µL, 0.58 mmol) in CH_2Cl_2 (1.5 mL) and the resulting mixture was stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL), and then dried ($MgSO_4$) and concentrated in vacuo to give the corresponding benzyl bromide **21** (503 mg, 100%) as a yellow oil, which displayed identical physical properties to those reported.[42]

*4.2.9. [3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-benzyl]-triphenylphosphonium bromide (**9**)*

To a solution of benzyl bromide **21** (503 mg, 1.17 mmol) in toluene (5.5 mL) was added PPh_3 (300 mg, 1.17 mmol) and the resulting mixture was heated at reflux overnight. The precipitate was collected by filtration and dried under vacuum to give phosphonium bromide **9** (720 mg, 89%) as a white solid, which displayed identical physical properties to those reported.[43]

*4.2.10. 3-{2-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl]-vinyl}-1,5-dimethoxy-2,4-bis-(3-methyl-but-2-enyl)-benzene (**22**)*

To a solution of phosphonium bromide **9** (127 mg, 0.18 mmol) in THF (9.0 mL) at −78 °C was added *n*-BuLi (71 µL, 0.18 mmol, 2.5 M solution in hexanes) and the resulting red mixture was stirred for 30 min. A solution of aldehyde **17** (45 mg, 0.15 mmol) in THF (1.0 mL) was added via cannula and the reaction mixture was warmed to room temperature over 30 min. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (5 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (30% CH_2Cl_2 in hexanes) to give *Z*-**22** (17 mg, 18%) followed by *E*-**22** (68 mg, 72%) as clear oil. Physical data for *E*-**22**: R_f=0.29 (silica gel, 30% CH_2Cl_2 in hexanes); IR ν_{max} (film) 2951s, 2928s, 2857m, 1739w, 1585m, 1507s, 1462m, 1433m, 1309m, 1297m, 1253m, 1213w, 1160w, 1120w, 1081w, 991w, 908s, 839s, 806s, 782s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=6.94 (d, J=2.0 Hz, 1H), 6.89 (dd, J=8.0, 2.0 Hz, 1H), 6.88 (d, J=16.5 Hz, 1H), 6.80 (d, J=8.0 Hz, 1H), 6.46 (s, 1H), 6.38 (d, J=16.5 Hz, 1H), 5.14 (m, 2H), 3.85 (s, 6H), 3.34 (d, J=7.0 Hz, 4H), 1.66 (d, J=1.0 Hz, 6H), 1.63 (s, 6H), 1.01 (s, 18H), 0.23 (s, 6H), 0.22 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=156.3, 146.8, 146.5, 139.4, 133.9, 131.6, 130.4, 124.6, 124.1, 120.9, 120.8, 119.7, 118.9, 94.8, 55.9, 26.2, 26.0, 26.0, 25.8, 18.5, 18.5, 18.0, −4.1, −4.1 ppm.

*4.2.11. Artochamin I (**3**)*

To a solution of bis-TBS ether *E*-**22** (40 mg, 62.7 µmol) in THF (500 µL) at 0 °C was added HF·Py (500 µL, excess) and the resulting mixture was warmed to room temperature and stirred for an additional 2 h. The reaction mixture was diluted with Et_2O (10 mL) and then washed successively with saturated aqueous $CuSO_4$ (3×2 mL), saturated aqueous $NaHCO_3$ (2×2 mL), and brine (2 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. The residue was passed through a short plug of silica gel (30% EtOAc in hexanes) to give diol **23** (23 mg, 88%) as a clear oil, which was used directly in the following reaction.

A solution of stilbene **23** (10 mg, 24.2 µmol) in DMF (2 mL) was subjected to microwave heating at 180 °C for 20 min. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (2 mL) was added. The aqueous phase was acidified (pH 3) with HCl (1 M) and the layers were separated. The organic phase was further washed with H_2O (4×2 mL) and brine (2 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexanes) to give artochamin I (**3**) (8.0 mg; 80%) as a clear oil. R_f=0.17 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 3381br m, 2926s, 2856m, 1701w, 1600s, 1518m, 1492m, 1461s, 1451s, 1436s, 1365m, 1312s, 1282m, 1260m, 1202m, 1119s, 1086s, 1033w, 867w, 806m cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ=7.64 (br s, 2H), 6.79 (d, *J*=8.0 Hz, 1H), 6.76 (d, *J*=2.0 Hz, 1H), 6.64 (dd, *J*=8.0, 2.0 Hz, 1H), 6.47 (s, 1H), 4.92 (m, 1H), 3.95 (dd, *J*=8.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.03 (dd, *J*=16.0, 3.0 Hz, 1H), 2.94–2.91 (m, 1H), 2.88 (dd, *J*=17.0, 9.5 Hz, 1H), 2.84 (d, *J*=5.5 Hz, 1H), 2.76 (m, 2H), 1.51 (d, *J*=1.5 Hz, 3H), 1.42 (s, 3H), 1.01 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=159.6, 156.4, 150.9, 146.6, 145.2, 135.2, 131.5, 125.6, 125.6, 121.0, 119.0, 117.1, 116.7, 95.9, 59.6, 57.3, 56.5, 46.6, 46.4, 40.1, 31.7, 28.4, 27.6, 27.2, 26.8, 18.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{26}H_{32}O_4$ [M+H$^+$]: 409.2373, found: 409.2374.

*4.3. Julia–Kocieński approach to stilbenes and cascade strategy for artochamins H–J (**2–4**)*

*4.3.1. [4-Bromo-3,5-bis-(1,1-dimethyl-allyloxy)-phenyl]-methanol (**24**)*

To a solution of methyl ester **13** (1.90 g, 4.96 mmol) in THF (50 mL) at 0 °C was added a solution of $LiAlH_4$ (5.95 mL, 5.95 mmol, 1 M solution in THF). After 10 min, the reaction was quenched by the addition of H_2O (2 mL), NaOH (2 mL, 1 M aqueous solution), and H_2O (3 mL), and then $MgSO_4$ was added and the mixture was filtered. The solvent was concentrated in vacuo and the residue was purified by column chromatography (40% Et_2O in hexanes) to give alcohol **24** (1.67 g, 95%) as a clear oil. R_f=0.36 (silica gel, 60% Et_2O in hexanes); IR ν_{max} (film) 3404br w, 2981w, 1572m, 1422s, 1378m, 1363m, 1217w, 1127s, 1057s, 999m, 923m, 864m, 704m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=6.82 (s, 2H), 6.18 (dd, *J*=15.0, 9.0 Hz, 2H), 5.22 (d, *J*=15.0 Hz, 2H), 5.14 (d, *J*=9.0 Hz, 2H), 4.52 (d, *J*=5.0 Hz, 2H), 1.51 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=154.6, 144.2, 139.6, 113.9, 113.6, 111.9, 81.8, 65.0, 26.9 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{17}H_{23}BrO_3$ [M+H$^+$]: 355.0903, found: 355.0906.

*4.3.2. [4-Bromo-3,5-bis-(1,1-dimethyl-allyloxy)]-benzaldehyde (**7**)*

To a solution of alcohol **24** (1.66 g, 4.67 mmol) in CH_2Cl_2 (25 mL) at room temperature was added Dess–Martin periodinane (2.4 g, 5.61 mmol). After 30 min, the reaction mixture was diluted with Et_2O (100 mL) and a solution of $Na_2S_2O_3$ (9.6 g) in saturated aqueous $NaHCO_3$ (20 mL) was added and stirring was maintained until a clear biphase persisted. The aqueous phase was removed and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (30% Et_2O in hexanes) to give aldehyde **7** (1.60 g, 97%) as a clear oil. R_f=0.34 (silica gel, 30% Et_2O in hexanes); IR ν_{max} (film) 2982w, 1696s, 1570s, 1421s, 1379s, 1364m, 1325m, 1217w, 1124s, 1072s, 1035s, 1001m, 924m, 827m, 757m, 704m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.78 (s, 1H), 7.27 (s, 2H), 6.18 (dd, *J*=17.5, 11.0 Hz, 2H), 5.27 (d, *J*=17.5 Hz, 2H), 5.21 (d, *J*=11.0 Hz, 2H), 1.55 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=191.6, 155.7, 144.0, 135.3, 121.0, 115.1, 114.8, 82.8, 27.4 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{17}H_{21}BrO_3$ [M+H$^+$]: 353.0747, found: 353.0746.

