Cascade Reactions

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# Cascade Reactions Involving Formal [2+2] Thermal Cycloadditions: Total Synthesis of Artochamins F, H, I, and J**

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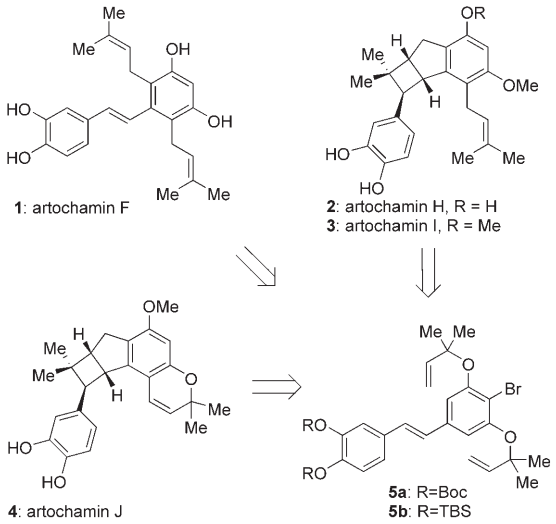
*Dedicated to Masakatsu Shibasaki on the occasion of his 60th birthday*

The *Artocarpus* genus encompasses approximately 60 species of trees that are distributed throughout the tropical regions of Asia. Selected members of this family of plants have been used as traditional folk medicines in Sri Lanka, Taiwan, Thailand, and Indonesia.[1–4] A search for the bioactive ingredients of these plants led to the isolation of several bioactive prenylated flavanoids from the roots of *Artocarpus chama*,[5] and more recently a number of weakly cytotoxic prenylated stilbenes and their derivatives.[6] Artochamins F, H, I, and J (**1**–**4**, Scheme 1) are among the most structurally fascinating members of this group of compounds. Herein we describe the total synthesis of all four natural products through an expedient route that involves a cascade sequence featuring a novel formal [2+2] thermal cycloaddition reaction.




***Scheme 1.*** Structures of artochamins F (**1**) and H–J (**2**–**4**). Boc = *tert*-butylcarbonate, TBS = *tert*-butyldimethylsilyl.

The unique bicyclo[3.2.0]heptane carbon frameworks of artochamins H–J (**2**–**4**) would appear to be biogenetically derived from artochamin F (**1**), or a derivative thereof, through a formal [2+2] cycloaddition reaction between the stilbene alkene and one of the prenyl groups.[6] Furthermore, the racemic nature[7] of **2**–**4** could implicate a non-enzymatic process for this transformation, given the pairwise enantiotopic relationship between both the top and bottom faces of the two prenyl moieties. We were intrigued by the possibility of accomplishing the required cycloaddition under thermal conditions[8] since we speculated that the realization of such a reaction would lead to a concise synthetic approach to the artochamins from stilbenes **5a** and/or **5b** through a cascade sequence that involved, in addition to the key cyclobutane-forming process, two consecutive Claisen rearrangements. Furthermore, protecting-group design on the intermediates was expected to modulate the cascade reaction and allow selective pathways so as to deliver any of the four targeted natural products (**1**–**4**).

The first objective was the stereoselective construction of an appropriately functionalized stilbene derivative from which the formal [2+2] cycloaddition reaction within the projected cascade could be investigated. The Julia–Kocienski olefination[9] was chosen[10] as the key step for this initial construction as shown in Scheme 2.

Thus, the substituted phenyltetrazolesulfones **7a** and **7b** were prepared from 3,4-dihydroxybenzaldehyde (**6**) in a straightforward manner that involved protection (either as the corresponding Boc derivative or silyl ether), reduction with $NaBH_4$, and Mitsunobu coupling with 1-phenyl-1*H*-tetrazole-5-thiol, followed by molybdenum-catalyzed oxidation of the resulting sulfides to the desired sulfones **7a** (73% overall yield from **6**) and **7b** (77% overall yield from **6**). The preparation of the other required coupling partner, aldehyde **10**, began with methyl ester **8**,[11] which was converted into the corresponding bis-reversed prenylated ester **9** through a copper-catalyzed etherification[12] with 1,1-dimethylpropynyl carbonate and Lindlar hydrogenation (72% overall yield). Chemoselective reduction of **9** with $LiAlH_4$, followed by oxidation with DMP led to aldehyde **10** in 92% overall yield for the two steps. Finally, treatment of sulfone **7a** with

