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Chemistry and Biology of the Caged *Garcinia* Xanthenes

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Abstract

Natural products have been a great source of many small molecule drugs for various diseases. In spite of recent advances in biochemical engineering and fermentation technologies that allow us to explore microorganisms and the marine environment as alternative sources of drugs, more than 70% of the current small molecule therapeutics derive their structures from plants used in traditional medicine. Natural-product-based drug discovery relies heavily on advances made in the sciences of biology and chemistry. Whereas biology aims to investigate the mode of action of a natural product, chemistry aims to overcome challenges related to its supply, bioactivity, and target selectivity. This review summarizes the explorations of the caged *Garcinia* xanthenes, a family of plant metabolites that possess a unique chemical structure, potent bioactivities, and a promising pharmacology for drug design and development.

Keywords

cyclic compounds; cycloaddition; domino reactions; natural products; synthesis design

Introduction

The trees of the genus *Garcinia* belong to the family of Guttiferae (Clusiaceae) and are found mostly in lowland rainforests of India, Indochina, Indonesia, West and Central Africa, and Brazil.^[1] They are slow-growing polygamous trees that produce scented flowers and fruits that often contain a fleshy, edible endocarp (Figure 1). Throughout the years *Garcinia* trees have retained considerable value as sources for medicines, pigments, gums, waxes, resins, foodstuffs (fruit), fuel (wood, seed oil), and lumber.^[2,3] Arguably, the most widely cultivated and well-known *Garcinia* tree is *Garcinia mangostana*. It yields one of the most highly prized tropical fruits, the mangosteen, valued for its delicious endocarp and rind, both of which are thought to have medicinal potential.^[4]

The utility of the *Garcinia* trees in the arts and sciences is well documented. In fact, gamboge, the pulverized gold-colored resin collected primarily from *Garcinia hanburyi*, and to a lesser extent from *Garcinia morella*, has a particularly long and rich history in the arts

and sciences.^[5,6] For instance, the yellow colorant used on 8th century artifacts from East Asia is presumed to be a gamboge-based water-color. The importation of gamboge in Europe took place in the 15–16th century where it was used mainly as a coloring material by Flemish painters. In fact, this pigment has been noted on a painting by Rembrandt, currently found in the Staatliche Kunstsammlungen Museum in Dresden.^[7] The toxicity of gamboge was also noted early on and several accounts warn against licking brushes containing gamboge. In the recent years, gamboge has been utilized primarily for research on identification of biologically active substances. Nonetheless, it is worth noting that Jean Baptiste Perrin used a colloidal suspension of gamboge particles to investigate Brownian motion and derive a value for the Avogadro number in a series of experiments that gave him the Nobel Prize in physics in 1926.^[8]

Family of Caged *Garcinia* Xanthenes

Isolation

Gamboge (tenghuang in Chinese) has been the subject of analytical and chemical studies for about 200 years.^[9] Depending on the originating tree, the resin composition changes but in all cases it contains about 70% of organic constituents that are insoluble in water. Studies with resin extracts of *Garcinia hanburyi* led to the identification of gambogic acid (**1**). Although this compound was initially isolated in 1934 as its monoacetyl derivative,^[10] its chemical structure was unambiguously determined in 2001 by an X-ray of its pyridine salt.^[11] Related investigations from the seeds and the resin of *Garcinia morella* led in 1937 to the isolation of morellin (**3**).^[12] In 1963 the *p*-bromobenzenesulfonyl ester of morellin was prepared and its constitution was determined by X-ray crystallography.^[13]

The crystal structures of **1** and **3** defined a new class of natural products that are collectively referred to as caged *Garcinia* xanthenes. Common to their structure is a xanthone backbone in which the C ring has been converted to an unusual 4-oxatricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (caged) scaffold.^[14] This motif (see structure **7**) is further customized through substitutions on the aromatic ring (ring A) and peripheral oxidations to produce a variety of structural subfamilies. This is exemplified by the structure of forbesione (**8**), a natural product isolated from *Garcinia forbesii*^[15] and *Garcinia hanburyi*.^[16] For example, prenylation at the C5 center of forbesione (gambogic acid numbering) gives access to the gaudichaudione scaffold,^[17] represented by deoxygaudichaudione (**10**).^[18] Oxidation at the C30 center could then lead to gaudichaudione A (**11**).^[17a] Alternatively, prenylation of **8** at C5, followed by cyclization with the pendant phenol gives access to the morellin scaffold,^[19] represented by desoxymorellin (**5**).^[20] Progressive oxidations at the C29 center of **5** produce morellinol (**4**), morellin (**3**), and morellic acid (**6**).^[21] Compounds arising from isomerization around the C27=C28 double bond of morellins have also been isolated. Thus, morellin (**3**), with the *cis* configuration about the C27=C28 double bond, is known to isomerize to the *trans* isomer, isomorellin (**12**).^[22] Similar observations have been reported for **1**.^[23]

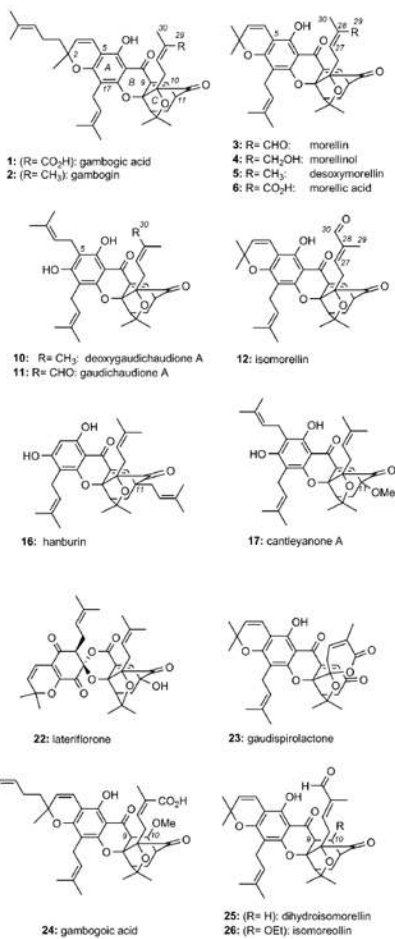
Geranylation at the C5 center of forbesione forms desoxygambogenin (**9**) and, after formation of the pyran ring, produces the structure of gambogin (**2**).^[24] Further oxidation at C29 leads to the structure of **1**.^[16a] Isolated from *Garcinia bracteata*, the bractatin subfamily (**13**, **14**, **15**)^[25] serves as an example of forbesione-type natural products that contain a reverse prenyl group at the C17 center. Interestingly, 6-*O*-methylneobractatin (**15**) is the only natural product known to contain a modified caged structure, referred to as the neo motif.^[25] The C11 center is another diversity point. For example, hanburin (**16**)^[24] is a C11 prenylated product of forbesione, while cantleyanone A (**17**)^[26] and scortechinones A (**18**)^[27] and B (**19**)^[28] contain a methoxy group at that position. This motif has also been

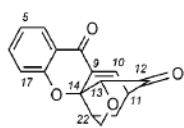
identified in the structures of cochinchinones C (**20**) and D (**21**), two natural products isolated from the roots of *Cratoxylum cochinchinense*.^[29]

In addition to the structures above, there are a number of *Garcinia* natural products containing a rearranged caged xanthone motif. For instance, in the structure of lateriflorone (**22**),^[30] the caged motif is attached to an unprecedented spiroxalactone core, likely a product of an oxidative rearrangement of the central xanthone ring. Similar rearrangements at the C ring may account for the structure of gaudispirolactone (**23**).^[31, 32] Gambogic acid (**24**),^[18, 33] dihydroisomorellin (**25**),^[20b] and isomorellin (**26**)^[34] are a few representative examples of caged xanthenes with a modified C9=C10 double bond.

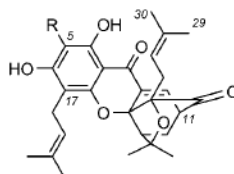
It should be noted that the chemical structures shown do not define the absolute stereochemistry of the caged motif. This is because the vast majority of the caged *Garcinia* xanthenes have been characterized by NMR spectroscopy methods and thus their absolute stereochemistry remains undetermined. It has been suggested that these natural products exist as racemic mixtures and their enantiomeric composition can be enriched by repeated crystallizations.^[25] For instance, chiral HPLC analysis of **13** showed that this compound exists as a 6:4 mixture of two enantiomers, the ratio of which varies with different crystallizations.^[25] Moreover, gambogic acid (**1**) occurs in nature as a mixture of epimers at the C2 center that can be separated by modern chromatographic and analytical techniques.^[35] The optical rotation recorded for the C2-*R* epimer is

$[\alpha]_D^{20} = -578$ ($c=0.201$, CHCl_3), whereas that recorded for the C2-*S* epimer, also referred to as epigambogic acid, is $[\alpha]_D^{20} = -486$ ($c=0.197$, CHCl_3).^[36] More recently, a combination of these techniques has been used for the identification of new bio-active xanthenes from *Garcinia* plants.^[37]

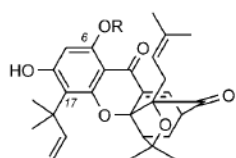




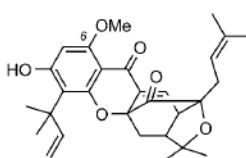
7: General motif of the caged xanthenes



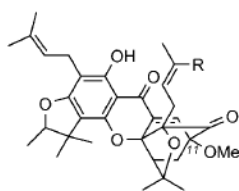
8: R= H: forbesione
9: R= geranyl: desoxygambogenin



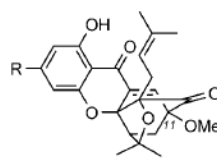
13: R= H: bractatin
14: R= Me: 6-O-methylbractatin



15: 6-O-methylneobractatin



18: R= CH₃: scortechinone A
19: R= CO₂H: scortechinone B



20: R= H: cochinchinone C
21: R= OH: cochinchinone D

Biogenesis studies

Biosynthetically, the xanthenone backbone of the caged *Garcinia* natural products is presumed to derive from common benzophenone intermediates of a mixed shikimate–acetate pathway.^[38] Whereas xanthenes produced in fungi have been shown to be wholly acetate derived,^[39] those found in higher plants exhibit oxygenation patterns that originate from a combination of the acetate (ring A) and shikimate (ring C) pathways. This proposed biogenetic scenario is illustrated with the synthesis of maclurin (**31**) and tetrahydroxy xanthenone **32** (Scheme 1).^[40] An aldol-type condensation of phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate leads to shikimic acid (**27**) that after oxidation, dehydration, and enolization forms protocatechuic acid (**28**). Reaction of **28** with coenzyme A (HSCoA) produces activated ester **29** that can then react with three units of malonyl coenzyme A (malonyl-CoA) to produce intermediate **30**. An intramolecular Claisen condensation followed by enolization leads to benzophenones such as maclurin (**31**). Depending upon the benzophenone produced, this may be a branch point in the biogenesis of other benzophenone-type natural products. It is generally accepted that the formation of xanthenes such as 1,3,5,6-tetrahydroxyxanthenone occurs by means of phenolic coupling of maclurin (**31**).^[40c,d]

Different hypotheses have been proposed for the biosynthetic conversion of xanthenes, such as **32**, to the unusual motif of the caged *Garcinia* xanthenes. The first proposal departed from prenylation of a xanthenone, such as **33**, at C11 and C13 centers to produce compound **34** (Scheme 2).^[13a] Oxidation at the C13 center would then introduce the essential tertiary alcohol, while reduction of the C10=C11 double bond would form compound **35** that can assume the geometry required for cyclization (structure **36**). Nucleophilic attack by the C13 tertiary alcohol on the pendant prenyl group was then presumed to initiate the cyclization cascade leading to caged structure **37**. The complete caged system **38** could then be formed

by oxidation between carbons C9 and C10. The biosynthetic scenarios that followed were variations of this proposal that simply reduced the number of oxidations and reductions.^[14a, 19] Unfortunately, both the molecular geometry and the reactivity required for the cascade of nucleophilic attacks from **35** to **37** would make this proposal implausible.

A more realistic biosynthetic scenario emerged from the pioneering work of Quillinan and Scheinmann.^[41] They proposed that “isoprenylation of tetrahydroxyxanthone **32** with four isoprene units can lead to desoxymorellin and related metabolites”. The caged motif of these compounds can thus be formed by a Claisen rearrangement followed by a Diels–Alder reaction on the intermediate dienone. This scenario is highlighted in Scheme 3. It is worth noting that although at that time there was sufficient precedence in support of the Claisen migration,^[42] there were no reports on intramolecular Diels–Alder adducts from rearrangements of aryl propargyl ethers. Along these lines, a retro Diels–Alder fragmentation pathway has been detected in mass spectrometry studies of several caged *Garcinia* xanthenes, providing additional support to this biosynthesis proposal.^[19e, 36]

Quillinan and Scheinmann also provided experimental evidence in support of the Claisen/Diels–Alder reaction cascade. Using mesuaxanthone B (**39**) as the starting material, they successfully prepared and tested their hypothesis on bis(allyloxy) xanthone **40** (Scheme 3). Despite the rather limited experimental details, they showed that heating **40** in boiling decalin (190 °C) for 14 h gave rise to the elusive caged structure, assigned as compound **42**, presumably by a Diels–Alder cyclization of Claisen intermediate **41**. Compound **42** had similar spectroscopic characteristics as those of morellin, suggesting that this reaction cascade could account for the biogenesis of the caged xanthenes.

