Unified synthesis of caged *Garcinia* natural products based on a site-selective Claisen/Diels–Alder/ Claisen rearrangement

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A unified synthetic strategy toward caged *Garcinia* natural products has been designed and implemented. Central to the strategy is a tandem Claisen/Diels–Alder/Claisen rearrangement of a suitably substituted xanthone precursor to form forbesione (1a). Serving as a template, forbesione is then used to deliver representative members of this family, including desoxygaudichaudione A (4), desoxymorellin (5), and gambogin (10). Studies on the timing of this reaction cascade suggest that the C-ring Claisen/Diels–Alder rearrangement proceeds initially and is followed by the A-ring Claisen reaction. The electronic and steric effects that govern the outcome of this cascade are presented.

The tropical trees and shrubs of the genus *Garcinia* (Guttiferae) are widely known for their pigments and use in folk medicines (1, 2). Phytochemically, they are recognized as a rich source of xanthone and xanthonoid natural products with high pharmaceutical potential (3). For example, gamboge, the commercially available exudate of *Garcinia hanburyii*, has been used in traditional Asian medicine for the treatment of indigestion, inflammation, and ulcers (4). Efforts to identify the bioactive components of these extracts have yielded an ever growing family of natural products, the chemical structures of which feature a unique 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one scaffold built into a common xanthone backbone (5). This motif, present in forbesione (1a) (6) (Fig. 1), is further customized by substitutions on the aromatic residue and peripheral oxidations to produce a variety of structural families such as the morellins (5–8) (7, 8), the gambogins (2, 9, 10) (9, 10), and the gaudichaudiones (3, 4) (11, 12).

Aside from their striking chemical architecture, these natural products exhibit interesting biological activity, as exemplified by recent reports indicating that gambogic acid (9) and gaudichaudione A (3) induce apoptosis in certain cancer cells by a novel mechanism of caspase activation (13, 14). Moreover, structure–activity relationship data suggest that the C9–C10 double bond of 9 (gambogic acid numbering) is essential to its biological profile, corroborating previous reports that the caged motif of these natural products is crucial to their biology (11). In fact, whereas gambogic acid (9) tolerates many changes to its hydroxyl and carboxyl functionalities without significant loss to its biological activity, reduction of the C9–C10 double bond with L-Selectride (lithium tri-*sec*-butylborohydride) breaks down the pharmacophore entirely (13).

The caged scaffold has been suggested to arise in nature by means of a tandem Claisen/Diels–Alder rearrangement. This scenario, highlighted in Fig. 2, was initially proposed and experimentally tested by Quillinan and Scheinmann in 1971 (15). Using the natural product mesuaxanthone B (11) (Fig. 2) as a starting material, they successfully prepared and tested their hypothesis on 5,6-bis(allyloxy)-1-hydroxy-9*H*-xanthen-9-one (12). Despite the limited details they provided, they showed that heating 12 in boiling decalin induced the Claisen and subsequently, the Diels–Alder rearrangement, to create the elusive caged structure. Although the site selectivity of the
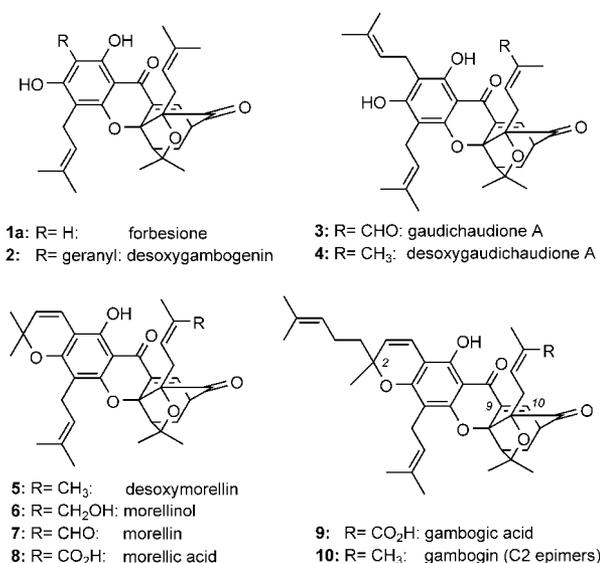
Fig. 1. Representative structures of caged *Garcinia* natural products.