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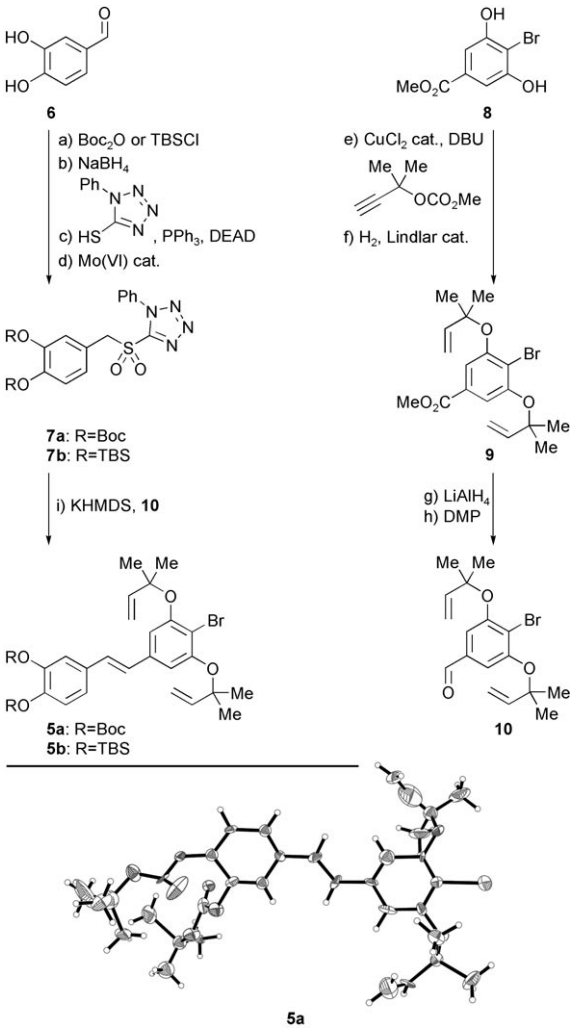
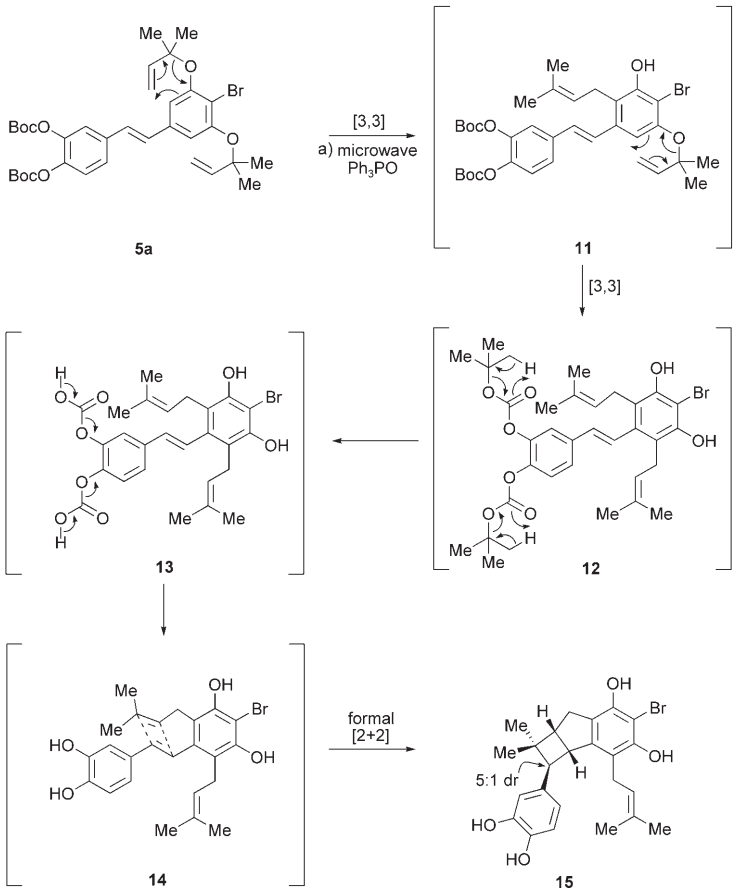