The lack of details on the synthesis of caged motif **42**, together with the high temperature and long reaction times required for the Claisen/Diels–Alder reaction, cast some doubts on the synthetic relevance of this reaction cascade. Likely due to these reasons, the proposal by Quillinan and Scheinmann remained dormant for over 30 years, until Nicolaou and Li masterfully demonstrated its value in a biomimetic synthesis of forbesione (**8**).^[43] Independently, Theodorakis and co-workers explored the site selectivity of the Claisen/Diels–Alder cyclization and further refined the biosynthesis scenario for all caged *Garcinia* xanthenes.^[44] These studies will be presented in the following sections.

Biological Activities of the Caged *Garcinia* Xanthenes

Antimicrobial and anticancer activities

Aside from their striking chemical structure and biosynthesis, the caged *Garcinia* natural products exhibit interesting bioactivities and have a documented value in traditional Eastern medicine. In fact, oral and injectable formulations of gamboge have been used in China for the treatment of patients with breast carcinoma and malignant lymphoma.^[45] In addition, gamboge has been used topically for treating infected wounds and systemically to alleviate pain and edema. Moreover, in Thai folk medicine, gamboge has been used as a topical anti-infective agent, and internally as a drastic purgative and a vermifuge to treat tapeworm.^[23, 46]

Initial biological studies with semipurified gamboge extracts documented its antiprotozoal activities, thus lending support for its indigenous use in the treatment of enteric diseases.^[47] Morellin (**3**) and gambogic acid (**1**), the major components of semipurified resin extracts of *Garcinia morella*,^[48] exhibited high in vitro specific growth inhibitory effects on Gram-positive bacteria in vitro and a protective action in experimental staphylococcal infections in mice.^[49] In particular, acid **1** exhibited high specific inhibitory effect (0.1–1 $\mu\text{g mL}^{-1}$) on the growth of Gram-positive bacteria, but had little effect against many Gram-negative

bacteria, fungi, yeast, and actinomycetes.^[50] Further experiments in mice indicated that topical applications of **1** in experimental septic wounds could offer protection against lethal staphylococcal infections at a dose level of 30 mg kg⁻¹ day⁻¹ for 2 days. Interestingly, the susceptibility of a morellin-resistant strain of *Staphylococcus aureus* to penicillin and erythromycin was unaffected, indicating that there is no cross-resistance between the morellin and the above antibiotics. Both morellin and **1** were well tolerated by rats at a dose of 40 mg kg⁻¹ day⁻¹ for 40 days. However, a dose of 120 mg kg⁻¹ day⁻¹ resulted in side effects including decreased growth and reduced blood cell counts.^[50b] More recently, scortechinone B (**19**) showed antibacterial activity on methicillin-resistant *Staphylococcus aureus* with an MIC value of 2.0 µg mL⁻¹.^[27c]

In addition to their antimicrobial activity, the caged *Garcinia* xanthenes, have received a great deal of attention for their anticancer activity. An ever increasing body of evidence indicates that these compounds are cytotoxic against various cancer cell lines at low µM concentrations.^[20c] For instance, desoxymorellin (**5**) inhibited the growth of HEL (human embryonic lung fibroblasts) and HeLa (Henrietta Lacks cervical cancer) cells with a minimum inhibitory concentration (MIC) of 0.39 µg mL⁻¹.^[24, 51] The bractatins (**13–15**) were cytotoxic against the KB cell line (human epidermoid carcinoma) with 6-*O*-methylneobractatin (**15**) showing the lowest IC₅₀ value of 0.20 µg mL⁻¹.^[25] The gaudichaudiones (**10** and **11**) have been tested against a panel of cell lines, and found to be broadly cytotoxic with effective dose (ED₅₀) values between 0.50 and 8.0 µg mL⁻¹.^[17a] Selected members of the cantleyanone (**17**) family displayed significant cytotoxicity against breast cancer (MDA-MB-231 and MCF-7), ovarian cancer (CaOV-3), and HeLa cells with EC₅₀ values ranging from 0.22 to 17.17 µg mL⁻¹.^[26] In addition, lateriflorone (**22**) was cytotoxic against the P388 cancer cell line with an ED₅₀ value of 5.4 µg mL⁻¹.^[30] In similar studies, gambogic acid (**1**) inhibited the proliferation of T47D and DLD-1 breast cancer cells with GI₅₀ values of 0.04 and 0.03 µM, respectively.^[52] Similar observations were reported upon screening **1** and related caged *Garcinia* xanthenes against a panel of solid and nonsolid tumor cells.^[53]

Of particular interest are the studies on the activity of **1** and related xanthenes against various drug-resistant cell lines.^[16a,23] For example, compound **1** and its C2 epimer, epigambogic acid, displayed similar cytotoxicity against doxorubicin-sensitive (EC₅₀ 1.3 µM) and doxorubicin-resistant (EC₅₀ 0.9 µM) human leukemia K562 cells in an MTT assay.^[36] More recently, compound **11** was reported to display strong growth inhibitory activity against both parental murine leukemia P388 and P388/doxorubicin-resistant cell lines at low micromolar concentrations.^[54] Studies from our own laboratories have confirmed these findings.^[53] Specifically, we have found that adriamycin-resistant HL-60 cells have similar sensitivity to the antiproliferative effects of several caged *Garcinia* xanthenes as the parental HL-60 cell line. These findings indicate that the caged *Garcinia* xanthenes are not subjects of the multidrug resistance mechanisms, often associated with overexpression of P glycoprotein that is typical of relapsed cancers. Thus, these compounds represent a pharmacologically promising chemical scaffold.^[55]

Mode-of-action studies

The induction of apoptosis has been established as one of the main mechanisms of cytotoxicity exhibited by the caged *Garcinia* xanthenes in several tumor cells.^[52, 53] Both **1**^[52] and **11**^[54] have been shown to activate caspase 3, a protein that plays a key role in apoptosis.^[56] In MGC-803 cells (human gastric carcinoma), apoptosis was induced by **1** after 48 h of treatment with an IC₅₀ of 0.96 µg mL⁻¹.^[57] Immunohistochemical studies indicated that **1** regulates the levels of Bax and Bcl-2, a family of proteins that play a crucial role during apoptosis.^[58, 59] Several reports have confirmed that **1** increases the expression of bax and decreases expression of bcl-2 genes in a variety of cancer cell lines, including

human gastric cancer cells MGC-803,^[59] BGC-82,^[60] and human malignant melanoma A375 cells.^[61] Induction of bax and suppression of bcl-2 is likely to contribute to the apoptosis mechanism in these cell lines. A recent study has reported that **1** competes with BH3 peptides for binding to the Bcl-2 family of proteins thereby inhibiting the antiapoptotic activity of these proteins.^[62] In this study, compound **1** inhibited binding of BH3 peptides to 6 members of the Bcl-2 family to various extents with IC₅₀ values of up to 2.0 μM. Importantly, analogues of **1** with reduced ability to compete with BH3 peptides also had lower cytotoxicity. However, compound **1** retained some cytotoxicity in bax^{-/-}/bak^{-/-} cells, suggesting that this compound has additional targets that contribute to its cytotoxicity.

In addition to the regulation of genes directly associated with apoptosis, a collection of work has revealed that multiple other genes are regulated by **1**, which may contribute to its anticancer activity. For instance, compound **1** enhanced p53 protein expression, but, interestingly, had no influence on p53 mRNA synthesis.^[63] This result is most likely to be due to the down-regulation of mdm2, a negative regulator of p53, at both mRNA and protein levels.

Gambogic acid (**1**) can affect the cell cycle in multiple ways, ultimately altering cell proliferation.^[64] In recent studies, compound **1** suppressed telomerase activity in human gastric carcinoma and lung cancer cells by repressing both the transcriptional activity and posttranslational modification of hTERT.^[64a-d] Another study reported that treatment of MCF-7 breast cancer cells with **1** (2.5 μM) caused microtubule cytoskeleton disruption and microtubule depolymerization.^[64e] In addition, compound **1** was proposed to inhibit the catalytic activity of human topoisomerase IIα by binding to its ATPase domain.^[64f] Other studies have shown that **1** induces G₂/M-phase cell-cycle arrest by disturbing the CDK7-mediated phosphorylation of CDC2/p34 in human gastric carcinoma cells.^[64g] The proteomic approach has also been used to reveal the molecular targets of **1** in hepatocellular carcinoma. This study showed that the expression of stathmin 1 (STMN1) was significantly down-regulated by **1**.^[65] This protein plays a major role in the regulation of microtubule dynamics, thus providing additional evidence on the effects of **1** on cell cycle progress.

Steroid receptor coactivator 3 (SRC-3), a member of the p160 family of nuclear receptor coactivators, is an important modulator of cell growth and is often over-expressed in cancer cells. In recent studies, compound **1** was found to decrease the expression of SRC-3 at both the mRNA and protein levels in human lung adenocarcinoma (A549) cells that over-express this receptor coactivator.^[66] This action presumably accounts for the observed inhibition of proliferation by **1** in a time- and dose-dependent manner with an IC₅₀ value of (3.17±0.13) μmol L⁻¹ after 24 h of treatment.

Evaluation of the antileukemic effect of **1** led to the observation that nucleoporin Nup88 expression was down-regulated in several leukemia cell lines upon treatment with **1**.^[67] In addition, the distribution of Nup88 was altered from widely dispersed in both nucleus and cytoplasm to that predominantly localized at the cytoplasmic side of the nuclear membrane. These results suggest that regulation of nucleocytoplasmic transport may be important for the anticancer effects of **1** in leukemia cells.

Of particular significance are the effects of **1** on cancer cell metastasis. The findings indicate that **1** inhibits the adhesion, migration, and invasion of a highly invasive human breast cancer cell line in vitro and in vivo.^[68] These effects have been attributed to the ability of **1** to down-regulate the expression of several matrix metalloproteinases. Similar studies in highly metastatic mouse melanoma cells suggest that **1** inhibits cell adhesion and migration by down-regulating α₄ integrin expression.^[69]

In addition to modulating cellular processes directly affecting cancer cells, compound **1** appears to also have an effect on angiogenesis thereby having the ability to affect tumor cells indirectly. Specifically, compound **1** inhibits angiogenesis by suppressing the activity of vascular endothelial growth factor receptor 2 (VEGFR2) and its downstream protein kinases, c-Src, focal adhesion kinase, and AKT.^[70]

The effect of **1** in combination with known anticancer drugs has also been explored. One study showed that **1** could reverse docetaxel resistance in BGC-823/Doc gastric cancer cells.^[71] Specifically, treatment of these cells with **1** at concentrations up to 0.2 μM led to a dramatic increase in docetaxel-induced apoptosis. Analysis of apoptosis-associated genes revealed that **1** singly, or in combination with docetaxel, significantly down-regulated the mRNA expression of survivin, a protein associated with resistance to apoptosis.^[71] A more recent study showed that the anticancer effect of a simultaneous administration of 5-fluorouridine (5-FU) with **1** was much greater than that of 5-FU or **1** alone.^[72] Furthermore, compound **1** was found to regulate the metabolic enzymes involved in 5-FU metabolism. Specifically, compound **1** decreased mRNA levels of thymidine synthetase (TS) and dihydropyrimidine dehydrogenase (DPD), whereas it increased the mRNA level of orotate phosphoribosyltransferase (OPRT). The authors of this study suggest that this mechanism accounts for the observed synergistic effect of **1** used in combination with 5-FU.^[72] These studies attest to the potential of **1** in combination therapies.