*4.3.3. Carbonic acid 2-tert-butoxycarbonyloxy-4-formyl-phenyl ester tert-butyl ester (**25**)*

To a solution of 3,4-dihydroxybenzaldehyde **18** (2.0 g, 14.5 mmol) in THF (50 mL) at room temperature were added di-*tert*-butyl dicarbonate (6.32 g, 29.0 mmol), *i*-Pr_2NEt (203 μL, 1.45 mmol), and DMAP (89 mg, 0.72 mmol). After 2 h, the reaction mixture was diluted with EtOAc (100 mL) and washed with NaOH (50 mL, 1 M aqueous solution) and brine, and then dried ($MgSO_4$) and concentrated in vacuo to give aldehyde **25** (4.90 g, 100%), which was used in the next reaction without further purification. R_f=0.38 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 2978w, 2936w, 2868w, 1767m, 1740m, 1704m, 1371m, 1243s, 1151s, 1136s, 1106s, 1045m, 886m, 865w, 776m, 728m, 634m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=9.95 (s, 1H), 7.79 (d, *J*=2.0 Hz, 1H), 7.76 (dd, *J*=8.5, 2.0 Hz, 1H), 7.44 (d, *J*=8.5 Hz, 1H), 1.55 (s, 18H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=190.0, 150.3, 149.8, 147.3, 143.2, 134.5, 127.9, 124.0, 123.7, 84.5, 84.4, 27.5 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{17}H_{22}O_7$ [M+Na$^+$]: 361.1258, found: 361.1259.

*4.3.4. Carbonic acid 2-tert-butoxycarbonyloxy-4-hydroxymethyl-phenyl ester tert-butyl ester (**26**)*

To a solution of aldehyde **25** (4.44 g, 13.1 mmol) in EtOH (70 mL) at 0 °C was added $NaBH_4$ (548 mg, 13.1 mmol), and the reaction mixture was warmed to room temperature and stirred for 10 min. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc in hexanes) to give alcohol **26** (4.24 g, 95%) as a clear oil. R_f=0.38 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 3377br s, 2976w, 2934w, 2874w, 1766m, 1371m, 1252s, 1154s, 1113s, 1046m, 880m, 777m, 734m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.31 (d, *J*=8.5 Hz, 1H), 7.30 (d, *J*=2.0 Hz, 1H), 7.11 (dd, *J*=8.5, 2.0 Hz, 1H), 4.67 (s, 2H), 1.58 (s, 18H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=150.8, 150.8, 142.4, 141.6, 139.8, 124.5, 122.9, 121.4, 83.8, 83.7, 27.6 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{24}H_{24}O_7$ [M+Na$^+$]: 363.1414, found: 363.1414.

*4.3.5. Carbonic acid 4-bromomethyl-2-tert-butoxycarbonyloxy-phenyl ester tert-butyl ester (**27**)*

To a solution of alcohol **26** (500 mg, 1.47 mmol) in CH_2Cl_2 (10 mL) was added PBr_3 (0.28 mL, 2.94 mmol) dropwise and the resulting solution was stirred at 0 °C for 1 h. The reaction was quenched with water (3 mL), and then extracted with Et_2O (3×5 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL), then dried (K_2CO_3) and concentrated in vacuo to yield the corresponding bromide (104 mg, 18%) as an orange oil. R_f=0.69 (silica gel, 50% EtOAc in hexanes); IR (film) ν_{max} 2981w, 2935w, 1761s, 1610w, 1508m, 1457w, 1433w, 1395m, 1370m, 1248s, 1143s, 1109s, 1046w, 1014w, 888m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.34 (d, J=1.5 Hz, 1H), 7.30–7.26 (m, 2H), 4.47 (s, 2H), 1.58 (s, 9H), 1.58 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=150.5, 150.4, 142.3, 142.2, 136.1, 126.9, 123.7, 123.2, 83.9, 31.9, 27.5 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{17}H_{23}BrO_6$ [M+Na$^+$]: 425.0570, found: 425.0564.

4.3.6. [3,4-Bis-(tert-butoxycarbonyloxy)-benzyl]-triphenyl-phosphonium bromide (**8**)

A mixture of bromide **27** (170 mg, 0.42 mmol) and triphenylphosphine (166 mg, 0.63 mmol) in toluene (3.0 mL) was heated to 60 °C and stirred overnight. The solvent was then removed in vacuo to give phosphonium bromide **8** (151 mg; 62%) as a white solid. IR (film) ν_{max} 2981w, 2870w, 2773w, 1769s, 1755s, 1589w, 1505w, 1438m, 1371m, 1284m, 1251s, 1157s, 1137m, 1113s, 886m cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ=7.93–7.90 (m, 5H), 7.77–7.62 (m, 10H), 7.17 (d, J=8.0 Hz, 1H), 6.96 (d, J=8.5 Hz, 1H), 6.89 (s, 1H), 5.25 (d, J=15.5 Hz, 2H), 1.46 (s, 9H), 1.44 (s, 9H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6) δ=149.6 (d, J=8.6 Hz), 149.5 (d, J=8.1 Hz), 142.0 (d, J=4.2 Hz), 141.7 (d, J=3.6 Hz), 135.1 (d, J=2.7 Hz), 134.0 (d, J=9.9 Hz), 130.1 (d, J=12.5 Hz), 126.7 (d, J=8.6 Hz), 125.5 (d, J=5.4 Hz), 123.6 (d, J=2.9 Hz), 117.3 (d, J=85.1 Hz), 84.0 (s), 83.9 (s), 27.5 (d, J=47.0 Hz), 27.0 (s), 26.9 (s) ppm; HRMS (ESI TOF) *m/z* calcd for $C_{35}H_{38}O_6P$ [$M^{+\bullet}$]: 585.2406, found: 585.2392.

4.3.7. Carbonic acid 4-{2-[4-bromo-3,5-bis-(1,1-dimethyl-allyloxy)-phenyl]-vinyl}-2-tert-butoxycarbonyloxy-phenyl ester tert-butyl ester (**5**)

To a solution of phosphonium bromide **8** (200 mg, 0.30 mmol) in THF (1.2 mL) at −78 °C was added *t*-BuOK (34 mg, 0.30 mmol) and the resulting red mixture was stirred for 30 min. A solution of aldehyde **7** (88 mg, 0.25 mmol) in THF (500 μL) was added via cannula and the reaction mixture was warmed to room temperature over 30 min. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with Et_2O (3×15 mL). The combined organic extracts were washed with brine (5 mL), and then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (30% CH_2Cl_2 in hexanes) to give *Z*-**22** (16.5 mg, 44%) followed by *E*-**22** (17.5 mg, 46%) as clear oils. Physical data for *E*-**22**: R_f=0.23 (silica gel, 15% Et_2O in hexanes); IR ν_{max} (film) 2981w, 1767s, 1582w, 1506w, 1414w, 1370w, 1253s, 1156s, 1115m, 1072w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.37 (d, J=2.4 Hz, 1H), 7.32 (dd, J=8.4, 2.4 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 6.95 (s, 2H), 6.83 (s, 2H), 6.22 (dd, J=17.6, 10.8 Hz, 2H), 5.25 (dd, J=17.6, 0.8 Hz, 2H), 5.19 (dd, J=10.8, 0.8 Hz, 2H), 1.56 (s, 9H), 1.55 (s, 9H) 1.53 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=150.8, 150.7, 144.6, 144.4, 144.3, 144.3, 142.8, 141.9, 135.9, 135.5, 129.5, 127.4, 127.3, 124.6, 123.3, 120.9, 120.9, 120.8, 113.9, 113.8, 112.7, 83.9, 82.0, 27.8, 27.7, 27.0, 26.9 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{34}H_{43}BrO_8$ [M+H$^+$]: 659.2214, found: 659.2197.

4.3.8. Carbonic acid 2-tert-butoxycarbonyloxy-4-(1-phenyl-1H-tetrazole-5-sulfonylmethyl)-phenyl ester tert-butyl ester (**10**)

To a solution of alcohol **26** (5.4 g, 17.5 mmol) in THF (175 mL) at 0 °C were added PPh_3 (5.1 g, 19.3 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (3.12 g, 17.5 mmol), and DEAD (3.31 mL, 21.0 mmol). After stirring for 30 min at 0 °C, saturated aqueous $NaHCO_3$ (75 mL) was added and the reaction mixture was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc in hexanes) to give the sulfide (6.74 g, 77%) as a yellow oil.

To a solution of the sulfide (5.04 g, 10.1 mmol) in EtOH (120 mL) at room temperature was added a cooled (0 °C) solution of ammonium molybdate tetrahydrate (1.25 g, 0.10 mmol) in H_2O_2 (120 mL). The resulting yellow mixture was allowed to stir for 14 h before being diluted with H_2O (100 mL) and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (40% EtOAc in hexanes) to give sulfone **10** (5.31 g, 99%) as a white powder. R_f=0.44 (silica gel, 40% EtOAc in hexanes); IR ν_{max} (film) 2982w, 2935w, 1763s, 1508w, 1497w, 1371m, 1356m, 1249s, 1148s, 1112s, 1046m, 1014m, 890m, 763m, 733m, 688m, 535m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.56–7.52 (m, 1H), 7.50–7.47 (m, 2H), 7.33–7.31 (m, 2H), 7.22 (d, J=2.0 Hz, 1H), 7.22 (d, J=8.5 Hz, 1H), 7.16 (dd, J=8.5, 2.0 Hz, 1H), 4.87 (s, 2H), 1.54 (s, 9H), 1.53 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=152.6, 150.2, 143.8, 142.8, 132.6, 131.3, 129.5, 129.4, 126.3, 125.4, 123.8, 123.3, 84.2, 61.4, 27.5 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{24}H_{28}N_4O_8S$ [M+Na$^+$]: 555.1520, found: 555.1512.