***Scheme 2.*** Construction of the common intermediate stilbenes **5a** and **5b**, and an ORTEP drawing of **5a** with the thermal ellipsoids at the 30% probability level. Reagents and conditions: a) $Boc_2O$ (2.0 equiv), DMAP (0.05 equiv), $iPr_2NEt$ (0.1 equiv), THF, 23 °C, 2 h; or TBSCl (2.0 equiv), imidazole (2.0 equiv), DMF, 23 °C, 2 h; b) $NaBH_4$ (1.0 equiv), EtOH, 23 °C, 30 min; c) 1-phenyl-1*H*-tetrazole-5-thiol (1.0 equiv), DEAD (1.2 equiv), $PPh_3$ (1.1 equiv), THF, 0 °C, 6 h; d) ammonium molybdate tetrahydrate (0.1 equiv), $H_2O_2$, (20 equiv), EtOH, 0→23 °C, 14 h, 73% for **7a**, 77% for **7b** over 4 steps; e) 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; f) $H_2$ (balloon), Lindlar cat. (10% w/w), quinoline (0.5 equiv), EtOAc, 23 °C, 3 h, 72% over 2 steps; g) $LiAlH_4$ (1.2 equiv), THF, 0 °C, 5 mins; h) DMP (1.2 equiv), $CH_2Cl_2$, 23 °C, 30 min, 92% over 2 steps; i) **7a** or **7b** (1.5 equiv), KHMDS (1.55 equiv), THF, −78 °C, 30 min; then **10** (1.0 equiv), THF, −78→23 °C, 3 h, 80% for **5a** (*E* isomer only), 95% for **5b** (*E*/*Z* ca. 2:1). DBU = 1,8-diaxabicyclo[5.4.0]undec-7-ene, DEAD = diethylazodicarboxylate, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane; KHMDS = potassium bis(trimethylsilyl)-amide.

KHMDS, followed by addition of aldehyde **10**, resulted in the formation of the desired (*E*)-stilbene **5a** with complete stereoselectivity (80% yield). The geometry of **5a** could not be discerned from NMR spectroscopic data and was therefore determined by X-ray crystallographic analysis[13] (see ORTEP drawing, Scheme 2). Interestingly, the Julia–Kocienski olefination between the bis(*tert*-butyldimethylsilyl) sulfone **7b** and aldehyde **10** delivered stilbene **5b** with similar efficiency (95% yield), but lower stereoselectivity (*E*/*Z* ca. 2:1).