The combination of published reports on the anticancer activity of **1** clearly indicates that this compound affects several cellular processes and has multiple targets. Studies have indicated that **1** binds to transferrin receptor type 1 (TfR1), a membrane-bound protein involved in iron homeostasis.^[73] The authors of this study have proposed that such binding induces a unique signal leading to rapid apoptosis of tumor cells.^[74] In this study, the cytotoxicity of **1** and its derivatives correlated with their ability to bind to TfR1. Furthermore, down-regulation of TfR1 in T47D and 293T cells by RNAi, significantly decreased their sensitivity to **1**-induced apoptosis. Further evidence for a role of the TfR in the induction of apoptosis by **1** is the finding that **1** potentiated tumor necrosis factor (TNF)-induced apoptosis in human leukemia cells through modulation of the NF- κ B signaling pathway, and that this was dependent on the expression of TfR.^[75] Down-regulation of TfR by RNAi reversed the effects of **1** on NF- κ B signaling and apoptosis. Furthermore, this study demonstrated that **1** enhanced the effect of TNF and chemotherapeutic agents in inhibiting the expression of gene products involved in antiapoptosis, cell proliferation, invasion, and angiogenesis; all of which are known to be regulated by NF- κ B. In addition, compound **1** suppressed NF- κ B activation induced by various inflammatory agents and carcinogens. Noteworthy, however, is that **1** alone had no effect on NF- κ B signaling, in contrast to results of other studies.^[76] The authors concluded that **1** inhibits TNF-induced NF- κ B signaling and potentiates apoptosis through its interaction with the TfR-1. Although the results of this study indicate that TfR-1 plays a role in potentiating TNF-induced apoptosis, the direct binding of **1** to TfR-1 has not been determined. Hence, it is not clear whether TfR-1 is a primary target of **1** in this case. Interestingly, in another study, **1** was equally cytotoxic against CHO (Chinese hamster ovary) cells deficient in endogenous TfR1 (TRVb-neo) and those expressing exogenous human TfR1 (TRVb-hTfR1), suggesting that the cytotoxicity of **1** is independent of TfR1.^[77] These results clearly indicate that **1** has multiple targets, and that binding to TfR1 may or may not be required for the induction of cytotoxic effects; this is likely to depend on the cell context.

More recently, compound **1** was found to induce production of reactive oxygen species (ROS) in human hepatoma SMMC-7721 cells, resulting in the collapse of the mitochondrial membrane potential. This led to the release of cytochrome c and apoptosis-inducing factor from mitochondria, ultimately leading to apoptosis.^[78] Moreover, compound **1** elevated the

phosphorylation of c-Jun-*N*-terminal protein kinase (JNK) and p38, downstream effects of ROS accumulation. *N*-Acetylcysteine, an inhibitor of ROS production, partly reversed the activation of JNK and p38 and the induction of apoptosis in cells treated with **1**. These results indicate that **1** induces apoptosis, in part, by activating the cell stress associated MAPK pathway through the production of ROS.

In summary, compound **1** and related molecules appear to have multiple targets and mechanisms accounting for their cytotoxicity against cancer cells. It is likely that the mechanisms involved will depend on the cellular context. Importantly, further work by independent laboratories will be needed to verify the primary target(s) and most relevant key signaling pathways involved in the action of **1**.

Pharmacology and animal model studies

Several studies with **1** in animal models have documented its low toxicity and promising chemotherapeutic value. Of note, in a study using a rat glioma model, it was shown that **1** was taken up by brain microvascular endothelial cells (rBMEC) in a time-dependent fashion, indicating that this compound could pass through the blood brain barrier. Furthermore, intravenous injection of **1** once a day for two weeks could significantly reduce tumor volume by inhibiting angiogenesis and inducing apoptosis of glioma cells.^[79] As such, this study reveals a possible new therapeutic lead in glioma therapy. In a study using a rat gastric carcinoma model,^[57] intravenous (iv) injection of **1** at 6 mg kg⁻¹ (4 doses on alternate days) did not affect the body weight or white blood cell count of healthy rats, but induced apoptosis of MGC-803 gastric carcinoma cells. These findings support the notion that **1** has little toxicity at therapeutic doses and displays significant tumor selectivity.

Further evidence for the tumor selectivity of **1** is provided by multiple studies both in vitro and in vivo.^[80] For instance, compound **1** selectively induced apoptosis of human hepatoma SMMC-7721 cells, whereas it had relatively less effect on human normal embryonic hepatic L02 cells and primary rat hepatic cells.^[80a] This study showed that treatment of mice with SMMC-7721 tumors with **1** at dosages of 2, 4, 8 mg kg⁻¹ resulted in 33.1, 50.3, and 64.2% inhibition of tumor growth, respectively, compared with vehicle control. Moreover, compound **1** was more potent than the standard agent cyclophosphamide (66% inhibition of tumor growth at 30 mg kg⁻¹). The authors suggest that the tumor selectivity of **1** may be partly due to its longer retention time in grafted tumor than in the liver, renal system, and other organs. Additional evidence for the tumor selectivity and efficacy of **1** in animal tumor models is the finding that **1** activated T lymphocytes to induce cancer cell apoptosis in H22 transplanted mice.^[80c] Hence, the anticancer effects of **1** appear to be at two levels, including direct effects on tumor cells as well as activation of immune cells against tumor cells.

In a study examining the acute and chronic toxicity in experimental animals, the LD₅₀ of **1** in albino mice was in the range of 43.18–48.45 mg kg⁻¹.^[81] The results from the chronic toxicity studies using beagles demonstrated that the toxicity targets were liver and kidney. The innocuous dose was established to be 4 mg kg⁻¹ after administration to dogs for a total of 13 weeks at a frequency of one injection every other day. This dose was approximately 9.6 (body weight) or 5.1 (body surface area) times the dosage (25 mg/60 kg, every other day) usually recommended for human trials. Similarly, in a chronic toxicity study using Sprague Dawley rats, oral administration of **1** at 120 mg kg⁻¹ for 13 weeks resulted in damage of the kidney and liver.^[82] An innocuous dose was established to be 60 mg kg⁻¹ upon oral administration for a total of 13 weeks at a frequency of one administration every other day. This dose was approximately 18.0 (body weight) or 9.6 (body surface area) times higher than that of the dose (200 mg/60 kg, every other day) used for human trials.^[82] Additional toxicology studies using beagles revealed that doses of **1** up to 4 mg kg⁻¹

administered intravenously had no effect on blood pressure, heart rate, or rate of respiration.^[83] However, higher doses of **1** in mice could reduce motor co-ordination in a dose-dependent manner. The most significant toxicity effects of **1** in this study were the reduction of maternal and fetal body weight as well as inhibition of fetal skeletal development at doses of 15 mg kg⁻¹ and above. Also of note was the analgesic activity of **1**, which was hypothesized to be due to the anti-inflammatory properties of **1**.^[83]

The plasma pharmacokinetics, excretion, and tissue distribution of **1** were investigated in several recent studies.^[84] The results showed that **1** was not detected in the urine after iv administration and was rapidly eliminated from the blood and transferred to the tissues. The tissue distribution of **1** was limited with the highest concentrations found in the liver. Moreover, the majority of **1** appeared to be excreted into the bile within 16 h of iv administration. In metabolism studies using rat liver microsomes, compound **1** was rapidly converted to 10-hydroxygambogic acid, 9,10-epoxygambogic acid, and their glucuronyl derivatives.^[85] The formation of 10-hydroxygambogic acid via cytochrome P-450 1A2 was found to be crucial for the elimination of **1** in rats. Hence, inhibitors of cytochrome P-450 1A2 can affect the metabolism of **1** and its bioactivity. This finding suggests that possible drug–drug interactions may result in combination therapies if cytochrome P-450 1A2 activity is affected. Moreover, issues related to the stability and tissue distribution of **1** can be addressed by developing appropriate delivery platforms. For instance, gambogic acid (**1**)-loaded micelles based on chitosan derivatives showed increased stability and decreased acute toxicity and vein irritation than a non formulated delivery of this compound.^[86]

In summary, potent anticancer activity, both in vitro and in vivo, and relatively low toxicity indicate that **1** may be an effective chemotherapeutic agent warranting further study in clinical trials. In fact, this compound has entered clinical trials in cancer patients in China.^[87] In turn, this suggests that the caged *Garcinia* xanthenes and designed analogues thereof have promising clinical potential.

Synthetic Strategies Toward the Caged *Garcinia* Xanthenes

Due to the impressive combination of unique chemical architecture, intriguing biological activities, and good potential in medicine, the chemical scaffold of the caged *Garcinia* xanthenes received significant attention as synthetic targets. The synthesis efforts rely on two general strategies for the construction of the caged motif: a tandem Wessely oxidation/Diels–Alder reaction and a sequence of Claisen rearrangements and Diels–Alder reaction.

Tandem Wessely oxidation/Diels–Alder reaction

Since Wessely's first reports in 1950s,^[88] lead tetraacetate mediated oxidation of phenols has become a convenient method to generate *o*-benzoquinones that, in the presence of a dienophile, can participate in a Diels–Alder cycloaddition reaction. If the phenol and the dienophile are covalently linked in the starting material, then the tandem Wessely oxidation/Diels–Alder reaction can produce tricyclic motifs. Yates and co-workers applied this reaction for the synthesis of compounds reminiscent to the structures of the caged *Garcinia* xanthenes (Scheme 4). Thus treatment of phenol **43** with Pb(OAc)₄ in acetic acid produced 2,4-cyclohexadienone **44** that, upon heating at 140 °C, formed compound **45** (gambogic acid numbering).^[89] In a subsequent study, xanthene **46** was treated with lead tetraacrylate (formed in situ by Pb(OAc)₄ and acrylic acid) to produce dienone **47** and, after an intramolecular Diels–Alder reaction, caged compound **48**.^[90]

Theodorakis and co-workers^[91] investigated the application of this strategy for the synthesis of a more hydroxylated caged motif reminiscent to the structure of lateriflorone (**22**) (Scheme 5). Treatment of **49** with Pb(OAc)₄ in acrylic acid/dichloromethane produced, after

heating in benzene at reflux (80 °C), tricyclic lactone **51** in 82% combined yield. Crystallographic studies established that **51** is a constitutional isomer of desired structure **54** and is reminiscent of the so-called neo caged structure. The connectivity of compound **51** suggested that during the Wessely oxidation the acrylate unit was attached exclusively at the more electronically rich C11 center of **49**, instead of the desired C13 carbon. In turn, this produced dienone **50** that subsequently underwent an efficient Diels–Alder cycloaddition with the pendant acrylate dienophile. To alter the connectivity of the caged structure, one could have the acetoxo group preinstalled at the C13 center and promote the migration of the prenyl group. Along these lines, heating of allyl ether **52** in *m*-xylene (140 °C), gave rise exclusively to caged motif **54** through a Claisen rearrangement and Diels–Alder cycloaddition. The selectivity of the Claisen rearrangement at the C13 center can be explained by considering that intermediate **53** has the necessary geometry that allows it to be trapped as the Diels–Alder adduct.

The tandem Wessely oxidation/Diels–Alder sequence was revived recently by Mehta and Maity (Scheme 6).^[92] Exposure of phenol **55** to lead tetraacrylate followed by heating in benzene at reflux produced a mixture of two caged structures **56** and **57**, reminiscent of the regular and neo caged motifs respectively, in 1:1 ratio and 71% combined yield. In this case, the acrylate addition proceeds at both C11 and C13 centers with low selectivity due to their similar electronic density.

Tandem Claisen/Diels–Alder reaction

Inspired by the Quillinan and Sheinman proposed biosynthesis, Nicolaou and Li evaluated the tandem Claisen/Diels–Alder sequence for the conversion of bis(allylated) coumarin **59** to a caged scaffold (Scheme 7).^[43] In principle, two competing migrations can occur during the initial Claisen rearrangement of **59** to form intermediates **60** and **61** (path A and path B, respectively). Each one of these intermediates can participate in two intramolecular Diels–Alder reactions with the coumarin core producing compounds **62–65** (Scheme 7). Indeed, upon heating of **59** at 125 °C, these compounds were isolated in 91% combined yield.

Application of this approach to the synthesis of forbesione^[43] and lateriflorone^[93, 94] provided further support for the Quillinan–Scheinmann biosynthetic hypothesis. For example, heating of allyl ether **66** at 120 °C produced a 1:1 mixture of **67** and **68** and in 89% combined yield (Scheme 8).^[93] The carbon connectivity of these products corresponds to that of the regular and neo caged scaffolds and indicates that, under these conditions, the Claisen rearrangement proceeds with no significant site selectivity. Interestingly, heating of compound **69** to 110 °C proceeded through a selective Claisen rearrangement to form dienone **70**, which after the Diels–Alder cycloaddition afforded exclusively the regular caged structure **71** (85% isolated yield).^[94] Comparison of these results suggests that the selectivity of the opening Claisen rearrangement can be controlled by the electronic density of the C8 carbon. It is reasonable to postulate that the C8 carbonyl group, which is *para* to the C12 allyloxy group, facilitates its Claisen migration at the C13 center.