4.3.9. 5-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl-methanesulfonyl]-1-phenyl-1H-tetrazole (**11**)

To a solution of benzyl alcohol **20** (2.14 g, 5.80 mmol), Ph_3P (1.67 g, 6.39 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (1.03 g, 5.80 mmol) at 0 °C in THF (58 mL) was added DEAD (3.17 mL, 6.97 mmol). The mixture was stirred for 30 min at 0 °C and then treated with saturated aqueous $NaHCO_3$ (30 mL) and diluted with Et_2O (55 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2×40 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to yield the sulfide as a yellow oil.

A solution of the sulfide prepared above (4.47 g, 8.45 mmol) in EtOH (84.5 mL), THF (16.9 mL), and H_2O_2 (31.7 mL) was treated with ammonium molybdate tetrahydrate (2.1 g, 1.69 mmol) at room temperature. The mixture was stirred overnight, and then partitioned with CH_2Cl_2 (60 mL) and saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to yield **11** (4.09 g, 86%, over two steps) as a white foam. R_f=0.26 (silica gel, 10% EtOAc in hexanes); IR (film) ν_{max} 2954w, 2930m, 2887w, 2858m, 1599w, 1577w, 1509s, 1472m, 1424m, 1346s, 1304s, 1253s, 1154s, 1137s, 985s, 905s, 780s, 761s cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ=7.59–7.55 (m, 1H), 7.52–7.49 (m, 2H), 7.38 (m, 2H), 6.82 (d, J=2.5 Hz, 1H), 6.78 (d, J=8.5 Hz, 1H), 6.74 (dd, J=8.0, 2.0 Hz, 1H), 4.81 (s, 2H), 0.97 (s, 9H), 0.96 (s, 9H), 0.19 (s, 6H), 0.15 (s, 6H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ=153.0, 148.6, 147.3, 132.9, 131.3, 129.4, 125.3, 124.7, 124.1, 121.2, 117.0, 62.0, 25.8, 25.8, 18.4, 18.3, −4.1, −4.2 ppm; HRMS (ESI TOF) m/z calcd for $C_{26}H_{40}N_4O_4SSi_2$ [M+H$^+$]: 561.2381, found: 561.2379.

*4.3.10. Carbonic acid 4-{2-[4-bromo-3,5-bis-(1,1-dimethyl-allyloxy)-phenyl]-vinyl}-2-tert-butoxycarbonyloxy-phenyl ester tert-butyl ester (**5**)*

To a solution of sulfone **10** (1.13 g, 2.12 mmol) in THF (20 mL) at −78 °C was added KHMDS (4.24 mL, 2.12 mmol, 0.5 M solution in toluene) and the resulting bright yellow solution was stirred for 30 min. A solution of aldehyde **7** (500 mg, 1.42 mmol) in THF (5 mL) was then added via cannula and the reaction mixture was slowly warmed to room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and then extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (15% Et_2O in hexanes) to give stilbene **5** (747 mg, 80%, 100% *E*) as a white powder. For physical data see Section 4.3.7.

*4.3.11. 5-{2-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl]-vinyl}-2-bromo-1,3-bis-(1,1-dimethyl-allyloxy)-benzene (**6**)*

To a solution of sulfone **11** (163 mg, 0.29 mmol) in DME (26 mL) at −78 °C was added KHMDS (0.6 mL, 0.30 mmol, 0.5 M solution in toluene) and the resulting bright yellow solution was stirred for 30 min. A solution of aldehyde **7** (57.0 mg, 0.16 mmol) in DME (1.4 mL) was then added via cannula and the reaction mixture was slowly warmed to room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) and the mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (25% benzene in hexanes) to give stilbene **6** (107 mg, 95%, *E*/*Z* ca. 2:1) as a yellow oil. R_f=0.57 (silica, 10% EtOAc in hexanes); IR (film) ν_{max} 2951m, 2930s, 2858m, 1566m, 1508s, 1472w, 1421m, 1291m, 1253m, 1128m, 1069m, 994w, 906m, 839s, 804w, 782s cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ=6.98–6.91 (m, 4H), 6.81–6.79 (m, 1H), 6.76 (d, J=16.2 Hz, 1H), 6.68 (d, J=16.2 Hz, 1H), 6.23 (dd, J=17.4, 10.8 Hz, 2H), 5.24 (d, J=17.4 Hz, 2H), 5.17 (d, J=17.4 Hz, 2H), 1.54 (s, 6H), 1.53 (s, 6H), 1.01 (s, 9H), 0.98 (s, 9H), 0.22 (s, 6H), 0.21 (s, 6H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ=154.5, 147.1, 147.0, 144.4, 136.3, 130.7, 129.0, 126.4, 121.2, 120.1, 119.2, 113.8, 113.5, 112.1, 81.9, 26.8, 26.0, 25.9, 18.4, −4.1, −4.1 ppm; HRMS (ESI TOF) m/z calcd for $C_{36}H_{55}BrO_4Si_2$ [M+H$^+$]: 687.2895, found: 687.2879.

*4.3.12. 5-Bromo-2-(3,4-dihydroxy-phenyl)-1,1-dimethyl-3-(3-methyl-but-2-enyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta-[a]indene-4,6-diol (**32**)*

Stilbene **31** (12.2 mg, 18.5 μmol) and Ph_3PO (0.6 mg, 5% w/w) were dissolved in *o*-xylene (1.5 mL), and the resulting solution was subjected to microwave heating at 180 °C for 20 min. Alternatively, heating could be conducted conventionally with an oil bath at 165 °C for 1 h. The cooled reaction mixture was directly loaded onto a silica gel column packed with hexanes as the eluant and the *o*-xylene was run off. The eluant was switched to 10% Et_2O in CH_2Cl_2 and the cycloaddition product **32** (4.7 mg, 55%) was obtained as an inseparable 5:1 mixture of diastereomers. Major diastereomer: R_f=0.13 (silica gel, 5% MeOH in CH_2Cl_2); IR ν_{max} (film) 3475br s, 2956m, 2928m, 2855m, 1719w, 1600m, 1517m, 1441s, 1367m, 1285s, 1249s, 1188m, 1158m, 1105m, 1093m, 966w, 804w, 786w, 766w, 741w cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ=6.82 (d, J=8.0 Hz, 1H), 6.76 (d, J=2.0 Hz, 1H), 6.67 (dd, J=8.0, 2.0 Hz, 1H), 5.48 (s, 1H), 5.25 (s, 1H), 5.11 (s, 1H), 5.00 (m, 1H), 4.97 (s, 1H), 3.95 (ddd, J=8.0, 6.0, 1.0 Hz, 1H), 3.13 (ddd, J=16.0, 3.0, 1.0 Hz, 1H), 3.08 (d, J=7.0 Hz, 1H), 3.01 (dd, J=16.5, 9.5 Hz, 1H), 3.00 (m, 1H), 2.89 (d, J=6.0 Hz, 1H), 2.80 (m, 1H), 1.61 (d, J=1.0 Hz, 3H), 1.54 (s, 3H), 1.05 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ=149.8, 149.3, 146.6, 143.2, 141.6, 134.6, 133.5, 122.8, 121.9, 120.4, 115.6, 115.1, 115.0, 97.6, 57.4, 44.7, 44.6, 38.7, 30.5, 27.3, 27.0, 25.8, 25.7, 17.5 ppm; HRMS (ESI TOF) m/z calcd for $C_{24}H_{27}BrO_4$ [M+H$^+$]: 459.1165, found: 459.1145.

*4.3.13. 2,2-Dimethyl-propionic acid 5-[5-bromo-6-(2,2-dimethyl-propionyloxy)-4-hydroxy-1,1-dimethyl-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-2-yl]-2-(2,2-dimethyl-propionyloxy)-phenyl ester (**33**)*

To a solution of tetraol **32** (16.0 mg, 34.8 μmol) in CH_2Cl_2 (300 μL) at room temperature was added Et_3N (29 μL, 209 μmol) followed by trimethylacetyl chloride (105 μL, 104.5 μmol, 1 M solution in CH_2Cl_2). After 30 min, the reaction mixture was diluted with EtOAc (2 mL) and the aqueous layer was acidified to pH 3 with aqueous HCl (1 M). The layers were separated and the aqueous phase was further extracted with EtOAc (3×2 mL). The combined extracts were washed with brine (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (10–20% Et_2O in hexanes) to afford the tris-protected compound **33** (18.6 mg, 75%) as a white foam. R_f=0.23 (silica gel, 20% Et_2O in hexanes); IR ν_{max} (film) 3473br s, 2962m, 2929m, 2855m, 1760s, 1505m, 1480m, 1460m, 1397s, 1368s, 1271m, 1259m, 1115s, 1029s, 890w cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ=7.10–7.07 (m, 2H), 6.96 (d, J=2.0 Hz, 1H), 5.56 (s, 1H), 4.99 (m, 1H), 4.00 (dd, J=7.0, 5.0 Hz, 1H), 3.03 (dd, J=16.0, 4.5 Hz, 1H), 2.99 (d, J=5.0 Hz, 1H), 2.96–2.86 (m, 3H), 2.82 (m, 1H), 1.60 (d, J=1.0 Hz, 3H), 1.47 (s, 3H), 1.42 (s, 9H), 1.36 (s, 9H), 1.35 (s, 9H), 1.05 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, CDCl$_3$) δ=176.0, 175.7, 175.2, 150.3, 147.9, 142.4, 142.2, 140.8, 139.7, 133.4, 130.0, 125.5, 125.4, 122.8, 122.5, 121.2, 103.2, 57.0, 44.7, 44.6, 39.4, 39.1, 38.9, 30.3, 29.7, 27.3, 25.6, 17.8 ppm; HRMS (ESI

TOF) *m/z* calcd for $C_{39}H_{51}BrO_7$ [M+Na$^+$]: 733.2710, found: 733.2724.