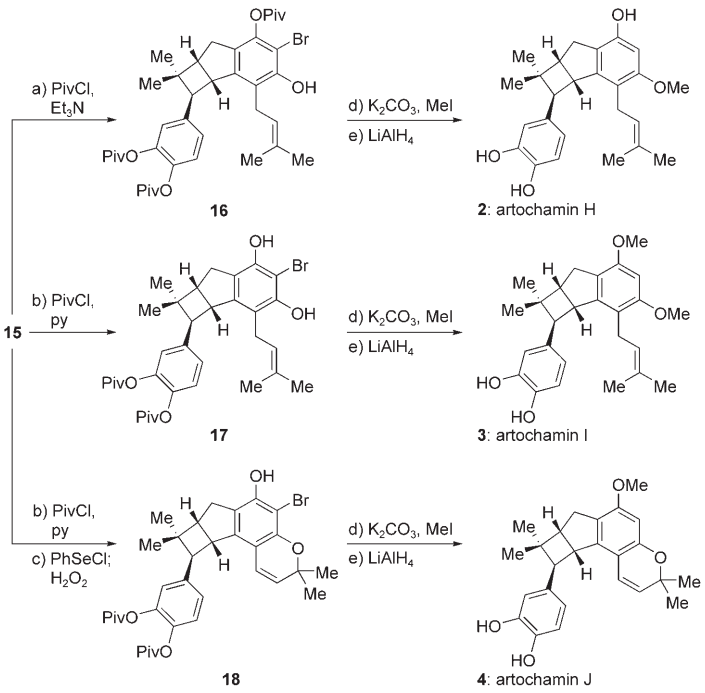
With an appropriately functionalized stilbene substrate in hand, the projected cascade sequence could be investigated. It was discovered that when **5a** was subjected to microwave heating[14] at 180 °C in the presence of catalytic amounts of $Ph_3PO$ in *ortho*-xylene for 20 minutes, the tetracyclic core **15** of the artochamins H, I, and J was formed in 55% overall yield as shown in Scheme 3. A reasonable mechanism for this remarkable transformation that generates two new rings and three stereogenic centers (ca. d.r. 5:1 in favor of **15** with respect to the benzylic stereocenter) is depicted in Scheme 3 (Table 1). Thus, rapid Claisen rearrangements[15] are followed by collapse of the two Boc groups leading to **14**. The stilbene is then converted into **15** through a formal [2+2] cycloaddition reaction. The precise role of $Ph_3PO$ remains to be determined,[16] as do the mechanistic details of the cycloaddition reaction itself (see below).

The completion of the synthesis of artochamins H, I, and J from **15**, which served as a common intermediate for all three

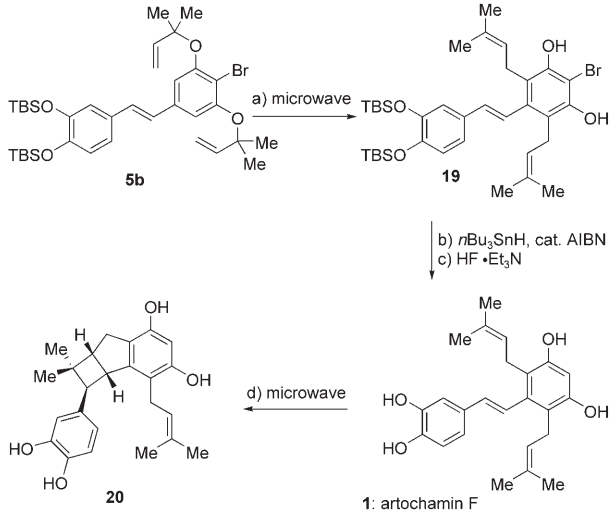



***Scheme 3.*** Construction of the artochamin skeleton **15** through a microwave-promoted cascade sequence. Reagents and conditions: a) *ortho*-xylene, $Ph_3PO$ (5% w/w), microwave, 180 °C, 20 min, 55%.




***Scheme 4.*** Total synthesis of **2**, **3**, and **4** from the common intermediate **15**. Reagents and conditions: a) PivCl (3.0 equiv), $Et_3N$ (6.0 equiv), $CH_2Cl_2$, 23 °C, 30 min, 75%; b) PivCl (2.0 equiv), py (6.0 equiv), $CH_2Cl_2$, 23 °C, 24 h, 64%; c) PhSeCl (1.0 equiv), $CH_2Cl_2$, 23 °C, 1 h; then $H_2O_2$ (20 equiv), $CH_2Cl_2$, 0 °C, 1 h 85% over 2 steps; d) $K_2CO_3$ (5.0 equiv), MeI (6.0 equiv), DMF, 100 °C, 1 h; e) $LiAlH_4$ (6.0 equiv), THF, 23 °C, 14 h, 88% for **2**, 91% for **3**, and 88% for **4** over 2 steps. Piv = trimethylacetyl, py = pyridine.