Parallel studies by the Nicolaou^[43] and Theodorakis^[95] laboratories evaluated the possibility to synthesize forbesione (**8**) in one pot by using tris(allylated) xanthone **72** as the starting material (Scheme 9). In principle, exposure of such a motif to heat could produce four products arising from a combination of two competing C-ring Claisen/Diels–Alder reactions (producing regular and neo caged structures) and two competing A-ring Claisen migrations (producing C17 and C5 prenylations). Working with methoxy xanthone **72 c** (R = Me), the Nicolaou group was the first to describe its conversion to methyl forbesione (**73 c**) and methyl neoforbesione (**74 c**) in a 2.4:1 ratio and 89% combined yield.^[43] On the other hand, studies by the Theodorakis group showed that heating of xanthone **72 a** to 120 °C led only to isolation of forbesione (**73 a**) and isoforbesione (**75 a**) in 84% combined yield. The

neo C-ring isomers **74 a** and **76 a** were not detected in this case. More impressively, the O6-acetylated xanthone **72 b** afforded, upon heating, solely acetyl forbesione (**73 b**, 79% isolated yield).^[95] Similar observations have recently been reported by other groups.^[96] Several model studies were designed to rationalize these findings.^[44] The results can be summarized as follows:

1. The C-ring Claisen/Diels–Alder rearrangement proceeds first and is followed by the A-ring Claisen reaction.
2. The site selectivity of the A-ring Claisen rearrangement (C5 versus C17 prenylation) is controlled by the steric and electronic effects of the C6 phenolic substituent.
3. The site-selectivity of the C-ring Claisen/Diels–Alder reaction is attributed to and governed by the electronic density of the C8 carbonyl group. Being para to the C12 allyloxy unit, the electronically deficient C8 carbonyl carbon polarizes selectively the O–C28 bond and facilitates its rupture. In turn, this leads to a site-selective Claisen rearrangement of the C12 allyloxy unit onto the C13 center, thereby producing exclusively the regular caged motif found in the structure of forbesione (**73 a**).
4. The substitution of the C6 phenol can regulate the electronic density of the C8 carbonyl group and thus affect the site selectivity of the C-ring Claisen/Diels Alder reaction.

The experimental findings on the tandem Claisen/Diels–Alder/Claisen reaction cascade provide useful insights regarding the biosynthesis of all known caged *Garcinia* xanthenes.^[44] All natural products share a common caged motif, exemplified by structure **7**, except 6-*O*-methylneobractatin (**15**), which contains the neo caged motif. The remote electronic effects of the seemingly innocuous 6-*O*-methyl group may explain the concomitant biosynthesis of both 6-*O*-methylbractatin (**14**) and 6-*O*-methylneobractatin (**15**).

Recent studies by the Nicolaou group have shown that the Claisen/Diels–Alder reaction can be accelerated in the presence of polar solvents.^[97] For instance, the conversion of allyl ether **77** to caged structure **78 a** and its neo isomer **78 b** (structure shown in Scheme 13) was dramatically accelerated upon changing the solvent from benzene (100 °C, 4 h, 0%) to DMF (100 °C, 2 h, 75%) to a 1:2 mixture of MeOH/water (100 °C, 0.5 h, 100%) (Scheme 10). It has been proposed that polar aprotic solvents, such as DMF, and more impressively protic solvents, such as water, can accelerate the Claisen rearrangement by stabilizing its polar transition state.^[98] The concurrent acceleration of the Diels–Alder component of this cascade is likely due to the hydrophobic effect of water^[99] rather than to a polarity or hydrogen-bonding phenomena.^[100] Computational studies on the reaction depicted in Scheme 10 have also concluded that the Claisen rearrangement is reversible and the energetics of the irreversible Diels–Alder cyclization can determine the product formation.^[101]

Synthesis of selected caged *Garcinia* xanthenes

Biomimetic synthesis of 6-*O*-methylforbesione

Developed by Nicolaou and Li,^[43] the synthetic strategy toward 6-*O*-methylforbesione is highlighted in Scheme 11. Construction of xanthone **81** proceeded in 5 steps: a) coupling of the lithium salt of **79** with aldehyde **80**; b) deprotection of the C14 silyl ether; c) oxidation of the C8 alcohol; d) cyclization of the C14 alkoxy group; and e) deprotection of the C12 and C13 benzyl ethers (78% combined yield). Treatment of **81** with α -bromoisobutyraldehyde

(**82**) and *t*BuOK followed by Wittig olefination produced a mixture of **83 a** and **83b** that, after reiteration of the alkylation/olefination steps, gave rise to tris(prenylated) xanthone **72 c** in 55% combined yield. Heating of **72 c** in DMF at 120 °C for 20 min induced the anticipated Claisen/Diels–Alder/Claisen reaction and produced compound **73 c** together with its neo isomer **74 c** in 89% combined yield.

Unified synthesis of caged *Garcinia* xanthenes

The common structural features of several caged *Garcinia* natural products suggest that these compounds can be synthesized by decorating the A ring of forbesione (**8**). Such a strategy, developed by the Theodorakis group, uses forbesione (**8**) as a node in a unified synthesis of representative members of the gaudichaudiones (**10**), morellins (**5**), and gambogins (**2**).^[44] Scheme 12 highlights this plan. ZnCl₂-mediated condensation of phloroglucinol (**84**) with benzoic acid **85** produced xanthone **32** in 46% yield. Propargylation of **32** with propargyl chloride **86** followed by partial reduction of the alkyne units and acetylation of the C6 phenol formed compound **72b** in 16% combined yield. The Claisen/Diels–Alder/Claisen reaction cascade gave rise, after deacetylation, forbesione (**8**) in 72% combined yield. Propargylation of the C18 phenol with chloride **86** afforded, after Lindlar reduction and Claisen rearrangement desoxygaudichaudione A (**10**) in 34% yield. On the other hand, propargylation and Claisen rearrangement of forbesione formed desoxymorellin (**5**) in 61% combined yield. In a similar manner, condensation of **8** with citral (**88**) in Et₃N produced gambogin (**2**) in 75% overall yield.

Synthesis of **2**

An alternative synthesis of **2** has recently been reported by the Nicolaou group (Scheme 13).^[97] The plan involved construction of partially protected xanthone **90**, available in 5 steps from coupling of bromide **89** with aldehyde **80** (44% overall yield). Two rounds of alkylation with α -bromoisobutyraldehyde (**82**) and Wittig olefination produced compound **77** in 42% combined yield. The Claisen/Diels–Alder reaction proceeded in quantitative yield in MeOH/H₂O (1:2) at reflux to form regular caged motif **78 a** together with the neo isomer **78b** in a 3:1 ratio. MOM deprotection of **78 a** followed by propargylation with **92 a** at the C18 center and Lindlar reduction afforded compound **93** in 48% combined yield. This compound was then converted to **2** by a sequence of steps that involved acetylation of the C6 phenol, Claisen rearrangement to install the prenyl group at the C17 center, propargylation of the resulting phenol with alkyne **94**, and Claisen rearrangement to form the dihydropyran ring of the natural product (12% over 4 steps).

Studies toward the synthesis of lateriflorone

It has been proposed that the unprecedented spiroxalactone motif of lateriflorone (**22**) could be formed by condensation of two fully functionalized fragments **95** and **96** (Scheme 14). An alternative and likely more biosynthetically relevant hypothesis could involve conversion of xanthone **97** into dioxepanone **98** that, upon hydrolysis and spirocyclization at the C16 center, could form the spiroxalactone ring system of lateriflorone.

The Theodorakis group has reported an approach toward the synthesis of quinone **95** representing the A ring of lateriflorone (Scheme 15).^[102] A sequence of six steps was used to convert phloroglucinol (**84**) to chromanol **99**, which, upon propargylation with **92b**, Lindlar reduction and Claisen rearrangement, gave rise to phenol **100** (32% combined yield). Oxidation of **100** at the C7 center using Fremy's salt and deprotection of the MEM ether then formed chromenequinone **95** in 66% combined yield.

The synthesis of caged motif **96** and its coupling with quinone **95** are summarized in Scheme 16. 4-Hydroxysalicylic acid (**101**), containing only two of the four hydroxy groups

needed, was selectively brominated at the C11 center and then converted to benzopyran **102** (50% combined yield). Oxygenation at the C11 center via the intermediacy of a boronic acid, followed by oxygenation and reverse prenylation at the C13 center, produced compound **69**.^[94] A site-selective Claisen/Diels–Alder reaction gave rise, after deprotection, to desired fragment **96** (45% combined yield). Coupling of **95** with **96** then produced secolateriflorone (**104**), which did not undergo the desired spiroxalactonization reaction.

More recently, the Nicolaou group has reported a synthesis of C11-methylateriflorone (**110**) (Scheme 17).^[103] Key to the strategy was the coupling of orthogonally protected hydroquinone **105** with acid **106**, which after selective deprotection of the C7 MOM ether produced compound **107** (61% combined yield). Oxidation of **107** in the presence of iodosobenzene bis(trifluoroacetate) in methanol, followed by heating under acidic conditions formed spiroxalactone **109** in 42% combined yield. Acid-catalyzed hydrolysis of **109** gave rise to C11-methylateriflorone (**110**) in 66% yield.

Structure–Activity Relationship (SAR) Studies

The underexplored chemical structures and promising biological activities of the caged *Garcinia* xanthenes have fuelled several structure-activity relationship studies. The majority of this effort has been focused on the evaluation of derivatives of **1**. Early SAR studies showed that the carboxylic acid of **1** can be functionalized with groups that modulate the solubility and selectivity properties of the parent molecule without affecting substantially its bioactivity.^[52] For example, 2-ethoxyethyl-gambogamide (**111**)^[104] and glycine conjugate **112**^[105] exhibited comparable antitumor efficacy, but improved water solubility as compared with **1** (Scheme 18). More recently, studies with neurons showed that gambogic amide **113** can bind to and activate tyrosine kinase A (TrkA) by promoting its dimerization and auto-phosphorylation. Furthermore, this compound prevents neuronal cell death and provokes prominent neurotrophic activity.^[106] Under the same conditions, gambogic acid (**1**) fails to induce TrkA phosphorylation. The carboxylic acid has also been used for the incorporation of biotin and related probes, such as in compound **114**, in an effort to identify the cellular target of **1**.^[52]

Recent studies have shown that oxidation and/or epoxidation of the prenyl groups of **1** can lead to analogues with improved solubilities and cytotoxicities.^[107] On the other hand, the caged core of **1** is needed for bioactivity, since regular xanthenes display reduced cytotoxicities.^[108] More importantly, the α,β -unsaturated motif of **1** is critical to its bioactivity and metabolic stability. In fact, conjugate reduction or alkylation of the C9=C10 double bond, to form compounds **115** and **116**, respectively, decreased the cytotoxicity of the parent molecule by more than two orders of magnitude (Scheme 19).^[52] A similar decrease in activity has been recorded for compounds **24** and **117**.^[20c,33] These compounds have been identified upon prolonged storage (one week at room temperature) of **24** in methanol and ethanol, respectively. Moreover, the C10 hydroxygambogic acid (**118**) was identified as one of the main metabolites of **1** formed in vivo in rat bile.^[85] These findings indicate that **1** and related caged *Garcinia* xanthenes could exert their bioactivities by reacting in cells as conjugate electrophiles across the C9–C10 enone motif.

To evaluate whether the entire xanthone backbone of the caged natural products is essential to the bioactivity, the Theodorakis group synthesized several simplified analogues of the caged xanthone motif, containing progressively smaller fragments of the caged structure.^[53, 109] Representative examples of this effort are shown in Scheme 20. Comparison of the cytotoxicity values indicated that compound **119**, which contains the central caged xanthone structure but lacks the prenyl groups at the periphery of the A ring, maintains the bioactivity of **1** and related natural products. However, compounds **120**, **121**,

and **122**, containing further deletions of the xanthone backbone, have substantially decreased bioactivities. Similar observations have been made for compounds **123** and **124**.^[110]

Scheme 21 summarizes the SAR studies with **1**. The minimum pharmacophoric motif is represented by the red structure and includes the ABC tricyclic xanthone backbone and the C-ring caged structure. Functionalization at the periphery of this motif is not essential to bioactivity, but could be used to address issues related to solubility and target selectivity of the parent molecule.

An optimized synthesis of **119**, referred to as cluvenone, has been recently reported (Scheme 22).^[109] Xanthone **128** can be prepared by a Friedel–Crafts acylation of 2-fluorobenzoyl chloride (**125**) with pyrrogallol (**126**) followed a base-induced cyclization of the resulting benzophenone **127** (two steps, 34% combined yield). A new palladium-catalyzed reverse prenylation of **128** with 1,1-dimethylpropenyl *tert*-butyl carbonate formed compound **129**, which upon heating at 120 °C gave **119** in 81% yield together with small amounts of the neo isomer **130** (14%). The streamlined synthesis of this compound allows further preclinical investigation of this and related caged *Garcinia* xanthone analogues.

Summary and Outlook

Gamboge, the golden resin of certain *Garcinia* trees, has a spectacular history in the arts and sciences. Its use in traditional medicine led, in the recent years, to the discovery of a new family of natural products, collectively referred to as caged *Garcinia* xanthones. The chemical structure, biosynthesis, biology, and medicinal potential of these compounds are remarkable. Their chemical structure is represented by an unusual xanthone backbone in which the C ring has been converted to a 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (caged) scaffold. Their biosynthesis is proposed to involve a cascade of Claisen and Diels–Alder reactions and has provided the inspiration for the development of efficient laboratory syntheses of the parent molecules and designed analogues. Their biology is fascinating and complex. This is evident by the nearly one hundred recent publications describing just the biology of **1**, the most studied member of this family. The biology of other members of the *Garcinia* family remains largely unexplored. Preclinical and clinical studies with **1** and a few other family members are preliminary, but appear promising, in part due to their low toxicity. With many biological questions relating to mode-of-action as yet unanswered, interest in this family of natural products is likely to increase in the near future. It is conceivable that this family will enrich the armamentarium of anticancer medicines, such as podophyllotoxin and camptothecin, which originate from plant ethnomedicine. Along these lines, chemistry in conjunction with biology can generate analogues of these natural products with the desired pharmacological and clinical profile.