*4.3.14. 2,2-Dimethyl-propionic acid 5-[5-bromo-6-(2,2-dimethyl-propionyloxy)-4-methoxy-1,1-dimethyl-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-2-yl]-2-(2,2-dimethyl-propionyloxy)-phenyl ester (**34**)*

To a solution of phenol **33** (5.5 mg, 7.73 μmol) in DMF (250 μL) was added K_2CO_3 (5.3 mg, 38.5 μmol) followed by MeI (3.0 μL, 46.2 μmol) and the resulting mixture was stirred at 100 °C for 1 h. Upon cooling the reaction mixture was diluted with EtOAc (2 mL), washed with H_2O (5×1 mL) and brine (1 mL), and finally dried ($MgSO_4$) before removal of the solvent in vacuo. The residue was purified by column chromatography (20% Et_2O in hexanes) to afford the methylated compound **34** (5.3 mg, 95%) as a white foam. R_f=0.36 (silica gel, 20% Et_2O in hexanes); IR ν_{max} (film) 2956m, 2925m, 2860m, 1760s, 1501w, 1476w, 1458w, 1395w, 1365w, 1319w, 1260m, 1111s, 1026m, 800w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.08 (d, *J*=8.0 Hz, 1H), 7.02 (dd, *J*=8.0, 2.0 Hz, 1H), 6.94 (d, *J*=2.0 Hz, 1H), 4.91 (m, 1H), 4.02 (dd, *J*=8.0, 6.0 Hz, 1H), 3.76 (s, 3H), 3.04–2.87 (m, 5H), 2.81 (m, 1H), 1.56 (s, 3H), 1.43 (s, 9H), 1.42 (s, 3H), 1.35 (s, 9H), 1.35 (s, 9H), 1.06 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=176.0, 175.7, 175.3, 155.1, 148.1, 143.2, 142.2, 140.8, 139.6, 134.5, 132.5, 129.8, 125.3, 122.8, 122.4, 121.9, 110.1, 61.1, 56.9, 44.6, 44.4, 39.4, 39.1, 39.1, 38.9, 31.0, 30.3, 27.3, 27.3, 27.3, 25.8, 25.5, 17.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{40}H_{53}BrO_7$ [M+H$^+$]: 725.3047, found: 725.3042.

*4.3.15. Artochamin H (**2**)*

To a solution of compound **34** (4.0 mg, 5.51 μmol) in THF (100 μL) at 0 °C was added $LiAlH_4$ (33 μL, 33.1 μmol, 1 M solution in THF). The resulting mixture was warmed to room temperature and allowed to stir for 24 h. Excess $LiAlH_4$ was destroyed by the addition of EtOAc and the mixture was acidified to pH 3 with aqueous HCl (1 M). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford artochamin H (**2**) (2.0 mg, 93%) as a clear oil. R_f=0.43 (silica gel, 50% EtOAc in hexanes); IR ν_{max} (film) 3366s, 2955m, 2925m, 2856m, 1691m, 1599s, 1518m, 1445s, 1365m, 1347m, 1309m, 1280s, 1256s, 1191s, 1160m, 1109s, 1059m, 960w, 868m, 806m, 784m cm^{-1}; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ=7.79 (br s, 1H), 7.66 (br s, 2H), 6.79 (d, *J*=7.8 Hz, 1H), 6.78 (d, *J*=1.8 Hz, 1H), 6.64 (dd, *J*=7.8, 1.8 Hz, 1H), 6.31 (s, 1H), 4.91 (m, 1H), 3.96 (dd, *J*=7.8, 6.0 Hz, 1H), 3.70 (s, 3H), 3.07 (ddd, *J*=16.8, 3.0, 1.2 Hz, 1H), 3.01 (dd, *J*=14.4, 6.0 Hz, 1H), 2.90 (dd, *J*=16.8, 9.6 Hz, 1H), 2.80 (m, 2H), 2.75 (m, 1H), 1.50 (d, *J*=1.2 Hz, 3H), 1.41 (s, 3H), 1.03 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=159.5, 153.6, 151.1, 146.5, 145.1, 135.3, 131.3, 125.8, 124.0, 121.2, 118.2, 117.1, 116.6, 99.4, 59.6, 57.0, 46.7, 46.5, 40.1, 31.4, 28.5, 27.6, 27.2, 26.8, 18.7 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{25}H_{30}O_4$ [M−H$^-$]: 393.2071, found: 393.2079.

*4.3.16. 2,2-Dimethyl-propionic acid 5-(5-bromo-4,6-dihydroxy-1,1-dimethyl-2,2a,7,7a-tetrahydro-1H-cyclobuta-[a]inden-2-yl)-2-(2,2-dimethyl-propionyloxy)-phenyl ester (**35**)*

To a solution of tetraol **32** (15.0 mg, 32.7 μmol) in CH_2Cl_2 (300 μL) at room temperature was added pyridine (16.0 μL, 196 μmol) followed by trimethylacetyl chloride (66 μL, 66.0 μmol, 1 M solution in CH_2Cl_2). After stirring at room temperature overnight, the reaction mixture was diluted with EtOAc (2 mL) and the aqueous layer was acidified to pH 3 with aqueous HCl (1 M). The layers were separated and the aqueous phase was further extracted with EtOAc (3×2 mL). The combined extracts were washed with brine (1 mL), dried ($MgSO_4$), and then concentrated in vacuo. The residue was purified by column chromatography (30–40% Et_2O in hexanes) to afford the bis-protected compound **35** (13.1 mg, 64%) as a white foam. R_f=0.24 (silica gel, 30% Et_2O in hexanes); IR ν_{max} (film) 3450brm, 2970m, 2931m, 2865w, 1758m, 1737m, 1595w, 1505w, 1480w, 1458w, 1367w, 1276w, 1259m, 1228m, 1117s, 1032w, 891w, 790w cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.10–7.07 (m, 2H), 6.96 (d, *J*=1.2 Hz, 1H), 5.51 (s, 1H), 5.26 (s, 1H), 5.02 (m, 1H), 3.95 (dd, *J*=7.8, 5.4 Hz, 1H), 3.14–3.09 (m, 2H), 3.04–2.98 (m, 3H), 2.85 (m, 1H), 1.62 (d, *J*=1.2 Hz, 3H), 1.54 (s, 3H), 1.35 (s, 9H), 1.35 (s, 9H), 1.07 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=176.0, 175.7, 149.9, 147.9, 146.6, 142.2, 140.7, 139.8, 133.9, 125.4, 122.8, 122.8, 122.5, 121.7, 115.7, 97.8, 57.1, 44.7, 44.6, 39.1, 39.1, 39.0, 30.5, 27.3, 27.3, 27.3, 27.1, 25.9, 25.7, 17.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{34}H_{43}BrO_6$ [M+Na$^+$]: 649.2135, found: 649.2123.

*4.3.17. Artochamin I (**3**)*

To a solution of bis-phenol **35** (6.0 mg, 9.56 μmol) in DMF (300 μL) was added K_2CO_3 (6.6 mg, 47.8 μmol) followed by MeI (3.6 μL, 57.4 μmol) and the resulting mixture was stirred at 100 °C for 1 h. Upon cooling the reaction mixture was diluted with EtOAc (2 mL), washed with H_2O (5×1 mL) and brine (1 mL), and finally dried ($MgSO_4$) before removal of the solvent in vacuo. The residue was purified by column chromatography (20% Et_2O in hexanes) to afford the methylated compound **36** (6.0 mg, 96%) as a foam, which was used directly in the following reaction.