1a: R= H: forbesione
2: R= geranyl: desoxygambogenin

3: R= CHO: gaudichaudione A
4: R= CH$_3$: desoxygaudichaudione A

5: R= CH$_3$: desoxymorellin
6: R= CH$_2$OH: morellinol
7: R= CHO: morellin
8: R= CO$_2$H: morellic acid

9: R= CO$_2$H: gambogic acid
10: R= CH$_3$: gambogin (C2 epimers)

opening Claisen reaction was not addressed, there is a possibility of concomitant allylation at both the C5 and C6 centers, giving intermediates 13 and 15, respectively. These products could then produce an isomeric mixture of 14 and 16, representing the regular caged scaffold and its constitutional isomer, the so-called neo scaffold, respectively. Nicolaou and Li (16) reported similar observations during their application of the Claisen/Diels–Alder reaction cascade to a biomimetic synthesis of 1-*O*-methylforbesione.

Inspired by the unusual 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one scaffold and the biosynthetic issues mentioned above, we sought to design a general synthetic approach to the caged *Garcinia* natural products that would allow us to tap into their full biological potential (17). Herein we present a biomimetic synthesis of forbesione (1a) by using a site-selective Claisen/Diels–Alder/Claisen reaction cascade (18). Using forbesione as a base structure, we also report a unified synthetic approach to several other members of this family, including deoxygaudichaudione A (4), desoxymorellin (5), and gambogin (10). In addition, we examine the timing of the Claisen/Diels–Alder/Claisen and issues governing the site selectivity of this tandem rearrangement. Finally, we discuss applications of these rearrangements as they relate to the biosynthesis of related caged natural products.
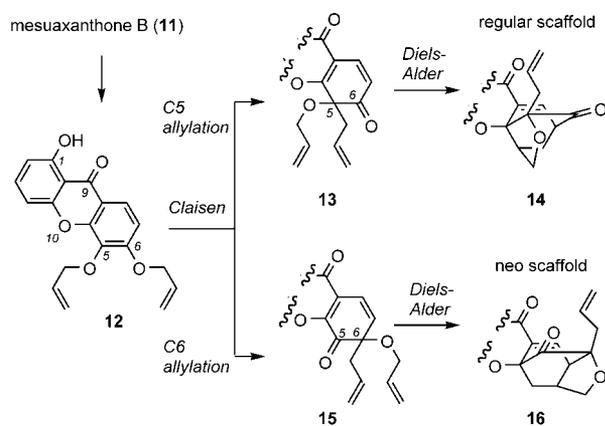
Fig. 2. Structural motifs arising from the Claisen/Diels–Alder reaction on **12**.

Materials and Methods

General. Phloroglucinol (**19**) and 2,3,4-trihydroxybenzoic acid (**20**) were commercially available and used without any additional purification. Compounds **1a**, **1b**, **1c**, **17a**, **17b**, **17c**, **22a**, **23c**, and **5** were synthesized as described previously (18). Full experimental details and analytical and spectroscopic information for all synthetic compounds are provided in supporting information, which is published on the PNAS web site. Tetrahydrofuran, diethyl ether (Et$_2$O), dichloromethane, toluene, and benzene were purified by passage through a bed of activated alumina. Pyridine, triethylamine, and boron trifluoride etherate (BF$_3$·Et$_2$O) were distilled from calcium hydride before use. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure [20 mmHg (1 mmHg = 133 Pa)] and stored over 4-Å molecular sieves until needed. Yields refer to chromatographically and spectroscopically (^{1}H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by TLC carried out on 0.25-mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of 10% ethanolic phosphomolybdic acid or p-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative TLC separations were carried out on 0.25- or 0.50-mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300- or 400-MHz and/or Unity 500-MHz instruments and calibrated by using the residual undeuterated solvent as an internal reference. IR spectra were recorded on a Nicolet 320 Avatar Fourier transform IR spectrometer and values are reported in cm^{-1} units. High-resolution mass spectra were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZABZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Synthesis of Desoxygaudichaudione A (4). A solution of **40** (13.4 mg, 25.2 μmol) in DMF (1.00 ml) was heated at 125°C and the reaction was continuously monitored by TLC (50% Et$_2$O/hexane). After 2 h, the reaction mixture was diluted with toluene and concentrated several times at 60°C under reduced pressure to remove DMF by azeotropic distillation. The crude material was then purified by preparative TLC (50% Et$_2$O/hexane) to yield desoxygaudichaudione A (**4**) (10.5 mg, 78%). **4**: yellow foam; R_f = 0.41 (50% Et$_2$O/hexane); IR (film) ν_{max} 3,416, 2,968, 2,923, 2,854, 1,738, 1,634, 1,601, 1,441, 1,403, 1,380, 1,334, 1,276, 1,220, 1,181, 1,135, 1,099, 1,065, 1,046, 985, 960, 824 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.92 (s, 1H), 7.44 (d, J = 6.8 Hz, 1H), 6.46 (br s, 1H), 5.23–5.20 (m, 2H), 4.45–4.41 (m, 1H), 3.50 (dd,