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References

1. a) Gustafsson MHG, Bittrich V, Stevens PF. *Int J Plant Sci.* 2002; 163:1045–1054. b) Sultanbawa MUS. *Tetrahedron.* 1980; 36:1465–1506.
2. Mabberley, DJ. *The Plant-book: A Portable Dictionary of the Vascular Plants.* 2. Cambridge University Press; New York: 1997. p. 293
3. Kumar P, Baslas RK. *Herba Hung.* 1980; 19:81–91.
4. Morton, JF. *Fruits of Warm Climates.* Dowling, CF., Jr, editor. Florida Flair Books; Miami: 1987. p. 301-304. Howes, FN. *Vegetable Gums and Resins.* Waltham, Mass: 1949. p. 161
5. Winter, J. *Artists' Pigments: A Handbook of their History and Characteristics.* Fitzhugh, EW., editor. Vol. 3. Oxford University Press; New York: 1997. p. 143-155.
6. For selected publications on this topic, see: a) Eremin K, Stenger J, Green ML. *J Raman Spectrosc.* 2006; 37:1119–1124.; b) Yamasaki K, Emoto Y. *Ars Orientalis.* 1979; 11:1–14.; c) Yamasaki K, Nishikawa K. *Stud Conserv.* 1970; 15:278–293.; d) Eremin K, Stenger J, Huang J-F, Aspuru-Guzik A, Betley T, Vogt L, Kassal I, Speakman S, Khandekar N. *J Raman Spectrosc.* 2008; 39:1057–1065.
7. Kuehn H. *Maltechnik-Restauro.* 1977; 83:223–233.
8. a) Perrin J. *Ann Chim Phys.* 1909; 18:1–114. b) Perrin J. *Compt Rend.* 1909; 147:530–532. c) Oseen, CW. [12.28.2009] Nobel Prize in Physics, **1926**—Presentation Speech. http://nobelprize.org/nobel_prizes/physics/laureates/1926/press.html
9. For selected reviews on this topic, see: a) Sousa ME, Pinto MMM. *Curr Med Chem.* 2005; 12:2447–2479. [PubMed: 16250872] ; b) Pouli N, Marakos P. *Anti-Cancer Agents Med Chem.* 2009; 9:77–98.; c) Han Q-B, Xu H-X. *Curr Med Chem.* 2009; 16:3775–3796. [PubMed: 19747141] ; Xu H-X. *Curr Med Chem.* 2009; 16:3775–3796. [PubMed: 19747141] ; d) El-Seedi HR, El-Ghorab DMH, El-Barbary MA, Zayed MF, Goransson U, Larsson S, Verpoorte R. *Curr Med Chem.* 2009; 16:2581–2626. [PubMed: 19601799]
10. Yates P, Karmarkar SS, Rosenthal D, Stout GH, Stout VF. *Tetrahedron Lett.* 1963; 4:1623–1629.. According to the authors, acetyl gambogic acid was initially reported by Furrer M. Dissertation. University of Basel (Switzerland)1934
11. a) Anthony A, Desiraju GR. *Supramol Chem.* 2001; 13:11–23. b) Weakley TJR, Cai SX, Zhang H-Z, Keana JFW. *J Chem Crystallogr.* 2001; 31:501–505.
12. Rao BS. *J Chem Soc.* 1937:853–855.
13. Kartha G, Ramachandran GN, Bhat HB, Nair PM, Raghavan VKV, Venkataraman K. *Tetrahedron Lett.* 1963; 4:459–472.. Previous efforts to determine the chemical structure of morellin led to incomplete structural assignments: a) Kartha G. *Curr Sci.* 1954; 23:8.; b) Rao RVGS, Padmanabhan VM, Kartha G. *Curr Sci.* 1954; 23:216.; c) Krishna Murthy DV, Rao PLN. *Experientia.* 1961; 17:445–446.; d) Dayal B, Mathur BSC. *Acta Crystallogr.* 1960; 13:269.; e) Rao PLN, Murthy DVK, Verma SCL. *Naturwissenschaften.* 1954; 41:66–67.
14. a) Ollis WD, Ramsay MVJ, Sutherland IO, Mongolsuk S. *Tetrahedron.* 1965; 21:1453–1470. b) Ahmad SA, Rigby W, Taylor RB. *J Chem Soc C.* 1966:772–779.
15. Leong YW, Harrison LJ, Bennett GJ, Tan HTW. *J Chem Res Synop.* 1996:392–393.
16. a) Wang LL, Li ZL, Xu YP, Liu XQ, Pei YH, Jing YK, Hua HM. *Chin Chem Lett.* 2008; 19:1221–1223. Xu YP, Liu XQ, Pei YH, Jing YK, Hua HM. *Chin Chem Lett.* 2008; 19:1221–1223. b) Li S-L, Song J-Z, Han Q-B, Qiao C-F, Xu H-X. *Biomed Chromatogr.* 2008; 22:637–644. [PubMed: 18254140]
17. a) Cao SG, Sng VHL, Wu XH, Sim KY, Tan BHK, Pereira JT, Goh SH. *Tetrahedron.* 1998; 54:10915–10924. b) Cao SG, Wu XH, Sim KY, Tan BKH, Pereira JT, Wong WH, Hew NF, Goh SH. *Tetrahedron Lett.* 1998; 39:3353–3356. c) Xu YJ, Yip SC, Kosela S, Fitri E, Hana M, Goh SH, Sim KY. *Org Lett.* 2000; 2:3945–3948. [PubMed: 11101460] d) Wu XH, Tan BKH, Cao SG, Sim KY, Goh SH. *Nat Prod Lett.* 2000; 12:453–458.
18. Han Q-B, Wang YL, Yang L, Tso TF, Qiao C-F, Song JZ, Xu LJ, Chen SL, Yang DJ, Xu HX. *Chem Pharm Bull.* 2006; 54:265–267. [PubMed: 16462081]
19. a) Venkataraman K. *Proc Indian Nat Sci Acad Part A.* 1974; 39:365–381. b) Adawadkar PD, Srinivasan R, Yemul SS. *Indian J Chem Sect B.* 1976; 14:19–21. c) Feng F, Liu WY, Chen YS,

- Guo QL, You QD. *J Asian Nat Prod Res.* 2007; 9:735–741. [PubMed: 17994391] d) Karanjaonkar CG, Nair PM, Venkataraman K. *Tetrahedron Lett.* 1966; 7:687–691.e) Yemul SS, Rama Rao AV. *Org Mass Spectrom.* 1974; 9:1063–1072.
20. a) Bhat HB, Nair PM, Venkataraman K. *Indian J Chem.* 1964; 2:405–410.b) Reutrakul V, Anantachoke N, Pohmakot M, Jaipetch T, Sophasan S, Yoosook C, Kasisit J, Napaswat C, Santisuk T, Tuchinda P. *Planta Med.* 2007; 73:33–40. [PubMed: 17117343] c) Tao S-J, Guan SH, Wang W, Lu Z-Q, Chen GT, Sha N, Yue Q-X, Liu X, Guo DA. *J Nat Prod.* 2009; 72:117–124. [PubMed: 19072548]
21. Sukpondma Y, Rukachaisirikul V, Phongpaichit S. *Chem Pharm Bull.* 2005; 53:850–852. [PubMed: 15997152]
22. a) Rao PLN, Verma SCL, Murthy DVK. *Curr Sci.* 1951; 20:234.b) Nair PM, Venkataraman K. *Indian J Chem.* 1964; 2:402–404.
23. Lin L-J, Lin LZ, Pezzuto JM, Cordell GA, Ruangrunsi N. *Magn Reson Chem.* 1993; 31:340–347.
24. Asano J, Chiba K, Tada M, Yoshii T. *Phytochemistry.* 1996; 41:815–820. [PubMed: 8835458]
25. a) Thoison O, Fahy J, Dumontet V, Chiaroni A, Riche C, Tri MV, Sevenet T. *J Nat Prod.* 2000; 63:441–446. [PubMed: 10785410] b) Thoison O, Cuong DD, Gramain A, Chiaroni A, Hung NV, Sevenet T. *Tetrahedron.* 2005; 61:8529–8535.
26. Shadida KA, Shaari K, Abas F, Israf DA, Hamzah AS, Syakroni N, Saha K, Lajis NH. *Phytochemistry.* 2007; 68:2537–2544. [PubMed: 17602714]
27. a) Rukachaisirikul V, Kaewnok W, Koysomboon S, Phongpaichit S, Taylor WC. *Tetrahedron.* 2000; 56:8539–8543.b) Sukpondma Y, Rukachaisirikul V, Phongpaichit S. *J Nat Prod.* 2005; 68:1010–1017. [PubMed: 16038540] c) Rukachaisirikul V, Phainuphong P, Sukpondma Y, Phongpaichit S, Taylor SWC. *Planta Med.* 2005; 71:165–170. [PubMed: 15729626]
28. Rukachaisirikul V, Painuphong P, Sukpondma Y, Koysomboon S, Sawangchote P, Taylor WC. *J Nat Prod.* 2003; 66:933–938. [PubMed: 12880309]
29. Mahabusarakam W, Nuangnaowarat W, Taylor WC. *Phytochemistry.* 2006; 67:470–474. [PubMed: 16310231]
30. Kosela S, Cao SG, Wu X-H, Vittal JJ, Sukri T, Masdianto, Goh S-H, Kim K-Y. *Tetrahedron Lett.* 1999; 40:157–160.
31. Wu J, Xu YJ, Cheng XF, Harrison LJ, Sim KY, Goh SH. *Tetrahedron Lett.* 2001; 42:727–729.
32. a) Hunt BJ, Rigby W. *J Chem Soc C.* 1970:2459–2462.b) Rao DR, Gurudutt KN, Mamatha S, Rao LJM. *Magn Reson Chem.* 2007; 45:578–582. [PubMed: 17534879]
33. Han QB, Cheung S, Tai J, Qiao CF, Song JZ, Xu HX. *Biol Pharm Bull.* 2005; 28:2335–2337. [PubMed: 16327177]
34. a) Rao GSRS, Rathnamala S, Sivaramakrishnan R. *Proc Indian Acad Sci Sect A.* 1978; 87:75–86.b) Rao GSRS, Mala SR, Surendranath V, Gupta VS, Rao PLN. *Tetrahedron Lett.* 1974; 15:1259–1262.
35. a) Han QB, Song JZ, Qiao JZ, Wong L, Xu HX. *J Chromatogr A.* 2006; 1127:298–301. [PubMed: 16887130] b) Cardillo G, Merlini L. *Tetrahedron Lett.* 1967; 8:2529–2530.
36. Han Q, Yang L, Liu Y, Wang Y, Qiao C, Song J, Xu L, Yang D, Chen S, Xu H. *Planta Med.* 2006; 72:281–284. [PubMed: 16534739]
37. a) Zhou Y, Liu X, Yang J, Han Q-B, Song J-Z, Li S-L, Qiao C-F, Ding L-S, Xu H-X. *Anal Chim Acta.* 2008; 629:104–118. [PubMed: 18940327] b) Han Q-B, Zhou Y, Feng C, Xu G, Huang S-X, Li S-L, Qiao C-F, Song J-Z, Chang DC, Luo KQ, Xu H-X. *J Chromatogr B.* 2009; 877:401–407.
38. For selected reviews and monographs on this topic, see: a) Dewick PM. *Nat Prod Rep.* 1998; 15:17–58. [PubMed: 9493397] ; b) Knaggs AR. *Nat Prod Rep.* 2003; 20:119–136. [PubMed: 12636087] ; c) Herrmann KM, Weaver LM. *Annu Rev Plant Physiol Plant Mol Biol.* 1999; 50:473–503. [PubMed: 15012217] ; d) Beerhues L, Liu B. *Phytochemistry.* 2009; 70:1719–1727. [PubMed: 19699497] ; e) Dewick PM, P M. *Medicinal Natural Products: a Biosynthetic Approach (2).* WileyNew York 2002:121–164.; f) Gottlieb OR. *Phytochemistry.* 1968; 7:411–421.
39. a) Birch AJ, Baldas J, Hlubucek JR, Simpson TJ, Westerman PW. *J Chem Soc Perkin Trans.* 1976; 1:898–904.b) Holker JSE, Lapper RD, Simpson TJ. *J Chem Soc Perkin Trans.* 1974; 1:2135–2140.c) Hill JG, Nakashima TT, Vederas JC. *J Am Chem Soc.* 1982; 104:1745–1748.