To a solution of compound **36** (3.7 mg, 5.64 μmol) in THF (100 μL) at 0 °C was added $LiAlH_4$ (33.6 μL, 33.6 μmol, 1 M solution in THF). The resulting mixture was warmed to room temperature and allowed to stir for 24 h. Excess $LiAlH_4$ was destroyed by the addition of EtOAc and the mixture was acidified to pH 3 with aqueous HCl (1 M). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (30% EtOAc in hexanes) to afford artochamin I (**3**) (2.2 mg, 95%) as a clear oil. R_f=0.17 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 3381br m, 2926s, 2856m, 1701w, 1600s, 1518m, 1492m, 1461s, 1451s, 1436s, 1365m, 1312s, 1282m, 1260m, 1202m, 1119s, 1086s, 1033w, 867w, 806m cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ=7.64 (br s, 2H), 6.79 (d, *J*=8.0 Hz, 1H), 6.76 (d, *J*=2.0 Hz, 1H), 6.64 (dd, *J*=8.0, 2.0 Hz, 1H), 6.47

(s, 1H), 4.92 (m, 1H), 3.95 (dd, *J*=8.0, 6.0 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.03 (dd, *J*=16.0, 3.0 Hz, 1H), 2.94–2.91 (m, 1H), 2.88 (dd, *J*=17.0, 9.5 Hz, 1H), 2.84 (d, *J*=5.5 Hz, 1H), 2.76 (m, 2H), 1.51 (d, *J*=1.5 Hz, 3H), 1.42 (s, 3H), 1.01 (s, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=159.6, 156.4, 150.9, 146.6, 145.2, 135.2, 131.5, 125.6, 125.6, 121.0, 119.0, 117.1, 116.7, 95.9, 59.6, 56.5, 46.6, 46.4, 40.1, 31.7, 28.4, 27.6, 27.2, 26.8, 18.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{26}H_{32}O_4$ [M+H$^+$]: 409.2373, found: 409.2374.

*4.3.18. Benzopyran **37***

To a solution of the bis-protected compound **35** (8.6 mg, 13.7 μmol) in CH_2Cl_2 (350 μL) at −78 °C was added a solution of PhSeCl (3.0 mg, 13.7 μmol) in CH_2Cl_2 (50 μL). After 30 min, the reaction mixture was briefly warmed to room temperature before being diluted with CH_2Cl_2 (2 mL) and washed with H_2O (1 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (20% Et_2O in hexanes) to afford the corresponding selenide (10.2 mg, 95%) as a yellow oil, which was subjected to oxidation without further analysis.

To a solution of the above selenide (10.2 mg, 13.0 μmol) in CH_2Cl_2 (200 μL) at 0 °C was added H_2O_2 (16.0 μL, 30% aq). The resulting biphase was warmed to room temperature and stirred rapidly for 3 h before being diluted with CH_2Cl_2 (2 mL), washed with H_2O (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (20% Et_2O in hexanes) to afford benzopyran **37** (7.3 mg, 89%) as a white foam. R_f=0.46 (silica gel, 20% Et_2O in hexanes); IR ν_{max} (film) 3483br w, 2956m, 2929m, 2860m, 1716m, 1596w, 1505w, 1479w, 1462w, 1393w, 1367w, 1259w, 1226w, 1201w, 1120s, 1029w, 943w, 895w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.10 (m, 2H), 6.98 (m, 1H), 5.92 (d, *J*=10.2 Hz, 1H), 5.61 (s, 1H), 5.36 (d, *J*=10.2 Hz, 1H), 3.98 (t, *J*=6.0 Hz, 1H), 3.12 (dd, *J*=16.5, 2.0 Hz, 1H), 3.02 (d, *J*=6.0 Hz, 1H), 3.00 (dd, *J*=16.5, 9.6 Hz, 1H), 2.85 (m, 1H), 1.38 (s, 3H), 1.36 (s, 9H), 1.35 (s, 9H), 1.35 (s, 3H), 1.09 (s, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=176.1, 175.9, 149.3, 148.3, 144.2, 142.2, 140.7, 139.7, 135.7, 128.3, 125.5, 125.3, 123.0, 122.7, 122.4, 119.5, 110.1, 97.7, 56.7, 45.0, 43.4, 39.2, 39.2, 34.2, 30.4, 30.3, 29.7, 28.1, 27.5, 27.3, 27.3, 27.1, 25.8, 16.2 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{34}H_{41}BrO_6$ [M+H$^+$]: 625.2159, found: 625.2141.

*4.3.19. Methylbenzopyran **38***

To a solution of pyran **37** (5.0 mg, 7.99 μmol) in DMF (150 μL) was added K_2CO_3 (5.5 mg, 40.0 μmol) followed by MeI (3.0 μL, 48.0 μmol), and the resulting mixture was stirred at 100 °C for 1 h. Upon cooling the reaction mixture was diluted with EtOAc (2 mL), washed with H_2O (5×1 mL) and brine (1 mL), and finally dried ($MgSO_4$) before removal of the solvent in vacuo. The residue was purified by column chromatography (10% Et_2O in hexanes) to afford the methylated compound **38** (4.8 mg, 94%) as a foam. R_f=0.36 (silica gel, 20% Et_2O in hexanes); IR ν_{max} (film) 2962m, 2933m, 2870w, 1760s, 1590w, 1505w, 1480w, 1460w, 1417w, 1397w, 1367w, 1258m, 1119s, 1097s, 1029w, 993w, 891w cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.12–708 (m, 2H), 6.99 (d, *J*=1.8 Hz, 1H), 5.93 (d, *J*=10.2 Hz, 1H), 5.45 (d, *J*=10.2 Hz, 1H), 3.96 (dd, *J*=8.4, 5.4 Hz, 1H), 3.87 (s, 3H), 3.17 (dd, *J*=16.8, 1.8 Hz, 1H), 3.07 (dd, *J*=16.8, 9.6 Hz, 1H), 3.00 (d, *J*=5.4 Hz, 1H), 2.85 (m, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.36 (s, 9H), 1.35 (s, 9H), 1.07 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=176.1, 175.9, 153.1, 149.9, 144.1, 142.2, 140.7, 139.7, 135.8, 130.1, 129.8, 125.5, 125.4, 122.9, 122.5, 119.4, 114.2, 103.9, 59.9, 56.7, 44.9, 43.3, 39.2, 39.1, 34.7, 34.2, 30.9, 30.3, 28.1, 27.6, 27.3, 27.3, 27.1, 25.8, 14.1 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{35}H_{43}BrO_6$ [M+H$^+$]: 639.2316, found: 639.2319.

*4.3.20. Artochamin J (**4**)*

To a solution of methylbenzopyran **38** (4.3 mg, 6.72 μmol) in THF (100 μL) at 0 °C was added $LiAlH_4$ (40 μL, 40.2 μmol, 1 M solution in THF). The resulting mixture was warmed to room temperature and allowed to stir for 24 h. Excess $LiAlH_4$ was destroyed by the addition of EtOAc and the mixture was acidified to pH 3 with aqueous HCl (1 M). The layers were separated and the aqueous phase was extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (1 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (40% EtOAc in hexanes) to afford artochamin J (**4**) (2.5 mg, 94%) as a clear oil. R_f=0.32 (silica gel, 40% EtOAc in hexanes); IR ν_{max} (film) 3387s, 2951s, 2926s, 2855m, 1706w, 1605s, 1519m, 1483m, 1461m, 1440m, 1364m, 1317m, 1259m, 1199m, 1124s, 1065w, 1019w, 910w, 857w, 802m cm^{-1}; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ=7.72 (br s, 2H), 6.81 (d, *J*=7.8 Hz, 1H), 6.79 (d, *J*=1.8 Hz, 1H), 6.66 (dd, *J*=7.8, 1.8 Hz, 1H), 6.20 (s, 1H), 6.00 (d, *J*=10.2 Hz, 1H), 5.37 (d, *J*=10.2 Hz, 1H), 3.96 (dd, *J*=7.8, 6.6 Hz, 1H), 3.80 (s, 3H), 3.01 (dd, *J*=16.8, 1.8 Hz, 1H), 2.89–2.76 (m, 2H), 2.75 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.05 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=157.4, 154.7, 146.6, 145.8, 144.4, 133.8, 128.1, 125.3, 120.7, 120.0, 115.9, 115.9, 110.5, 98.6, 76.5, 58.3, 55.6, 45.8, 44.5, 39.4, 30.8, 28.4, 27.8, 27.4, 26.1 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{25}H_{28}O_4$ [M+H$^+$]: 393.2060, found: 393.2062.

*4.3.21. 5-{2-[3,4-Bis-(tert-butyl-dimethyl-silanyloxy)-phenyl]-vinyl}-2-bromo-4,6-bis-(3-methyl-but-2-enyl)-benzene-1,3-diol (**39**)*

Stilbene **6** (10.0 mg, 14.5 μmol) was dissolved in *o*-xylene (1.0 mL) and the resulting solution was subjected to microwave heating at 180 °C for 5 min. The reaction mixture was then directly loaded onto a silica gel column packed with hexanes as the eluant and *o*-xylene was run off. The eluant was switched to 2% EtOAc in hexanes and the Claisen product **39** (9.5 mg, 95%) was obtained as a yellow oil. R_f=0.11 (silica gel, 4% EtOAc in hexanes); IR (film) ν_{max} 3423br m, 2956m, 2929m, 2858m, 1569m, 1507s, 1472w, 1440w, 1299s, 1252s, 1151m, 1123m, 1091m, 981m, 905s, 837s, 805s, 732s cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=6.93–6.90 (m, 2H), 6.82 (d, *J*=16.2 Hz, 1H), 6.80 (d, *J*=7.8 Hz, 1H), 6.36 (d, *J*=16.8 Hz, 1H), 5.54 (s, 2H), 5.18 (m, 2H), 3.42 (d, *J*=6.6 Hz, 4H), 1.70 (s, 6H), 1.68 (s, 6H), 1.00 (s, 9H), 0.99 (s, 9H), 0.22 (s, 6H), 0.21 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=149.1, 146.9, 146.8, 1138.4, 134.7, 132.8, 130.9, 125.5, 123.7, 122.7, 121.0, 119.8, 118.9, 118.8, 98.7, 30.3, 27.4, 25.9, 25.8, 18.5, 18.4, 18.0 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{36}H_{55}BrO_4Si_2$ $[M+H^+]$: 687.2895, found: 687.2896.