J = 6.4, 5.2 Hz, 1H), 3.42–3.36 (m, 4H), 2.57–2.55 (m, 2H), 2.47 (d, J = 9.2 Hz, 1H), 2.34 (dd, J = 13.2, 4.8 Hz, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H), 1.38 (s, 3H), 1.35 (dd, J = 12.4, 6.8 Hz, 1H), 1.29 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.3, 179.4, 162.7, 160.0, 156.0, 135.1, 134.8, 134.3, 133.7, 133.6, 121.6, 121.4, 117.7, 107.2, 106.0, 100.7, 90.2, 84.5, 83.1, 49.1, 47.0, 30.2, 29.2, 29.0, 26.0, 25.9, 25.7, 25.6, 22.3, 21.4, 18.2, 18.1, 16.9; high-resolution MS: calculated for C$_{33}$H$_{41}$O$_6$ (M + H$^+$) 533.2898, found 533.2910.

Synthesis of Gambogin (10). To a sealed tube containing forbesione (**1a**) (33.7 mg, 72.4 μmol) in MeOH (2.50 ml) was added freshly prepared citral (**24**) (33.1 mg, 0.22 mmol), CaCl$_2$·H$_2$O (21.3 mg, 0.14 mmol), and triethylamine (33.3 μl, 0.22 mmol). The reaction mixture was then heated for 3 h. After cooling to 25°C, the reaction mixture was poured into a separatory funnel and partitioned between Et$_2$O and brine. The ethereal extract was dried over MgSO$_4$, filtered, and concentrated. The crude material was then column chromatographed (15% Et$_2$O/hexane) to yield gambogin (**10**) (27.5 mg, 75%). **10**: yellow foam; R_f = 0.40 (30% Et$_2$O/hexane); IR (film) ν_{max} 2,969, 2,925, 1,738, 1,634, 1,595, 1,438, 1,401, 1,380, 1,331, 1,224, 1,174, 1,139, 1,086, 1,048, 984, 960, 871, 840, 758 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.89 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 10.4 Hz, 1H), 5.464/5.456 (d, J = 9.6/10.4 Hz, 1H), 5.24–5.19 (m, 1H), 5.08 (m, 1H), 4.45 (m, 1H), 3.49 (dd, J = 6.4, 4.4 Hz, 1H), 3.38–3.26 (m, 2H), 2.58 (d, J = 7.2 Hz, 2H), 2.49 (d, J = 9.2 Hz, 1H), 2.35 (dd, J = 13.2, 4.4 Hz, 1H), 2.12–2.06 (m, 2H), 1.84–1.64 (m, 2H), 1.77 (s, 3H), 1.72 (s, 3H), 1.68 (s, 6H), 1.58 (s, 3H), 1.422/1.418 (s, 3H), 1.36 (dd, 13.2, 9.6 Hz, 1H), 1.39 (s, 3H), 1.30 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.20/203.17, 179.2, 160.7/160.6, 157.6, 157.2, 134.81/134.77, 133.6, 133.53/133.51, 131.8/131.7, 131.50/131.46, 124.62/124.56, 123.7/123.6, 122.1/ 122.0, 117.7, 115.9/115.8, 107.8/107.7, 102.5, 100.4, 90.4, 84.61/ 84.58, 83.2, 81.1/81.0, 49.2, 47.0, 42.0/41.9, 30.23/30.20, 29.2, 28.9, 27.5/27.4, 25.82, 25.76, 25.7, 25.6, 22.9/22.8, 21.8, 18.3, 17.7, 16.9/16.8; high-resolution MS: calculated for C$_{38}$H$_{47}$O$_6$ (M + H$^+$) 599.3367, found 599.3375.