40. a) Locksley HD, Moore I, Scheinmann F. *Tetrahedron*. 1967; 23:2229–2234. b) Carpenter I, Locksley HD, Scheinmann F. *Phytochemistry*. 1969; 8:2013–2025. c) Bennett GJ, Lee HH. *J Chem Soc Chem Commun*. 1988:619–620. d) Bennett GJ, Lee HH, Das N. *J Chem Soc Perkin Trans*. 1990; 1:2671–2676.
41. Quillinan AJ, Scheinmann F. *J Chem Soc Chem Commun*. 1971:966–967.
42. a) Jackson B, Locksley HD, Scheinmann F. *J Chem Soc C*. 1967:785–796. b) Jefferson A, Scheinmann F. *Q Rev Chem Soc*. 1968; 22:391–420. c) Locksley HD, Quillinan AJ, Scheinmann F. *J Chem Soc C*. 1971:3804–3814.
43. Nicolaou KC, Li J. *Angew Chem*. 2001; 113:4394–4398. *Angew Chem Int Ed*. 2001; 40:4264–4268.
44. Tisdale EJ, Slobodov I, Theodorakis EA. *Proc Natl Acad Sci USA*. 2004; 101:12030–12035. [PubMed: 15210986]
45. a) *Dictionary of Chinese Traditional Medicines*. Shanghai Scientific and Technical Publishers; Shanghai: 1977. p. 3805–3807. b) the anticancer gamboge research team. *Jiangxi Med J*. 1982; 17:1–5.
46. a) Panthong A, Norkaew P, Kanjanapothi D, Taesotikul T, Anantachoke N, Reutrakul V. *J Ethnopharmacol*. 2007; 111:335–340. [PubMed: 17360136] b) Evan, WC. *Trease and Evans Pharmacognosy*. 14. Saunders Company Limited; Nottingham: 1996. p. 290
47. a) Rao PLN, Verma SCL. *J Scient Ind Res*. 1951; 10B:184–185. b) Gupta VS, Rao AVSP, Rao PLN. *Ind J Exper Biol*. 1963; 1:146–147. c) Sani BP, Rao PLN. *Ind J Exper Biol*. 1966; 4:27–28. d) Santhaman K, Rao PLN. *Ind J Exper Biol*. 1968; 6:158–159. e) Puttanna CR, Rao PLN. *Ind J Exper Biol*. 1968; 6:150–152.
48. In the early chemical literature, *Garcinia* natural products were commonly named as guttiferins and **1** was also known as β -guttiferin; for selected references on this issue, see: a) Gupta VS, Rao PLN, Vaidya SN, Ramaseshan S. *Chem Ind*. 1962:1469–1470.; b) Rao KVN, Rao PLN. *Experientia*. 1961; 17:213–214. [PubMed: 13727450]
49. a) Santhanam K, Rao PLN. *Ind J Exper Biol*. 1969; 7:34–36. b) Sani BP, Rao PLN. *Ind J Chem*. 1969; 7:680–684. c) Verma SCL, Rao PLN. *Ind J Exper Biol*. 1967; 5:106–109. d) Rao DR, Gupta TR, Gupta VS, Rao KVN, Rao PLN. *Ind J Chem*. 1963; 1:276–277.
50. a) Rao KVN, Rao PLN. *Ind J Exper Biol*. 1967; 5:101–105. b) Rao KVN, Rao PLN. *Ind J Exper Biol*. 1967; 5:96–100.
51. Khalid RM, Jabit ML, Abas F, Stanslas J, Shaari K, Lajis NH. *Nat Prod Commun*. 2007; 2:271–276.
52. Zhang H-Z, Kasibhatla S, Wang Y, Herich J, Guastella J, Tseng B, Drewe J, Cai S-X. *Bioorg Med Chem*. 2004; 12:309–317. [PubMed: 14723951]
53. Batova A, Lam T, Wascholowski V, Yu AL, Giannis A, Theodorakis EA. *Org Biomol Chem*. 2007; 5:494–500. [PubMed: 17252132]
54. Wu X, Cao S, Goh S, Hsu A, Tan BKH. *Planta Med*. 2002; 68:198–203. [PubMed: 11914953]
55. For selected reviews, see: a) La Porta CAM. *Curr Med Chem*. 2007; 14:387–391. [PubMed: 17305541] ; b) Larsen AK, Escargueil AE, Skladanowski A. *Pharmacol Ther*. 2000; 85:217–229. [PubMed: 10739876]
56. For selected reviews, see: a) Earnshaw WC, Martins LM, Kaufmann SH. *Annu Rev Biochem*. 1999; 68:383–424. [PubMed: 10872455] ; b) Thornberry NA, Lazebnic Y. *Science*. 1998; 281:1312–1316. [PubMed: 9721091] ; c) Taylor RC, Cullen SP, Martin SJ. *Nat Rev Mol Cell Biol*. 2008; 9:231–241. [PubMed: 18073771] ; d) Hanahan D, Weinberg RA. *Cell*. 2000; 100:57–70. [PubMed: 10647931] ; e) Porter AG, Janicke RU. *Cell Death Differ*. 1999; 6:99–104. [PubMed: 10200555]
57. Zhao L, Guo QL, You QD, Wu ZQ, Gu HY. *Biol Pharm Bull*. 2004; 27:998–1003. [PubMed: 15256729]
58. For selected reviews on this topic, see: a) Yip KW, Reed JC. *Oncogene*. 2008; 27:6398–6406. [PubMed: 18955968] ; b) Reed JC, Pellecchia M. *Blood*. 2005; 106:408–418. [PubMed: 15797997] ; c) Cory S, Adams JM. *Nat Rev Cancer*. 2002; 2:647–656. [PubMed: 12209154] ; d) Reed JC. *Cancer Cell*. 2003; 3:17–22. [PubMed: 12559172] ; e) Kroemer G, Reed JC. *Nat Med*.

- 2000; 6:513–519. [PubMed: 10802706] ; f) Gupta S, Kass GEN, Svegezd E, Joseph B. *J Cell Mol Med.* 2009; 13:1004–1033. [PubMed: 19220575]
59. For selected reviews on the therapeutic value of Bcl-2 inhibitors, see: a) Doshi JM, Xing C. *Mini-Rev Org Chem.* 2008; 5:171–178.; b) Zhai D, Jin C, Satterthwait AC, Reed JC. *Cell Death Differ.* 2006; 13:1419–1421. [PubMed: 16645636] ; c) Vogler M, Dinsdale D, Dyer MJS, Cohen GM. *Cell Death Differ.* 2009; 16:360–367. [PubMed: 18806758]
60. a) Liu W, Guo QL, You QD, Zhao L, Gu HY, Yuan ST. *World J Gastroenterol.* 2005; 11:3655–3659. [PubMed: 15968715] b) Gu HY, Rao SY, Zhao J, Wang J, Mu R, Rong JJ, Tao L, Qi Q, You QD, Guo QL. *J Cancer Res Clin Oncol.* 2009; 135:1777–1782. [PubMed: 19582475]
61. Xu X, Liu Y, Wang L, He J, Zhang H, Chen X, Li Y, Yang J, Tao J. *Int J Dermatol.* 2009; 48:186–192. [PubMed: 19200201]
62. Zhai D, Jin C, Shiao C-W, Kitada S, Satterthwait AC, Reed JC. *Mol Cancer Ther.* 2008; 7:1639–1646. [PubMed: 18566235]
63. a) Gu H, Wang X, Rao S, Wang J, Zhao J, Ren FL, Mu R, Yang Y, Qi Q, Liu W, Lu N, Ling H, You Q, Guo Q. *Mol Cancer Ther.* 2008; 7:3298–3305. [PubMed: 18852133] b) Rong JJ, Hu R, Qi Q, Gu HY, Zhao Q, Wang J, Mu R, You QD, Guo QL. *Cancer Lett.* 2009; 284:102–112. [PubMed: 19428175] c) Gu HY, Guo QL, You QD, Liu W, Qi Q, Zhao L, Yuan ST, Zhang K. *Chin J Nat Med.* 2005; 3:168–172.
64. a) Wu ZQ, Guo QL, You QD, Zhao L, Gu HY. *Biol Pharm Bull.* 2004; 27:1769–1774. [PubMed: 15516720] b) Yu J, Guo Q-L, You Q-D, Lin S-S, Li Z, Gu H-Y, Zhang H-W, Tan Z, Wang X. *Cancer Chemother Pharmacol.* 2006; 58:434–443. [PubMed: 16470410] c) Zhao Q, Yang Y, Yu J, You QD, Zeng S, Gu HY, Lu N, Qi Q, Liu W, Wang XT, Guo QL. *Cancer Lett.* 2008; 262:223–231. [PubMed: 18226852] d) Guo QL, Lin SS, You QD, Yu J, Zhao L, Qi Q, Liang F, Tan Z, Wang XT. *Life Sci.* 2006; 78:1238–1245. [PubMed: 16257012] e) Chen J, Gu H-Y, Lu N, Yang Y, Liu W, Qi Q, Rong J-J, Wang X-T, You Q-D, Guo Q-L. *Life Sci.* 2008; 83:103–109. [PubMed: 18586278] f) Qin Y, Meng L, Hu C, Duan W, Zuo Z, Lin L, Zhang X, Ding J. *Mol Cancer Ther.* 2007; 6:2429–2440. [PubMed: 17876042] g) Yu J, Guo Q-L, You Q-D, Zhao L, Gu H-Y, Yang Y, Zhang H-w, Tan Z, Wang X. *Carcinogenesis.* 2006; 28:632–638. [PubMed: 17012222]
65. Wang X, Chen Y, Han Q-b, Chan C-y, Wang H, Liu Z, Cheng CH-k, Yew DT, Lin MCM, He M-l, Xu H-x, Sung JJY, Kung H-f. *Proteomics.* 2009; 9:242–253. [PubMed: 19086098]
66. a) Li R, Chen Y, Shu WX, Zhao F, Liu Y, Wen L. *Chin J Cancer Res.* 2009; 21:68–73. b) Li R, Chen Y, Zeng L-I, Shu W-x, Zhao F, Wen L, Liu Y. *Toxicology.* 2009; 262:98–105. [PubMed: 19433130]
67. a) Shu W-X, Chen Y, Li R, Wu Q, Cui G, Ke W, Chen Z. *Basic Clin Pharmacol Toxicol.* 2008; 103:530–537. [PubMed: 19067680] b) Shu WX, Chen Y, He J. *Chin J Oncol.* 2008; 30:484–489.
68. a) Qi Q, Gu HY, Yang Y, Lu N, Zhao J, Liu W, Ling H, You QD, Wang XT, Guo QL. *J Mol Med.* 2008; 86:1367–1377. [PubMed: 18777017] b) Qi Q, Lu N, Wang XT, Gu HY, Yang Y, Liu W, Li CL, You QD, Guo QL. *Biochem Cell Biol.* 2008; 86:386–395. [PubMed: 18923540]
69. Zhao J, Qi Q, Yang Y, Gu HY, Lu N, Liu W, Wang W, Qiang L, Zhang LB, You QD, Guo QL. *Eur J Pharmacol.* 2008; 589:127–131. [PubMed: 18539272]
70. a) Yi T, Yi Z, Cho S-G, Luo J, Pandley MK, Aggarwal BB, Liu M. *Cancer Res.* 2008; 68:1843–1850. [PubMed: 18339865] b) Lu N, Yang Y, You QD, Ling Y, Gao Y, Gu H-Y, Zhao L, Wang X-T, Guo Q-L. *Cancer Lett.* 2007; 258:80–89. [PubMed: 17920764]
71. Wang T, Wei J, Qian X, Ding Y, Yu L, Liu B. *Cancer Lett.* 2008; 262:214–222. [PubMed: 18248784]
72. Wang J, Liu W, Zhao Q, Qi Q, Lu N, Yang Y, Nei F-F, Rong J-J, You QD, Guo QL. *Toxicology.* 2009; 256:135–140. [PubMed: 19084572]
73. For selected reviews on the role of Tfr-1 in cancer, see: a) Aisen P. *Int J Biochem Cell Biol.* 2004; 36:2137–2143. [PubMed: 15313461] ; b) Prutki M, Poljak-Blazi M, Jakopovic M, Tomas D, Stipancic I, Zarkovic N. *Cancer Lett.* 2006; 238:188–196. [PubMed: 16111806] ; c) Ryschich E, Huszty G, Knaebel HP, Hartel M, Buechler MW, Schmidt J. *Eur J Cancer.* 2004; 40:1418–1422. [PubMed: 15177502]