*4.3.22. Artochamin F (**1**)*

A solution of Claisen product **39** (10.0 mg, 14.5 µmol) and Bu_3SnH (8.0 µL, 30.0 µmol) in benzene (200 µL) at room temperature was stirred for 30 min. Then a catalytic amount of AIBN was added and the mixture was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to give the de-brominated material (8.0 mg, 88%) as a brown oil. R_f=0.22 (silica gel, 30% EtOAc in hexanes); IR (film) ν_{max} 3427br s, 2929s, 2858s, 1594s, 1508s, 1472m, 1301s, 1253s, 1160m, 1124m, 1085m, 981m, 907s, 839s, 781s cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=6.93–6.91 (m, 2H), 6.86 (d, J=16.2 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 6.33 (d, J=16.8 Hz, 2H), 5.21–5.19 (m, 2H), 5.07 (s, 2H), 3.37 (d, J=6.6 Hz, 4H), 1.73 (s, 12H), 1.54 (s, 18H), 1.00 (s, 6H), 0.99 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=154.7, 146.8, 139.0, 134.5, 133.8, 131.0, 125.5, 124.6, 122.8, 121.0, 119.7, 118.9, 117.7, 102.7, 30.3, 26.9, 25.9, 25.8, 18.5, 18.4, 18.0 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{36}H_{56}O_4Si_2$ $[M+H^+]$: 609.3790, found: 609.3780.

To a solution of bis-silyl ether **39** (8.0 mg, 13.1 µmol) in THF (1.0 mL) at room temperature was added HF·NEt_3 (13 µL, excess) and the reaction mixture was stirred for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL), extracted with EtOAc (3×4 mL), and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo to yield artochamin F (**1**) (4.6 mg, 92%) as a white foam. R_f=0.14 (silica gel, 35% EtOAc in hexanes); IR ν_{max} (film) 3358br s, 2951m, 2925s, 2855m, 1718m, 1602m, 1512w, 1444s, 1260s, 1088s, 802m cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ=7.90 (br s, 1H), 7.88 (br s, 1H), 7.78 (s, 1H), 7.04 (d, J=1.5 Hz, 1H), 6.91 (d, J=16.5 Hz, 1H), 6.84 (dd, J=6.5, 2.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.42 (s, 1H), 6.36 (d, J=16.5 Hz, 1H), 5.18 (br t, J=6.5 Hz, 2H), 3.32 (d, J=7.0 Hz, 4H), 1.64 (br s, 6H), 1.62 (br s, 6H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=154.7, 146.5, 146.2, 140.8, 134.9, 131.6, 130.2, 126.2, 125.5, 120.0, 118.8, 116.6, 114.0, 102.6, 27.2, 26.3, 18.6 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{24}H_{28}O_4$ $[M+H^+]$: 381.2060, found: 381.2043.

*4.3.23. 2-(3,4-Dihydroxy-phenyl)-1,1-dimethyl-3-(3-methyl-but-2-enyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]indene-4,6-diol (**40**)*

Artochamin F (**1**) (5.0 mg, 13.1 µmol) was dissolved in *o*-xylene (0.5 mL) and the resulting solution was subjected to microwave heating at 180 °C for 10 min. The reaction mixture was then purified by preparatory thin-layer chromatography (50% EtOAc in hexanes, few drops AcOH) to yield cycloadduct **40** (4.0 mg, 82%) as a clear oil. R_f=0.11 (silica gel, 55% EtOAc in hexanes+0.5% AcOH); IR ν_{max} (film) 3364br s, 2956m, 2925s, 2856w, 2504br w, 1697s, 1602s, 1516s, 1440s, 1365s, 1255s, 1193m, 1160m, 1109m, 1088s, 971w cm^{-1}, ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ=7.67 (s, 1H), 7.66 (s, 1H), 7.41 (br s, 1H), 6.77 (s, 1H), 6.76 (d, J=8.4 Hz, 1H), 6.59 (dd, J=8.4, 1.5 Hz, 1H), 6.25 (s, 1H), 4.97 (br t, 1H), 3.89 (t, J=6.6 Hz, 1H), 3.01–2.98 (m, 2H), 2.87–2.79 (m, 3H), 2.70 (br t, J=6.6 Hz, 1H), 1.49 (br s, 3H), 1.38 (br s, 3H), 0.99 (br s, 3H), 0.71 (br s, 3H) ppm; ^{13}C NMR (150 MHz, $(CD_3)_2CO$) δ=156.6, 153.5, 151.2, 146.5, 145.1, 135.4, 131.2, 126.0, 123.3, 121.2, 117.1, 116.6, 103.0, 59.6, 46.7, 46.6, 40.0, 29.7, 28.5, 27.6, 27.2, 26.8, 18.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{24}H_{28}O_4$ $[M+H^+]$: 381.2060, found: 381.2051.

*4.3.24. 5-Bromo-2-(3,4-dihydroxy-phenyl)-1,1-dimethyl-3-(3-methyl-but-2-enyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]indene-4,6-diol (**32**)*

To a solution of bis-silyl ether **39** (82.2 mg, 0.12 mmol) in THF (500 µL) at 0 °C was added HF·Py (200 µL, excess) and the reaction mixture was warmed to ambient temperature and stirred for 2 h. The reaction mixture was diluted with Et_2O (20 mL) and then washed successively with saturated aqueous $CuSO_4$ (3×5 mL), saturated aqueous $NaHCO_3$ (2×5 mL), and brine (5 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. The residue was passed through a short plug of silica gel (30% EtOAc in hexanes) to give diol **31** (52 mg, 95%) as a clear oil, which was used directly in the following reaction. R_f=0.20 (silica gel, 30% EtOAc in hexanes); IR ν_{max} (film) 3440br s, 2974m, 2913m, 1595m, 1574m, 1515m, 1436s, 1404w, 1375w, 1348w, 1315w, 1283s, 1254s, 1191m, 1151m, 1090s, 1029w, 957w, 908w, 874w, 814w, 786m, 661w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=6.68 (d, J=8.5 Hz, 1H), 6.56–6.52 (m, 3H), 6.33 (d, J=12.5 Hz, 1H), 5.66 (s, 2H), 5.56 (br s, 1H), 5.47 (br s, 1H), 5.00–4.96 (m, 2H), 3.30 (d, J=7.0 Hz, 4H), 1.68 (s, 6H), 1.60 (d, J=1.0 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=149.5, 143.4, 142.8, 137.8, 133.2, 131.2, 130.1, 125.5, 122.5, 122.1, 118.1, 115.2, 115.0, 98.6, 27.4, 25.7, 17.8 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{24}H_{27}BrO_4$ $[M+H^+]$: 459.1165, found: 459.1166.

To a solution of stilbene **31** (5.9 mg, 12.8 µmol) in $CDCl_3$ (400 µL) was added a solution of DDQ (4.4 mg, 19.2 µmol) in $CDCl_3$ (200 µL) at ambient temperature. After 5 min, the mixture was filtered through cotton wool and the ^{1}H and ^{13}C NMR spectra were recorded. ^{1}H NMR (500 MHz, $CDCl_3$) δ=6.27 (dd, J=12.0, 1.0 Hz, 1H), 6.50 (d, J=12.0 Hz, 1H), 6.42 (dd, J=7.0, 1.5 Hz, 1H), 5.46 (s, 1H), 5.34 (s, 1H), 5.10–5.07 (m, 1H), 3.50–3.46 (m, 1H), 3.44 (dd, J=3.5, 2.0 Hz, 1H), 3.39 (dd, J=16.0, 7.0 Hz, 1H), 3.16 (d, J=6.5 Hz, 1H), 3.12 (dd, J=13.0, 5.0 Hz, 1H), 2.35 (ddd, J=13.0, 5.0, 3.5 Hz, 1H), 2.13 (t, J=13.0 Hz, 1H), 1.79 (s, 3H), 1.71 (d, J=1.0 Hz, 3H), 1.15 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=193.6, 190.0, 149.4, 148.9, 148.1, 144.5, 136.3, 133.6, 128.3, 128.1, 127.2, 121.3, 119.8, 117.3, 100.4, 62.3, 46.7, 44.5, 30.0, 28.4, 27.0, 25.7, 25.4, 18.0 ppm.