***Scheme 5.*** Total synthesis of **1**. Reagents and conditions: a) *ortho*-xylene, microwave, 180 °C, 20 min, 100%; b) AIBN (0.1 equiv), $nBu_3SnH$ (2.0 equiv), benzene, reflux, 1 h; c) $HF{\cdot}Et_3N$ (5.0 equiv), THF, 23 °C, 1 h, 92% over 2 steps; d) *ortho*-xylene, microwave, 180 °C, 10 min, 82%. AIBN = azobisisobutylonitrile.

targets, is shown in Scheme 4. Thus, chemoselective protection of **15** with PivCl/$Et_3N$ afforded the triply protected derivative **16** (75% yield),[17] which was methylated ($K_2CO_3$, MeI) and fully deprotected by exposure to $LiAlH_4$. The bromine atom, having served its dual role of ensuring the regiochemistry of the two Claisen rearrangements and directing the final functional group manipulation on the ring on which it was located, was also removed under the reductive conditions of the last step to furnish artochamin H (**2**, 88% yield for the 2 steps). Alternatively, treatment of **15** with PivCl in the presence of pyridine afforded the bis(pivalate) **17** (64% yield), which was dimethylated and its protecting groups removed as described above to afford artochamin I (**3**, 91% overall yield). Finally, selenoetherification[18] of bis(pivalate) **17** (PhSeCl), followed by oxidative removal of the phenylselenyl group from the resulting product, afforded benzopyran[17] derivative **18** (85% overall yield), which was

***Table 1:*** Selected physical properties for **5a**, **15**, **18**, and **20**.

**5a**: $R_f = 0.27$ (silica gel, 15% $Et_2O$ in hexanes; IR $\nu_{max}$ (film) 2981w, 1767s, 1582w, 1506w, 1414w, 1370w, 1253s, 1156s, 1115m, 1072w $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta = 7.37$ (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 ppm (s, 12H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta = 150.8$, 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.

**15**: $R_f = 0.13$ (silica gel, 5% MeOH in $CH_2Cl_2$); IR $\nu_{max}$ (film) 3475br. s, 2956m, 2928m, 2855m, 1719w, 1600m, 1517m, 1441s, 1367m, 1285s, 1249s, 1188m, 1158m, 1105m, 1093m, 966w, 804w, 786w, 766w, 741w $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 6.82$ (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), 5.15 (br. s, 1H), 5.00 (m, 1H), 3.95 (apt t, $J = 6.0$ Hz, 1H), 3.13 (dd, $J = 16.5$, 1.5 Hz, 1H), 3.09 (dd, $J = 15.5$, 6.0 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 (s, 3H), 1.54 (s, 3H), 1.05 (s, 3H), 0.76 ppm (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta = 149.8$, 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.

**18**: $R_f = 0.46$ (silica gel, 20% $Et_2O$ in hexanes); IR $\nu_{max}$ (film) 3483br. w, 2956m, 2929m, 2860m, 1716m, 1596w, 1505w, 1479w, 1462w, 1393w, 1367w, 1259w, 1226w, 1201w, 1120s, 1029w, 943w, 895w $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta = 7.10$ (m, 2H), 6.98 (m, 1H), 5.9 (d, $J = 10.2$ Hz, 1H), 5.61 (s, 1H), 5.36 (d, $J = 10.2$ Hz, 1H), 3.98 (apt 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 ppm (s, 3H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta = 176.1$, 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.

**20**: $R_f = 0.26$ (silica gel, 50% EtOAc in hexanes); IR $\nu_{max}$ (film) 3364br. m, 2956m, 2925m, 2856m, 2504br. w, 1697m, 1602m, 1516m, 1440m, 1365m, 1255m, 1193m, 1160m, 1109m, 1088s, 971m, 870m, 828m, 806m, 782m $cm^{-1}$; $^1H$ NMR (600 MHz, [$D_6$]acetone): $\delta = 6.77$ (d, $J = 7.8$ Hz, 1H), 6.76 (d, $J = 1.8$ Hz, 1H), 6.60 (dd, $J = 7.8$, 1.8 Hz, 1H), 6.25 (s, 1H), 4.97 (m, 1H), 3.90 (apt t, $J = 6.0$ Hz, 1H), 3.03–2.98 (m, 2H), 2.88–2.84 (m, 1H), 2.84 (dd, $J = 16.0$, 9.0 Hz, 1H), 2.80 (d, $J = 6.0$ Hz, 1H), 2.72–2.68 (m, 1H), 1.49 (s, 3H), 1.38 (s, 3H), 1.00 (s, 3H), 0.71 ppm (s, 3H); $^{13}C$ NMR (150 MHz, [$D_6$]acetone) $\delta = 156.6$, 153.5, 151.2, 146.5, 145.1, 135.4, 131.2, 127.0, 126.0, 123.4, 121.2, 117.1, 116.6, 103.0, 59.6, 46.8, 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.