Spectroscopic Study of the Claisen/Diels–Alder/Claisen Reaction. A solution of **17b** (10 mg, 19.7 μmol) in deuterated DMF was heated inside an NMR spectrometer along a temperature gradient from 80°C to 120°C in intervals of 5°C. At each temperature, the reaction was allowed to proceed for 5 min, after which a ^{1}H NMR spectrum of the reaction was taken. After reaching 120°C, the temperature was kept constant until **17b** was completely consumed.

Results and Discussion

Retrosynthetic Analysis of 1a, 4, 5, and 10. Forbesione (**1a**), the simplest of the caged *Garcinia* natural products, is unique in that it contains no substituent at the C2 center of the A ring. As such, it was envisioned to be a template upon which its congeners could be built, a node in a branching synthetic scheme to an array of natural products, such as **4**, **5**, and **10** (Fig. 3). On the basis of the biosynthetic hypothesis of Quillinan and Scheinmann (15), compound **1a** could arise from tris(dimethylallyloxy) precursor **17a**, the xanthone motif of which could be traced to 1,3,5,6-tetrahydroxyxanthone **18**. It is of interest to mention that **18** is also a natural product found in plants of the genus *Hypericum* (Guttiferae) (19, 20). Further disconnection across the central ring of xanthone **18** unveils phloroglucinol (**19**) and 2,3,4-trihydroxybenzoic acid as suitable starting materials. Implementation of this strategy is presented in Schemes 2 and 3.

Synthesis of 1a, 4, 5, and 10. Putting our plan into practice, we commenced our study with a ZnCl$_2$-mediated condensation of **19** and **20** in POCl$_3$ to produce xanthone **18** in 46% yield (Scheme

Fig. 3. Retrosynthetic analysis of **1a**, **4**, **5**, and **10**.
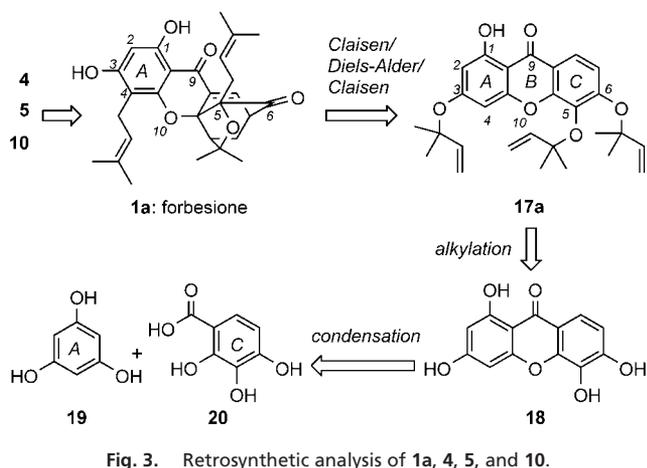
1) (**21**). Several conditions were tested for the conversion of **18** to the tris(dimethylallyloxy)xanthone **17a** (**22**). The most efficient proved to be a two-step procedure that involved propargylation of the more reactive C3, C5, and C6 phenols with 2-chloro-2-methylbutyne (**21**) in the presence of KI and K_2CO_3 under CuI catalysis (25% yield) (**23**), followed by Lindlar reduction of the pendant alkynes (75% yield) (**24**). Drawing on previous experience with related structures (**25**, **26**), we heated **17a** in DMF at 120°C and obtained a mixture of forbesione (**1a**) (49% yield) and isoforbesione (**22a**) (35% yield) (**18**).

Although these results demonstrated the excellent site selectivity of the C-ring Claisen/Diels–Alder rearrangement for the formation of the desired caged structure, the concomitant formation of isomers **1a** and **22a** decreased the efficiency of the overall process. However, converting the C1 hydroxyl group of **17a** to its corresponding acetate **17b** circumvented this issue. Heating **17b** in DMF gave rise to 1-O-acetylforbesione (**1b**) exclusively and, after deprotection, afforded forbesione (**1a**) in 71% combined yield. Intrigued by the effect of the acetyl group