The crude reaction mixture from above was concentrated in vacuo, and then re-dissolved in *o*-xylene (2 mL) and heated at 180 °C for 30 min by microwave irradiation. The reaction mixture was concentrated in vacuo and purified by column chromatography (10% Et_2O in CH_2Cl_2) to give cyclobutane

32 (2.4 mg, 40%, two steps), which displayed identical physical properties to those reported above.

*4.3.25. 5-(Benzo[1,3]dioxol-5-ylmethanesulfonyl)-1-phenyl-1H-tetrazole (**56**)*

To a solution of 1-phenyl-1*H*-tetrazole-5-thiol (432 mg, 2.42 mmol) in dry THF (9.0 mL) was added Et_3N (0.42 mL, 3.03 mmol) and the mixture was stirred at room temperature. After 40 min, 5-bromomethyl-benzo[1.3]dioxole **55** (651 mg, 3.03 mmol) was added and the reaction mixture was heated at reflux overnight, and then diluted with water (20 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the crude thioether.

m-CPBA (251 mg, 1.12 mmol, 77% w/w) was added in small portions to a solution of the crude thioether (100 mg, 0.32 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C and the mixture was then stirred at room temperature for 24 h. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ (2×5 mL) and saturated aqueous $NaHCO_3$ (3×2 mL). The organic layer was then dried ($MgSO_4$) and the solvent removed in vacuo to yield **56** (107 mg, 97%) as a white foam. R_f=0.30 (silica gel, 30% EtOAc in hexanes); IR (film) ν_{max} 3072w, 2997w, 2912w, 1765w, 1595w, 1489s, 1445s, 1339s, 1245s, 1216w, 1154s, 1134m, 1101m, 1015m, 1035s, 925s, 812s, 761s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.56 (tt, *J*=7.5, 1.5 Hz, 1H), 7.50 (m, 2H), 7.42 (m, 2H), 6.80 (d, *J*=1.5 Hz, 1H), 6.77 (dd, *J*=8.0, 2.0 Hz, 1H), 6.74 (d, *J*=8.0 Hz, 1H), 5.94 (s, 2H), 4.83 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=152.9, 148.9, 148.1, 132.7, 131.2, 129.3, 125.7, 125.1, 117.6, 111.4, 108.6, 101.5, 62.0 ppm; HRMS (ESI TOF) *m*/*z* for $C_{15}H_{12}N_4O_4S$ [M+H$^+$]: 345.0652, found: 345.0656.

*4.3.26. 5-{2-[4-Bromo-3,5-bis-(1,1-dimethyl-alloxy)-phenyl]-vinyl}-benzo[1,3]dioxole (**57**)*

To a solution of sulfone **56** (87.7 mg, 0.26 mmol) in THF (2.6 mL) at −78 °C was added KHMDS (540 μL, 0.27 mmol, 0.5 M solution in toluene) and the resulting bright yellow solution was stirred for 30 min. A solution of aldehyde **7** (50 mg, 0.14 mmol) in THF (1.4 mL) was then added via cannula and the reaction mixture was slowly warmed to room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and then extracted with Et_2O (3×15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (5−10% Et_2O in hexanes) to give stilbene **57** (57 mg, 85%, *E*/*Z* 2:1) as a white powder. R_f=0.15 (silica, 10% Et_2O in hexanes); IR (film) ν_{max} 2981m, 2931w, 1578m, 1560s, 1503s, 1489s, 1445s, 1413s, 1378m, 1363m, 1331w, 1252s, 1235m, 1196w, 1161w, 1128s, 1069m, 1039s, 1003w, 956m, 930m, 858w, 823w, 798w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.03 (d, *J*=1.5 Hz, 1H), 6.94 (s, 2H), 6.91 (dd, *J*=8.0, 1.5 Hz, 1H), 6.81 (d, *J*=16.0 Hz, 1H), 6.79 (d, *J*=8.0 Hz, 1H), 6.73 (d, *J*=16.0 Hz, 1H), 6.23 (dd, *J*=17.5, 11.0 Hz, 2H), 5.97 (s, 2H), 5.52 (dd, *J*=17.5, 1.0 Hz, 2H), 5.18 (dd, *J*=17.5, 1.0 Hz, 2H), 1.53 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=154.6, 148.2, 147.4, 144.4, 136.0, 131.5, 128.7, 126.6, 121.6, 113.7, 113.6, 112.1, 108.4, 105.5, 101.2, 81.8, 26.8 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{25}H_{27}BrO_4$ [M+H$^+$]: 471.1165, found: 471.1144.

*4.3.27. 5-(2-Benzo[1,3]dioxol-5-yl-vinyl)-2-bromo-4,6-bis-(3-methyl-but-2-enyl)-benzene-1,3-diol (**58**)*

Stilbene **57** (15 mg, 25.3 μmol) was dissolved in *o*-xylene (2 mL) and the resulting solution was subjected to microwave heating at 180 °C for 5 min. The reaction mixture was then directly loaded onto a silica gel column packed with hexanes as the eluant and the *o*-xylene was run off. The eluant was switched to 10−30% Et_2O in hexanes and the Claisen product **58** (10 mg, 65%) was obtained as a white powder. R_f=0.21 (silica, 20% Et_2O in hexanes); IR (film) ν_{max} 3452br m, 2956w, 2920w, 2855w, 1723w, 1568w, 1502m, 1487s, 1444s, 1365w, 1314w, 1253s, 1194m, 1155m, 1086m, 1040m, 975m, 933m, 869w, 801m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.02 (d, *J*=1.5 Hz, 1H), 6.86 (d, *J*=16.5 Hz, 1H), 6.85 (dd, *J*=8.0, 1.5 Hz 1H), 6.80 (d, *J*=8.0 Hz, 1H), 6.41 (d, *J*=16.5 Hz, 1H), 5.98 (s, 2H), 5.54 (s, 2H), 5.17 (m, 2H), 3.41 (d, *J*=7.0 Hz, 4H), 1.71 (d, *J*=1.0 Hz, 6H), 1.69 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=149.1, 148.1, 147.4, 138.2, 134.6, 132.8, 131.7, 124.0, 122.7, 121.3, 118.9, 108.5, 105.4, 101.1, 98.8, 27.4, 25.8, 18.0 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{25}H_{27}BrO_4$ [M−H$^-$]: 469.1009, found: 469.1014.

*4.3.28. 5-(4-Methoxy-phenylmethanesulfonyl)-1-phenyl-1H-tetrazole (**60**)*

To a solution of *p*-methoxybenzyl alcohol (500 mg, 3.62 mmol), Ph_3P (1.04 g, 3.98 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (645 mg, 3.62 mmol) at 0 °C in THF (36 mL) was added DEAD (2.0 mL, 4.34 mmol). The mixture was stirred for 30 min at 0 °C, treated with saturated aqueous $NaHCO_3$ (15 mL), and diluted with Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2×20 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (15% EtOAc in hexanes) to yield the corresponding sulfide (975 mg, 90%) as a yellow oil.

A solution of the sulfide from above (975 mg, 3.27 mmol) in EtOH (33 mL), THF (6.5 mL), and H_2O_2 (12.6 mL) was treated with ammonium molybdate (808 mg, 0.65 mmol) at room temperature. The mixture was stirred overnight and then partitioned between CH_2Cl_2 (15 mL) and saturated aqueous NH_4Cl (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo to yield sulfone **60** (1.09 g, 100%) as a white solid. R_f=0.26 (silica gel, 20% EtOAc in hexanes); IR (film) ν_{max} 2970w, 2913w, 1611m, 1512m, 1493m, 1463w, 1446w, 1352s, 1307m, 1251s, 1180m, 1154s, 1137s, 1025s, 878m, 849m, 838m, 754s, 684s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=7.56 (m, 1H), 7.49 (m, 2H), 7.36 (d, *J*=8.0 Hz, 2H), 7.24 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.87 (s, 2H), 3.80 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=160.8, 152.9, 132.9, 131.3, 129.3, 125.2, 116.3, 114.6, 61.8, 55.4 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{15}H_{14}N_4O_3S$ [M+H$^+$]: 331.0859, found: 331.0859.