methylated and deprotected as described above to furnish artochamin J (**4**, 88% overall yield).

The dependence of the thermal [2+2] cycloaddition reaction on the hydroxy groups was then examined. To this end, the bis(TBS) stilbene derivative **5b** (Scheme 1) was subjected to the same microwave conditions as those used for **5a**, both in the presence and absence of $Ph_3PO$. As shown in Scheme 5, here the cascade stopped prior to the [2+2] cycloaddition reaction and delivered instead the stilbene derivative **19** in quantitative yield. The absence of any detectable amounts of the corresponding cyclobutane derivative in this reaction provided proof that the thermal formal [2+2] cycloaddition reaction required the presence of the unprotected hydroxy groups on its aromatic nucleus. Debromination ($n$Bu$_3$SnH, AIBN) followed by desilylation (HF·Et$_3$N) of **19** gave artochamin F (**1**, 92% overall yield). The spectroscopic data of synthetic **1**, as well as those of synthetic **2**, **3**, and **4**, matched those reported for the natural products.[19] Subjection of synthetic artochamin F (**1**) to the microwave heating conditions in the absence of $Ph_3PO$ provided the expected tetracyclic skeleton **20** corresponding to artochamins H, I, and J in 82% yield, thereby demonstrating that neither the bromine atom nor $Ph_3PO$ are required for the thermal formal [2+2] cycloaddition reaction in this instance.

Upon consideration of these experimental results and the various mechanistic possibilities, we propose that artochamins H–J (**2**–**4**) most likely originate in nature from artochamin F (**1**), or a derivative thereof, through a stepwise ionic mechanism following an initial oxidation of the catechol moiety (**21**→**22**→**23**→**24**→**25**) as shown in Scheme 6.[20] The intervention of this redox/ionic mechanism in the microwave-promoted cascade sequence of Scheme 3 and the conversion of artochamin F (**1**) into **20** (Scheme 5) is also likely. [21]

The described total syntheses of artochamins F, H, I, and J (**1**–**4**) demonstrate the power of cascade reactions in total synthesis[20] and reveal the feasibility of the formal cycloaddition reaction between an electron-rich stilbene and a prenyl group. This latter process warrants further investigation with regard to its mechanism and scope because of its novelty and potential in chemical synthesis.

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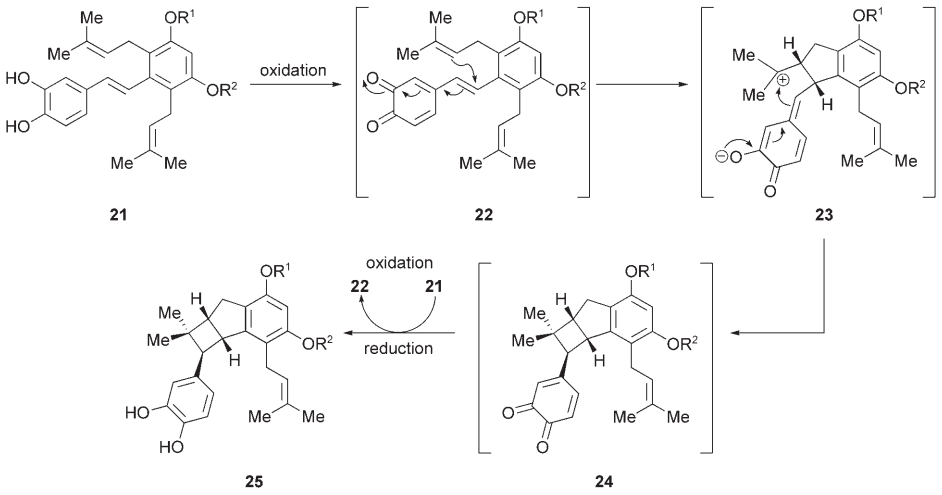