74. Kasibhatla S, Jessen KA, Maliartchouk S, Wang JY, English NM, Drewe J, Qiu L, Archer SP, Ponce AE, Sirisoma N, Jiang S, Zhang H-Z, Gehlsen KR, Cai SX, Green DR, Tsang B. *Proc Natl Acad Sci USA*. 2005; 102:12095–12100. [PubMed: 16103367]
75. a) Pandey MK, Sung B, Ahn KS, Kunnumakkara AB, Chaturvedi MM, Aggarwal BB. *Blood*. 2007; 110:3517–3525. [PubMed: 17673602] b) Zhu XL, Zhang HM, Lin Y, Chen PS, Min J, Wang ZZ, Xiao W, Chen BA. *J Chemother*. 2009; 21:666–672. [PubMed: 20071291]
76. a) Wang Y, Chen Y, Chen Z, Wu Q, Ke WJ, Wu QL. *Acta Phamacol Sin*. 2008; 29:349–354. b) Palempalli UD, Gandhi U, Kalantari P, Vunta H, Arner RJ, Narayan V, Ravindran A, Prabhu KS. *Biochem J*. 2009; 419:401–409. [PubMed: 19140805]
77. Ortiz-Sanchez E, Daniels TR, Helguera G, Martinez-Maza O, Bonavida B, Penichet ML. *Leukemia*. 2009; 23:59–70. [PubMed: 18946492]
78. Nie F, Zhang X, Qi Q, Yang L, Yang Y, Liu W, Lu N, Wu Z, You Q, Guo Q. *Toxicology*. 2009; 260:60–67. [PubMed: 19464570]
79. Qiang L, Yang Y, You Q-D, Ma Y-J, Yang L, Nie F-F, Gu H-Y, Zhao L, Lu N, Qi Q, Liu W, Wang X-T, Guo Q-L. *Biochem Pharmacol*. 2008; 75:1083–1092. [PubMed: 18070617]
80. a) Yang Y, Yang L, You QD, Nie FF, Gu HY, Zhao L, Wang XT, Guo QL. *Cancer Lett*. 2007; 256:259–266. [PubMed: 17693016] b) Guo Q-L, You Q-D, Wu Z-Q, Yuan S-T, Zhao L. *Acta Pharmacol Sin*. 2004; 25:769–774. [PubMed: 15169630] c) Gu H, You Q, Liu W, Yang Y, Zhao L, Qi Q, Zhao J, Wang J, Lu N, Ling H, Guo Q, Wang X. *Intern Immunopharmacol*. 2008; 8:1493–1502.
81. a) Guo Q, Qi Q, Gu H, Wu Z. *Basic Clin Pharmacol Toxicol*. 2006; 99:178–184. [PubMed: 16918721] b) Hao K, Zhao XP, Liu XQ, Wang GJ. *Biomed Chromatogr*. 2007; 21:279–283. [PubMed: 17221914]
82. Qi Q, You Q, Gu H, Zhao L, Liu WL, Lu N, Guo QL. *J Ethnopharmacol*. 2008; 117:433–438. [PubMed: 18384990]
83. Zhao L, Zhen C, Wu Z, Hu R, Zhou C, Guo Q. *Drug Chem Toxicol*. 2010; 33:88–96. [PubMed: 20001662]
84. Hao K, Liu XQ, Wang GJ, Zhao XP. *Eur J Drug Metab Pharmacokinet*. 2007; 32:63–68. [PubMed: 17702192]
85. a) Liu Y-T, Hao K, Liu X-Q, Wang G-J. *Acta Pharmacol Sin*. 2006; 27:1253–1258. [PubMed: 16923348] b) Feng F, Liu W, Wang Y, Guo Q, You Q. *J Chromatogr B*. 2007; 860:218–226. c) Ding L, Huang D, Wang JW, Li ST. *J Chromatogr B*. 2007; 846:112–118. d) Yang J, Ding L, Jin SH, Liu XX, Liu WY, Wang ZZ. *J Chromatogr B*. 2010; 878:659–666.
86. a) Qu G, Zhu X, Zhang C, Ping Q. *Drug Delivery*. 2009; 16:363–370. [PubMed: 19575591] b) Zhu X, Zhang C, Wu XL, Tang XY, Ping QN. *Drug Dev Ind Pharm*. 2008; 34:2–9. [PubMed: 18214750]
87. Zhou ZT, Wang JW. *Chin J New Drugs*. 2007; 16:79–82.
88. a) Wessely F, Lauterbach-Keil G, Sinwel F. *Monatsh Chem*. 1950; 81:811–818. b) Wessely F, Sinwel F. *Monatsh Chem*. 1950; 81:1055–1070. c) Wessely F, Kotlan J, Sinwel F. *Monatsh Chem*. 1952; 83:902–914. d) Metlesics W, Wessely F, Budzikiewicz H. *Monatsh Chem*. 1958; 89:102–109.
89. Bhamare NK, Granger T, John CR, Yates P. *Tetrahedron Lett*. 1991; 32:4439–4442.
90. Bichan DJ, Yates P. *J Am Chem Soc*. 1972; 94:4773–4774.
91. Tisdale EJ, Chowdhury C, Vong BG, Li H, Theodorakis EA. *Org Lett*. 2002; 4:909–912. [PubMed: 11893183]
92. Mehta G, Maity P. *Tetrahedron Lett*. 2008; 49:318–322.
93. Nicolaou KC, Sasmal PK, Xu H, Namoto K, Ritzen A. *Angew Chem*. 2003; 115:4357–4361. *Angew Chem Int Ed*. 2003; 42:4225–4229.
94. Tisdale EJ, Li H, Vong BG, Kim SH, Theodorakis EA. *Org Lett*. 2003; 5:1491–1494. [PubMed: 12713306]
95. Tisdale EJ, Slobodov I, Theodorakis EA. *Org Biomol Chem*. 2003; 1:4418–4422. [PubMed: 14727628]
96. Li NG, Wang J-J, Liu X-R, Lin C-J, You Q-D, Guo Q-L. *Tetrahedron Lett*. 2007; 48:6586–6589.

97. Nicolaou KC, Xu H, Wartmann M. *Angew Chem.* 2005; 117:766–771. *Angew Chem Int Ed.* 2005; 44:756–761.
98. For selected accounts on this topic, see: a) Gajewski JJ. *Acc Chem Res.* 1980; 13:142–148.; b) Ganem B. *Angew Chem.* 1996; 108:1014–1023.; *Angew Chem Int Ed Engl.* 1996; 35:936–945.; c) Severance DL, Jorgensen WL. *J Am Chem Soc.* 1992; 114:10966–10968.; d) Gajewski JJ. *Acc Chem Res.* 1997; 30:219–225.
99. For a review of hydrophobic effects, see: Tanford C. *The Hydrophobic Effect (2)*. WileyNew York 1980
100. For selected accounts on Diels–Alder reactions accelerated in water, see: a) Breslow R. *Acc Chem Res.* 2004; 37:471–478. [PubMed: 15260509] ; b) Lindstroem U. *Chem Rev.* 2002; 102:2751–2771. [PubMed: 12175267] ; c) Grieco PA, Kaufman MD. *J Org Chem.* 1999; 64:6041–6048.
101. Hayden AE, Xu H, Nicolaou KC, Houk KN. *Org Lett.* 2006; 8:2989–2992. [PubMed: 16805534]
102. Tisdale EJ, Vong BG, Li H, Kim SH, Chowdhury C, Theodorakis EA. *Tetrahedron.* 2003; 59:6873–6887.
103. Nicolaou KC, Sasmal PK, Xu H. *J Am Chem Soc.* 2004; 126:5493–5501. [PubMed: 15113221]
104. Tao Z, Zhou Y, Lu J, Duan W, Qin Y, He X, Lin L, Ding J. *Cancer Biol Ther.* 2007; 6:691–696. [PubMed: 17426447]
105. Xie H, Qin Y-X, Zhou Y-L, Tong L-J, Lin L-P, Geng M-Y, Duan W-H, Ding J. *Acta Pharmacol Sin.* 2009; 30:346–354. [PubMed: 19262558]
106. Jang S-W, Okada M, Sayeed I, Xiao G, Stein D, Jin P, Ye K. *Proc Natl Acad Sci USA.* 2007; 104:16329–16334. [PubMed: 17911251]
107. a) Wang J, Zhao L, Hu Y, Guo Q, Zhang L, Wang X, Li N, You Q. *Eur J Med Chem.* 2009; 44:2611–2620. [PubMed: 18996626] b) Mu R, Lu N, Wang J, Yin YH, Ding Y, Zhang XX, Gui H, Sun Q, Duan HQ, Zhang L, Zhang YC, Ke X, Guo QL. *Eur J Cancer Prev.* 2010; 19:61–67. [PubMed: 19934761] c) Li QL, Cheng H, Zhu GQ, Yang L, Zhou A, Wang XS, Fang NB, Xia LZ, Su JJ, Wang M, Peng DY, Xu Q. *Biol Pharm Bull.* 2010; 33:415–420. [PubMed: 20190402]
108. a) Li NG, You QD, Huang XF, Wang JX, Guo QL, Chen XG, Li Y, Li HY. *Chin Chem Lett.* 2007; 18:659–662. b) Han QB, Yang NY, Tian HL, Qiao C-F, Song J-Z, Chang DC, Chen S-L, Luo KQ, Xu H-X. *Phytochemistry.* 2008; 69:2187–2192. [PubMed: 18614188] c) Sousa EP, Silva AMS, Pinto MMM, Pedro MM, Cerqueira FAM, Nascimento MSJ. *Helv Chim Acta.* 2002; 85:2862–2876.
109. Chantarasriwong O, Cho WC, Batova A, Chavasiri W, Moore C, Rheingold AL, Theodorakis EA. *Org Biomol Chem.* 2009; 7:4886–4894. [PubMed: 19907779]
110. Kuemmerle J, Jiang S, Tseng B, Kasibhatla S, Drewe J, Cai SX. *Bioorg Med Chem.* 2008; 16:4233–4241. [PubMed: 18337106]

Biographies



Oraphin Chantarasriwong earned her B.Sc. and M.Sc. in chemistry from Chulalongkorn University in 2006, working with Professor Warinthorn Chavasiri. She is currently pursuing a Ph.D. in organic chemistry under the direction of Professor Warinthorn Chavasiri and Professor Emmanuel A. Theodorakis at Chulalongkorn University (Royal Golden Jubilee Ph.D. Fellowship). Her research interests include synthetic organic chemistry and the

development of new synthetic methods and the construction of pharmaceutically important compounds.



Ayse Batova received a B.A. in Chemistry from the College of Wooster (Wooster, OH). She obtained a Ph.D. in 1991 in Biochemistry from the University of South Carolina working on the mechanisms of growth inhibition by retinoic acid in human keratinocytes. Dr. Batova did post-doctoral work at Telios Pharmaceuticals in San Diego, and at the University of California, San Diego (UCSD) where she studied the molecular biology of leukemia and neuroblastoma and investigated novel molecularly targeted therapeutics. She is currently a member of the faculty at UCSD in the department of Pediatrics. Her research focuses on the discovery and development of natural products and analogues as cancer therapeutics.



Warinthorn Chavasiri received his B.Sc. and M.Sc. in chemistry from Chulalongkorn University under the supervision of Professor Udom Kokpol. After that he pursued his Ph.D. in chemistry at Texas A&M University under the supervision of Sir Derek H.R. Barton. Since 1993, he has joined the chemistry department at Chulalongkorn University. His research focuses on the methodologies in organic synthesis, metal organic chemistry, natural product chemistry, and chemical ecology.

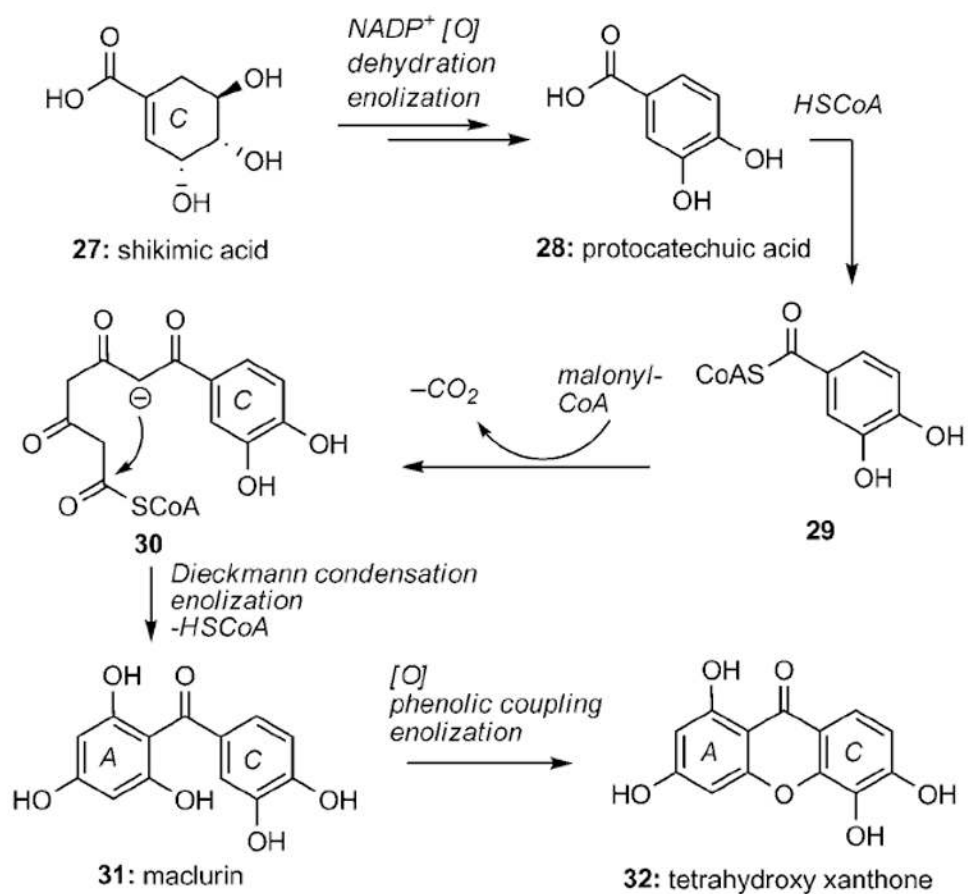


Emmanuel A. Theodorakis received his B.S. Degree in Chemistry from the University of Athens and his M.S. Degree (D.E.A.) and Ph.D. Degree in Organic Chemistry from Paris XI University (France). His M.S. studies were performed at the Institute of Chemistry of Natural Products (ICSN-CNRS) under the direction of Professor H.-P. Husson, while his Ph.D. studies were performed at Texas A&M University under the direction of Sir Derek H. R. Barton. Following a postdoctoral appointment at TSRI in the laboratories of Professor K.