Scheme 1. Reagents and conditions: reaction a, 1.0 eq of **19**, 1.0 eq of **20**, 6.5 eq of $ZnCl_2$, $POCl_3$, 65°C, 3 h, 46% yield; reaction b, 3.3 eq of K_2CO_3, 5.1 eq of **21**, 3.3 eq of KI, 10 mol % CuI, Me_2CO, 45°C, 6 h, 25% yield; reaction c, 10% $Pd/BaSO_4$, quinoline, EtOAc, 25°C, 6 h, 75% yield; reaction d, 25 eq of Ac_2O, 25 eq of pyridine, 10 mol % N,N-dimethylaminopyridine, CH_2Cl_2, 35°C, 24 h, 85% yield; reaction e, 5.0 eq of Cs_2CO_3, 5.0 eq of MeI, DMF, 25°C, 15 min, 61% yield; reaction f, DMF, 120°C, 1 h, 49% yield of **1a**, 35% yield of **22a**;, 79% of **1b**; 51% of **1c**, 24% of **23c**; and reaction g, 0.5 M K_2CO_3 (aq), MeOH, 25°C, 6 h, 91% yield. ND, not detected.

Scheme 2. Reagents and conditions: reaction a, 3.0 eq of K_2CO_3, 20 eq of **21**, 1.5 eq of KI, 10 mol % CuI, Me_2CO, 55°C, 4 h, 67% yield; reaction b, 10% $Pd/BaSO_4$, quinoline, EtOAc, 25°C, 15 min, 66% yield; reaction c, DMF, 120°C, 2 h, 78% yield; reaction d, DMF, 120°C, 4 h, 91% yield; and reaction e, 3.0 eq of triethylamine, 3.0 eq of **24**, 2.0 eq of $CaCl_2 \cdot H_2O$, MeOH (sealed tube) 3 h, 75% yield.

of **1b** on the site selectivity of the A-ring Claisen rearrangement, we repeated these studies using 1-O-methyl ether **17c** as the starting material. In this case we were able to isolate 1-O-methylforbesione (**1c**) together with 1-O-methylneoforbesione (**23c**) in 51% and 24% yield, respectively. The complete experimental procedures and spectroscopic data for all synthesized compounds are included in supporting information.

With forbesione (**1a**) in hand, attention was turned toward the development of conditions for the functionalization of the C2 center en route to other members of this family. We found that propargylation of the C3 phenol of **1a** by using **21** under the previously explored conditions, followed by Lindlar reduction and Claisen rearrangement of resulting alkene, produced desoxygaudichaudione (**4**) in 34% overall yield (Scheme 2). Along these lines, propargylation of **1a**, followed by a Claisen cyclization of the ensuing alkyne, afforded desoxymorellin (**5**) in 61% overall yield. In a similar manner, condensation of **1a** with citral (**24**) by using triethylamine and $CaCl_2 \cdot H_2O$ in MeOH, afforded gambogin (**10**) in a 75% overall yield.

Timing of the Claisen/Diels–Alder/Claisen Reaction Cascade. Having demonstrated the applicability of Claisen/Diels–Alder/Claisen cascade to a unified synthesis of the caged *Garcinia* natural products, we sought to examine the origins of the observed site selectivity. For this evaluation to be accurate, we needed to know whether the C-ring Claisen/Diels–Alder cascade preceded the A-ring Claisen rearrangement. Although we were unable to isolate the putative intermediate **25**, in which only the Claisen/Diels–Alder cascade has occurred, we have obtained spectroscopic evidence suggesting its short-lived existence. Our results are highlighted in Scheme 3. Gradual heating of **17b** produced a new doublet at 7.31 ppm ($J = 6.7$ Hz) that is indicative of the C8 vinylic proton of the 4-oxatricyclo[4.3.1.0^{3,7}]dec-8-en-2-one scaffold and specifically, of intermediate **25b**. This signal appeared only transiently and gradually disappeared with concomitant appearance of a new doublet at 7.34 ppm ($J = 7.0$ Hz), which corresponds to the C8 vinylic proton of 1-O-acetylforbesione (**1b**). Other, less conspicuous, regions of the ^{1}H NMR show the same trend and lead to the same conclusion: the C-ring Claisen/Diels–Alder rearrangement occurs first and is followed
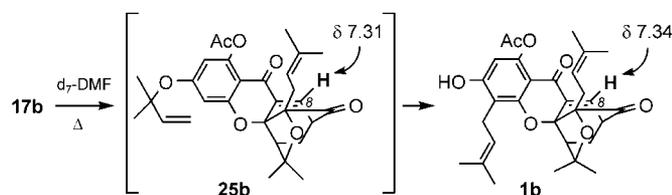
Scheme 3. Timing of the Claisen/Diels–Alder/Claisen rearrangement.

by the A-ring Claisen rearrangement, in this case, giving 1-*O*-acetylforbesione (**1b**). The spectroscopic data of this study are included in supporting information.