*4.3.29. 2-(3-Methyl-but-2-enyl)-benzaldehyde (**61**)*

Aldehyde **61** was prepared according to the literature and displayed identical physical properties to those reported.[44]

*4.3.30. 1-(3-Methyl-but-2-enyl)-2-(4-methoxystyryl)-benzene (**62**)*

To a solution of sulfone **60** (228 mg, 0.69 mmol) in THF (70 mL) at −78 °C was added KHMDS (1.4 mL, 0.69 mmol, 0.5 M solution in toluene) and the resulting solution was stirred for 30 min. A solution of aldehyde **61** (100 mg, 0.57 mmol) in THF (6.0 mL) was then added via cannula and the reaction mixture was slowly warmed to room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and then extracted with Et_2O (3×40 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (2% Et_2O in hexanes) to give stilbene **62** (118 mg, 74%, *E*/*Z* 4:1) as a yellow oil. R_f=0.08 (silica gel, 10% CH_2Cl_2 in hexanes); IR (film) ν_{max} 2911w, 2854w, 2835w, 1605s, 1509s, 1450m, 1440m, 1294m, 1247s, 1173s, 1033s, 960s, 816s, 746s cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.58 (d, *J*=6.6 Hz, 1H), 7.44 (d, *J*=8.4 Hz, 2H), 7.23 (d, *J*=15.6 Hz, 1H), 7.21−7.18 (m, 3H), 6.94 (d, *J*=16.2 Hz, 1H), 6.91 (d, *J*=9.0 Hz, 2H), 5.29−5.26 (t, *J*=7.2 Hz, 1H), 3.84 (s, 3H), 3.46 (d, *J*=7.2 Hz, 2H), 1.77 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=159.2, 139.1, 132.2, 130.6, 129.6, 129.3, 127.7, 127.3, 126.2, 125.5, 124.4, 123.0, 114.1, 55.3, 32.4, 25.7, 18.0 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{20}H_{22}O$ [M+H$^+$]: 278.1706, found: 279.1706.

*4.3.31. (4-Nitro-benzyl)-triphenylphosphonium bromide (**64**)*

Phosphonium bromide **64** was purchased from Aldrich Chemical Co.

*4.3.32. 1-(3-Methyl-but-2-enyl)-2-(4-nitrostyryl)-benzene (**65**)*

To a solution of (4-nitrobenzyl)triphenylphosphonium bromide (**64**) (329 mg, 0.69 mmol) in THF (7.0 mL) at 0 °C was added *n*-BuLi (274 μL, 0.69 mmol, 2.5 M solution in hexanes) dropwise, and the resulting mixture was warmed to room temperature and stirred for 30 min. The bright red solution was re-cooled to 0 °C and a solution of aldehyde **61** (100 mg, 0.57 mmol) in THF (6 mL) was added via cannula, and the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with addition of water (3 mL) and then extracted with Et_2O (3×10 mL). The organic phase was washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (25% benzene in hexanes) to yield stilbene **65** (113 mg, 67%, *E*/*Z* 1:1). R_f=0.24 (silica gel, 30% benzene in hexanes); IR (film) ν_{max} 2968w, 2926w, 2852w, 1593s, 1513s, 1449w, 1338s, 1182w, 1109m, 965w, 856m, 756m cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=8.23 (d, *J*=10.2 Hz, 2H), 7.63−7.60 (m, 3H), 7.55 (d, *J*=19.2 Hz, 1H), 7.30−7.28 (m, 1H), 7.26−7.22 (m, 2H), 7.03 (d, *J*=19.2 Hz, 1H), 5.27−5.24 (t, *J*=9.0 Hz, 1H), 3.49 (d, *J*=8.4 Hz, 2H), 1.78 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=144.2, 140.1, 135.0, 132.6, 131.2, 129.7, 128.8, 127.6, 126.9, 126.5, 125.9, 124.2, 123.4, 122.8, 32.4, 25.7, 18.0 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{19}NO_2$ [M+H$^+$]: 294.1488, found: 294.1480.

*4.3.33. 1-Phenyl-5-phenylmethanesulfonyl-1H-tetrazole (**67**)*

Sulfone **67** was prepared according to the literature and displayed identical physical properties to those reported.[45]

*4.3.34. 1-(3-Methyl-but-2-enyl)-2-styryl-benzene (**68**)*

To a solution of sulfone **67** (310 mg, 1.03 mmol) in THF (103 mL) at −78 °C was added KHMDS (2.2 mL, 1.1 mmol, 0.5 M solution in toluene) and the resulting solution was stirred for 30 min. A solution of aldehyde **61** (100 mg, 0.57 mmol) in THF (6.0 mL) was then added via cannula and the reaction mixture was slowly warmed to room temperature. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL) and then extracted with Et_2O (3×40 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (2% Et_2O in hexanes) to give stilbene **68** (136 mg, 95%, *E*/*Z* 4:1) as a yellow oil. R_f=0.28 (silica gel, 2% Et_2O in hexanes); IR (film) ν_{max} 3025w, 2967w, 2912w, 2854w, 1599m, 1577w, 1494m, 1480w, 1449m, 1375m, 959s, 757s, 689s cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ=7.62−7.61 (m, 1H), 7.51 (d, *J*=7.8 Hz, 2H), 7.40−7.37 (m, 2H), 7.37 (d, *J*=15.6 Hz, 1H), 7.28−7.27 (m, 1H), 7.23−7.21 (m, 3H), 6.99 (d, *J*=16.2 Hz, 1H), 5.28 (t, *J*=7.2 Hz, 1H), 3.48 (d, *J*=7.2 Hz, 2H), 1.77 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ=139.4, 137.7, 136.1, 132.3, 130.0, 129.3, 128.7, 127.7, 127.6, 127.5, 126.6, 126.5, 126.4, 126.3, 125.7, 123.0, 32.4, 25.7, 18.0 ppm; HRMS (ESI TOF) *m*/*z* calcd for $C_{19}H_{20}$ [M+H$^+$]: 248.1638, found: 249.1632.

*4.3.35. [4-[(tert-Butyldimethysilyl)oxy]benzyl]triphenylphosphonium bromide (**70**)*

Phosphonium bromide **70** was prepared according to the literature and displayed identical physical properties to those reported.[46]

*4.3.36. 1-(3-Methyl-but-2-enyl)-2-styryl-benzene (**71**)*

To a solution of phosphonium bromide **70** (388 mg, 0.69 mmol) in THF (10.0 mL) at −78 °C was added *n*-BuLi (275 μL, 0.69 mmol, 2.5 M solution in hexanes) dropwise, and the resulting mixture was stirred for 30 min. To the bright red solution was added a solution of aldehyde **61** (100 mg, 0.57 mmol) in THF (2 mL) via cannula, and the reaction mixture was warmed to room temperature over 30 min. The reaction was quenched with addition of saturated aqueous $NaHCO_3$ (10 mL) and then extracted with Et_2O (3×20 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (5% CH_2Cl_2 in hexanes) to yield first the *cis*-stilbene and then the *trans*-stilbene (206 mg; 92%; *E*/*Z* 1:1). R_f=0.20 (silica gel, 5% CH_2Cl_2 in hexanes); IR (film) ν_{max} 2956w, 2929w, 2857w, 1602m, 1507s, 1471w, 1463w, 1449w, 1390w, 1376w, 1362w, 1254s, 1168m, 1101w, 1048w, 1007w, 961w, 909s, 837s, 821s, 803m, 779s, 749m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.61−7.59 (m, 1H), 7.41 (d, J=8.5 Hz, 2H), 7.26 (d, J=16.0 Hz, 1H), 7.24−7.20 (m, 3H), 6.95 (d, J=16.0 Hz, 1H), 6.86 (d, J=8.5 Hz, 2H), 5.31 (m, 1H), 3.48 (d, J=7.0 Hz, 2H), 1.79 (s, 3H), 1.77 (d, J=1.0 Hz, 3H), 1.03 (s, 9H), 0.25 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=155.4, 139.2, 136.4, 132.2, 131.1, 130.1, 129.7, 129.3, 127.7, 127.3, 126.3, 125.5, 124.5, 123.1, 120.3, 32.4, 25.7, 25.7, 18.2, 18.0, −4.4 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{25}H_{34}OSi$ [M+H$^+$]: 379.2452, found: 379.2458.

To a solution of *trans*-stilbene from above (59 mg, 0.16 mmol) in THF (500 µL) at 0 °C was added HF·Py (300 µL, excess), and the resulting mixture was warmed to room temperature and stirred for an additional 2 h. The reaction mixture was diluted with Et_2O (20 mL) and then washed successively with saturated aqueous $CuSO_4$ (3×3 mL), saturated aqueous $NaHCO_3$ (2×3 mL), and brine (3 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (30% Et_2O in hexanes) to give stilbene **71** (43 mg, 95%) as a white powder. R_f=0.24 (silica gel, 30% Et_2O in hexanes); IR (film) ν_{max} 3362br m, 3025w, 2968w, 2912w, 1607m, 1591m, 1510s, 1481w, 1449m, 1375m, 1238s, 1171s, 1103m, 1047m, 963m, 923w, 856w, 838w, 815m, 777w, 750m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=7.61−7.59 (m, 1H), 7.42 (d, J=8.5 Hz, 2H), 7.25 (d, J=16.0 Hz, 1H), 7.24−7.20 (m, 3H), 6.95 (d, J=16.0 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 5.30 (m, 1H), 5.04 (br s, 1H), 3.50 (d, J=7.0 Hz, 2H), 1.79 (s, 3H), 1.76 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ=155.1, 139.2, 136.3, 132.2, 130.8, 129.5, 129.3, 127.9, 127.4, 126.3, 125.5, 124.5, 123.0, 115.6, 32.3, 25.7, 17.7 ppm; HRMS (ESI TOF) *m/z* calcd for $C_{19}H_{20}O$ [M+H$^+$]: 265.1587, found: 265.1587.

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