***Scheme 6.*** Postulated mechanistic pathway for the generation of the tetracyclic artochamins from stilbene precursors.

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[10] This choice was made after a Wittig reaction produced a mixture of stilbenes (*E*/*Z* ca. 1:1). To the best of our knowledge, this is the first application of the Julia–Kocienski reaction to stilbene synthesis, and it is recommended by virtue of its efficiency and apparently higher selectivity. For an alternative approach to stilbenes, see: J. E. Robinson, R. J. K. Taylor, *Chem. Commun.* **2007**, 1617–1619.

  

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[13] CCDC-648446 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[14] A Discovery System model number 908005 was used.
[15] TLC analysis indicated that the Claisen rearrangements proceed faster than cleavage of the Boc group or the formal cycloaddition. Given the fact that hydroxy groups must be liberated prior to formation of the cyclobutane, the sequence shown in Scheme 3 is proposed.
[16] The effect of $Ph_3PO$ was recognized when stilbene **5a** derived from the Julia–Kocienski olefination failed to perform well in this process, whilst the same substrate **5a** derived from a Wittig reaction (and therefore assumed to contain trace amounts of $Ph_3PO$) went through the cascade sequence smoothly; further investigations into the precise role of the $Ph_3PO$ are currently underway and full details will be reported in due course.
[17] The regiochemistry of this pivalate reaction was unambiguously proven by a ROESY NMR experiment on synthetic artochamin H (**2**) which exhibited cross signals between the O$CH_3$ and the prenyl C$H_2$ and vinyl C*H* protons.
[18] a) K. C. Nicolaou, J. A. Pfefferkorn, G.-Q. Cao, *Angew. Chem.* **2000**, *112*, 750 – 755; *Angew. Chem. Int. Ed.* **2000**, *39*, 734 – 739; b) K. C. Nicolaou, G.-Q. Cao, J. A. Pfefferkorn, *Angew. Chem.* **2000**, *112*, 755 – 759; *Angew. Chem. Int. Ed.* **2000**, *39*, 739 – 743; c) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939 – 9953.
[19] We are grateful to Dr. Ai-Jun Hou for kindly providing the $^1H$ and $^{13}C$ NMR spectra of natural artochamins F, H, I, and J for comparison purposes.
[20] We consider the stepwise mechanism shown in Scheme 6 to be a more plausible alternative to that originally proposed, see Ref. [6].
[21] We must also consider two further mechanistic alternatives for the microwave-promoted reactions. The first, and least probable, involves a [$\pi$2s + $\pi$2a] cycloaddition. The second involves a stepwise diradical mechanism in which formation of the five-membered ring precedes diradical recombination, see Ref. [8a]. Preliminary experiments with (*E*)- and (*Z*)-**5a** indicate that the formal cycloaddition reaction is not stereospecific with respect to the alkene geometry. On the basis of this observation a stepwise radical mechanism, in which bond rotation occurs to some extent before recombination of the diradical, or the redox mechanism shown in Scheme 6 are currently favored. These possibilities are under investigation and full details will be disclosed in due course.
[22] For selected reviews on cascade reactions, see: a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292 – 7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 – 7186; b) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, *5*, 551 – 564; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115 – 136; d) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137 – 170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131 – 163; e) H. Pellissier, *Tetrahedron* **2006**, *62*, 1619 – 1665; f) H. Pellissier, *Tetrahedron* **2006**, *62*, 2142 – 2173; g) R. A. Bunce, *Tetrahedron* **1995**, *51*, 13103 – 13159.

  