Selectivity of the C-Ring Claisen/Diels–Alder Rearrangement. The surprising results obtained during the cyclization of acyclic precursors **17a**, **17b**, and **17c** (see Scheme 1) triggered several questions regarding the selectivity of the Claisen/Diels–Alder rearrangement. Notably, why do adducts **17a** and **17b** form, upon heating, exclusively the forbesione caged motif (regular caged scaffold), whereas methyl ether **17c** produces both the regular caged scaffold and the isomeric the neo caged motif? Why does derivatization of the remote C1 hydroxyl group affect the selectivity of this cascade? Also why does the initial *ortho* Claisen rearrangement take place exclusively across the C5–C6 bond?

In principle, both the C5 and C6 allyl ethers can undergo the initial [3,3]-sigmatropic rearrangement to produce a set of 4 possible Claisen intermediates, represented by structures **26–29** (Scheme 4). The observed selectivity can be rationalized by the electronic effects of both the C9 carbonyl group and the xanthone oxygen (O10). Being *para* to the C6 allyloxy unit, the electronically deficient C9 carbonyl carbon can polarize the O–C18 bond and facilitate its rupture, leading to intermediate **26** (Scheme 4). This argument implies the development of partial charges during the transition state of the Claisen rearrangement. Such a polar transition state has been supported by both computational studies (27, 28) and kinetic isotope effects, showing that the O–C$^\alpha$ bond is more broken (50–60%) than the C–C$^\gamma$ bond is formed (10–20%) (29). Polar solvents offset the development of such charges (30, 31), which are further stabilized by the presence of the geminal dimethyl unit at the C18 carbon center.

The effect of the C9 carbonyl group during the formation of the caged motif becomes evident when it is absent. For example, in related studies directed toward the synthesis of lateriflorone, the Nicolaou group reported a complete loss of site selectivity during the key Claisen/Diels–Alder rearrangement of a substrate that did not have the C9 carbonyl group (32), whereas a similar substrate containing the C9 carbonyl functionality underwent a site-selective rearrangement (33).

Equally important to the influence of the C9 carbonyl group on the Claisen/Diels–Alder's selectivity is the stability conferred to the C6 carbonyl group of intermediate **26** by the xanthone oxygen (O10). Stabilization of the C5 carbonyl functionality of intermediate **27** cannot be achieved in the same way. In a similar manner, stabilization of the C9 carbonyl group by the O10 xanthone oxygen may explain why we do not observe formation of Claisen adducts **28** and **29**. This stabilization by resonance is possible in intermediates **26** and **27** but is interrupted in structures **28** and **29**. This argument could explain why the C-ring Claisen rearrangement occurs exclusively across the C5–C6 bond (Scheme 4) (34). Similar observations have been reported during a recent application of the aromatic Claisen rearrangement (35).

A combination of the above effects can explain the origins of the site selectivity of the Claisen/Diels–Alder rearrangement. In
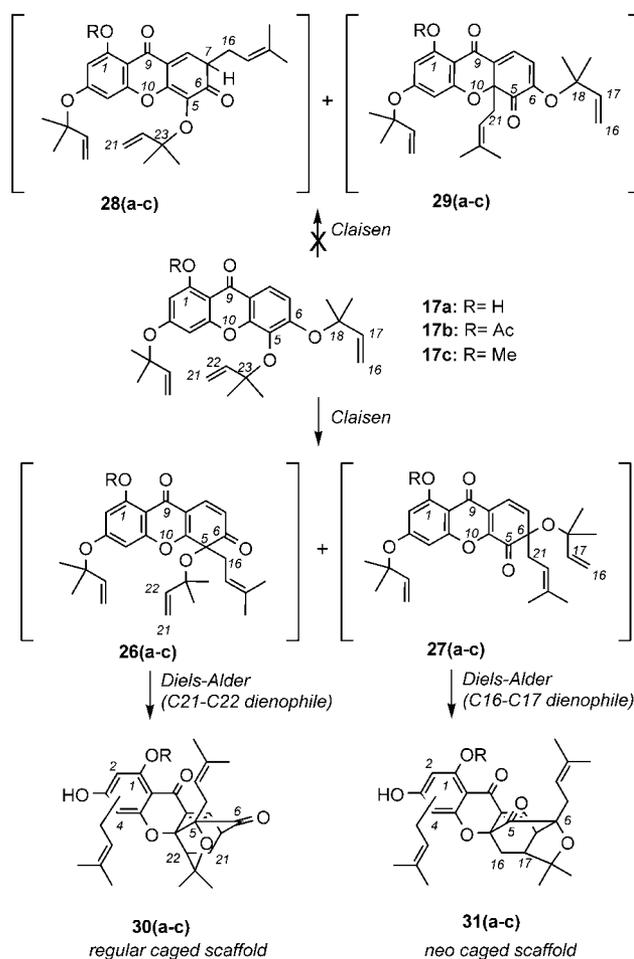
Scheme 4. Potential Claisen rearrangement intermediates.

the case of **17a** (R = H) the C9 carbonyl group is bound to the C1 OH by a hydrogen bond, which increases its electronic deficiency. This leads to a high selectivity of the Claisen rearrangement producing intermediate **26a** exclusively and, after Diels–Alder reaction with the pendant C21–C22 dienophile, affords only adduct **30a**, and thus, only the regular caged scaffold. The trisubstituted alkene cannot participate as a dienophile during the Diels–Alder reaction because of its decreased reactivity. Similar results are obtained when **17b** (R = Ac) is used as the acyclic xanthone precursor, suggesting that the inherent reactivity of the C9 carbonyl center suffices for the site selectivity of the Claisen/Diels–Alder rearrangement. However, a partial loss of the site selectivity is observed with the 1-*O*-methylated xanthone **17c** (R = Me). This result can be explained if we consider that in **17c** the presence of the C1 methyl ether attenuates the withdrawing effect of the C9 carbonyl group. This effect reduces the preference for cleavage of the O–C18 bond and allows a competing rearrangement using the C5 allyloxy ether to take place. In the case of **17c**, competition of these processes produces a mixture of Claisen adducts **26c** and **27c** and thereby a mixture of final products **30c** (regular caged scaffold) and **31c** (neo caged scaffold) in an approximate ratio of 2:1 (Scheme 4). Similar results were also reported by Nicolaou and Li (16) during their synthesis of 1-*O*-methylforbesione, although the role of the O1 substitution was not identified.

Selectivity of the A-Ring Claisen Rearrangement. Knowing the timing of the Claisen/Diels–Alder/Claisen cascade allowed
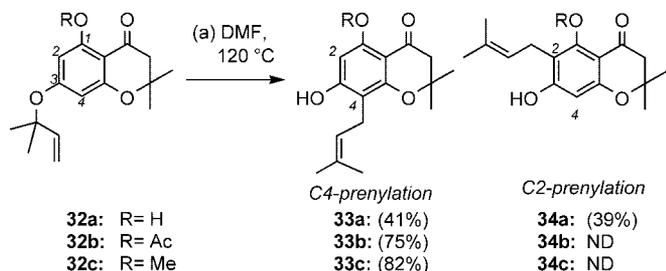
Scheme 5. Reagents and conditions: reaction a, DMF, 125°C, 1 h, 41% yield of **33a**, 39% yield of **34a**; 75% yield of **33b**; 82% yield of **33c**. ND, not detected.

35: R = H: bractatin
36: R = Me: 1-*O*-methylbractatin

37: 1-*O*-methylneobractatin

Fig. 4. Survey of natural products from *Garcinia bracteata*.

us to focus on the site selectivity of the A-ring Claisen rearrangement. Because the NMR experiments suggest that the 4-oxatricyclo[4.3.1.0³,⁷]dec-8-en-2-one system formed before the A-ring Claisen rearrangement, we decided to evaluate this reaction in a simpler system. Compounds **32a–c**, having a single aromatic residue, were selected for this study. Experimental procedures and spectroscopic data for these compounds are included in supporting information.

Heating the model systems **32a–c** at 125°C in DMF yielded results similar to those obtained during our synthesis of forbesione (Scheme 1). Using the underivatized **32a**, we obtained a 1/1 mixture of C2 and C4 prenylated products (**33a** and **34a**) (Scheme 5). When either the 1-*O*-acetyl or the 1-*O*-methyl model system was heated we saw exclusive formation of respective C4-prenylated products **33b** and **33c** in 75% and 82% yield. These results validate our use of these A-ring models to probe the site selectivity of the A-ring Claisen in our natural product systems and also support the conclusion of our high-temperature NMR studies.

The above results may be explained on the basis of increased steric hindrance by the R group during C2 prenylation. In the case of **32a** the C1 phenolic hydrogen is bound to the adjacent carbonyl group and does not hinder the [3,3]-sigmatropic rearrangement at the C2 carbon. This, in turn, leads to a mixture of C2 and C4 prenylation in an equal ratio. However, in the case of **32b** (R = Ac) and **32c** (R = Me) the R group is forced to reside away from the carbonyl oxygen and hinders any approach at the C2 carbon center. In these cases the Claisen rearrangement proceeds exclusively at the more accessible C4 carbon center.

Potential Implications of the Claisen/Diels–Alder/Claisen Rearrangement for the Biosynthesis of *Garcinia* Natural Products. Our findings on the tandem Claisen/Diels–Alder/Claisen rearrangement in allyloxy xanthones could provide useful insights regarding the biosynthesis of all known caged *Garcinia* natural products. A literature survey indicates that all these naturally occurring compounds share a common caged structure exemplified by the simplest among them, forbesione (**1a**). The only exception to this trend is provided by the structure of 1-*O*-methylneobractatin
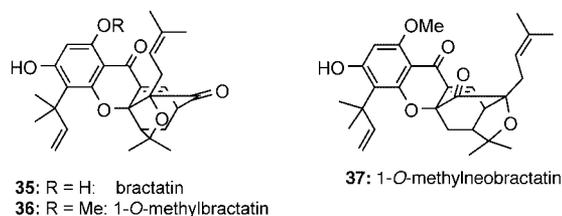
(**37**), which contains the alternative, neo scaffold (**3**) (Fig. 4). This compound was isolated from extracts of the dried and powdered leaves of *Garcinia bracteata* as a minor constituent along with 1-*O*-methylbractatin (**36**) and bractatin (**35**) (3). The presence of the seemingly innocuous 1-*O*-methyl group may explain the concomitant biosynthesis of both **37** and **36**. Guided by our results, we propose that, in the methylbractatin series, the 1-*O*-methyl group was incorporated by nature before the tandem Claisen/Diels–Alder/Claisen rearrangement.

Conclusion

In conclusion, we have planned and put into action a unified strategy for the synthesis of caged *Garcinia* natural products, namely forbesione (**1a**), desoxygaudichaudione A (**4**), desoxymorellin (**5**), and gambogin (**10**). In addition to the total syntheses presented herein, the timing of the Claisen/Diels–Alder/Claisen cascade has been investigated by high-temperature ¹H NMR and found to lead with the C-ring Claisen/Diels–Alder rearrangement and follow with the A-ring Claisen reaction. The site selectivity of both the A- and C-ring Claisen rearrangements have been rationalized, the former with models that mirror the reactivity of the natural product precursors to forbesione (**1a**), isoforbesione (**23a**), 1-*O*-acetylforbesione (**1b**), and 1-*O*-methylforbesione (**1c**).

It is apparent that every functionality present in the structure of xanthone precursor plays a crucial role in the biosynthesis of these natural products. The C9 carbonyl group, the O10 xanthone oxygen, and the C18 dimethylallyl substituent are strategically placed to facilitate the construction of the regular caged motif, by stabilizing the polar transition state of the C-ring Claisen rearrangement. Moreover, remote electronic effects influence the site selectivity of this rearrangement and may operate during the biosynthesis of the caged motif. In addition, the Claisen rearrangement at the A ring is controlled by steric effects that facilitate the C4 prenylation and pave the way for subsequent substitutions. The biological potential of the caged motif of these natural products still needs to be systematically evaluated. Our observations provide a testament to the unique opportunities offered by organic synthesis to decode information encrypted in the structures of natural products.

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