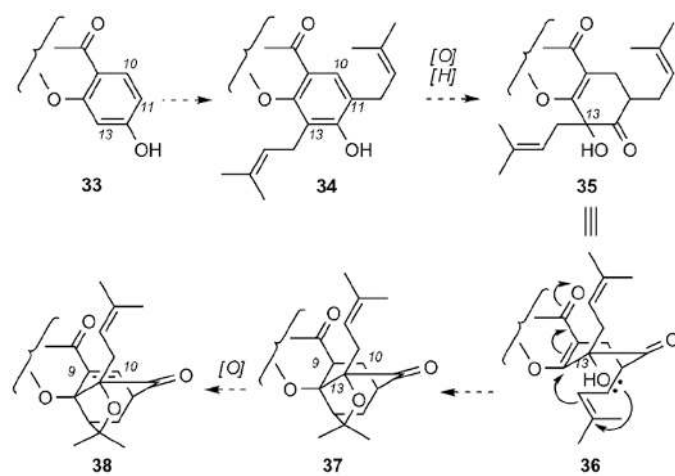
C. Nicolaou, in 1995 he joined the faculty at UCSD. His research focuses on the synthesis and bioorganic studies of natural products and designed small molecules with biological and medicinal interest.



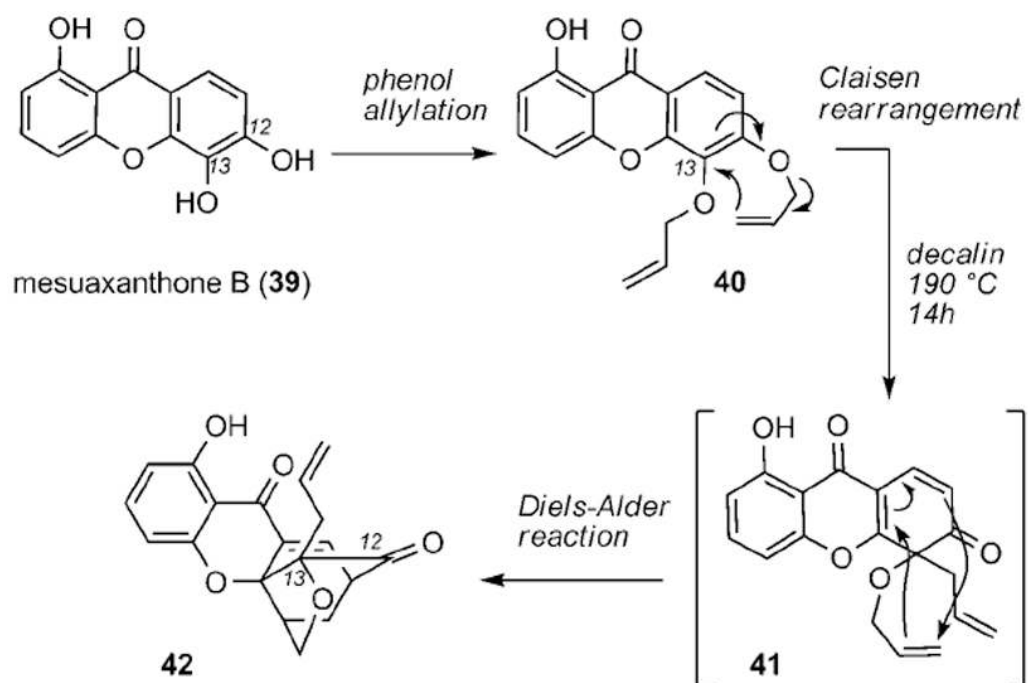
Figure 1.
a) *Garcinia mangostana*; b) mangosteen; c) gamboge and gambogic acid; and d) an extract from a Japanese painting in which gamboge was used as the yellow colorant.

**Scheme 1.**

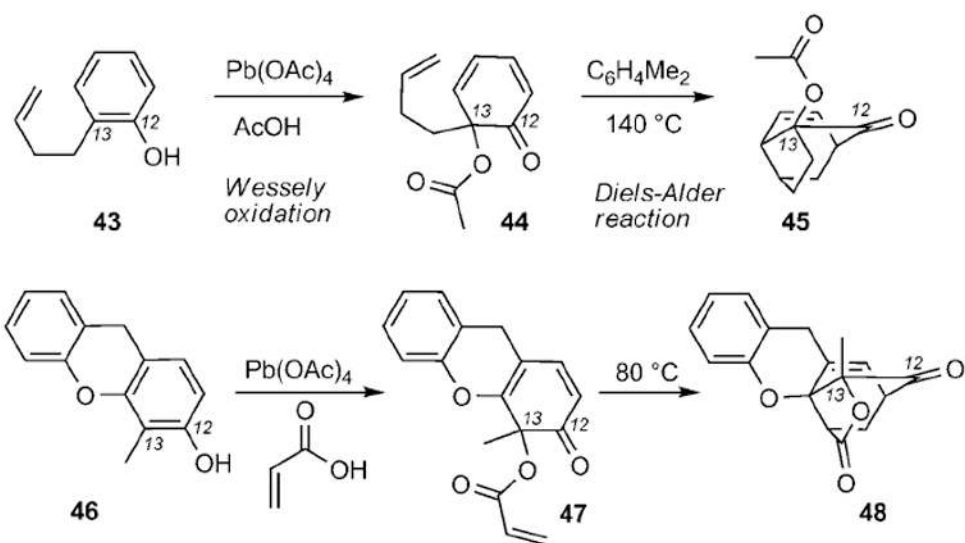
Proposed biosynthesis of benzophenones and xanthenes in higher plants. NADP^+ = Nicotinamide adenine dinucleotide phosphate.



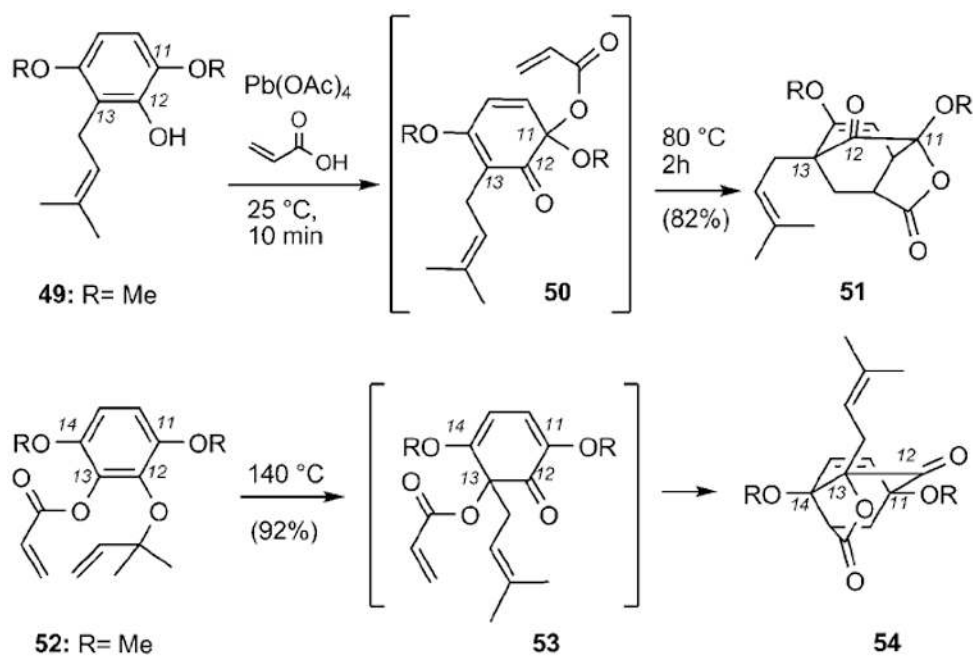
Scheme 2.
Proposed biosynthesis of the caged xanthone motif through a cascade of nucleophilic attacks.



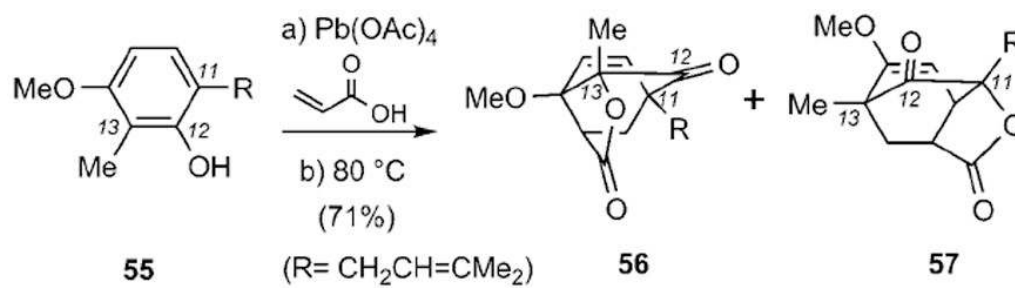
Scheme 3. Proposed biosynthesis of the caged xanthone motif by a Claisen/Diels-Alder reaction cascade.

**Scheme 4.**

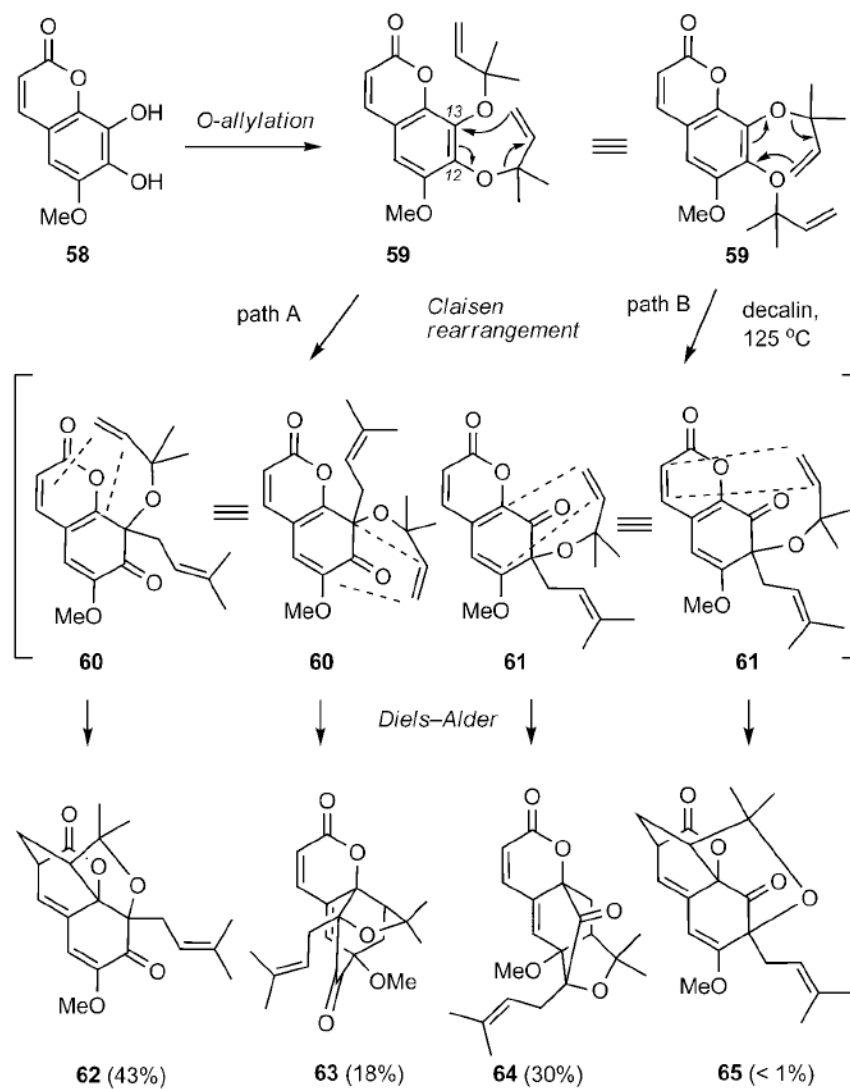
Representative examples of caged structures **45** and **48** formed by a Wessely oxidation/Diels-Alder reaction cascade.



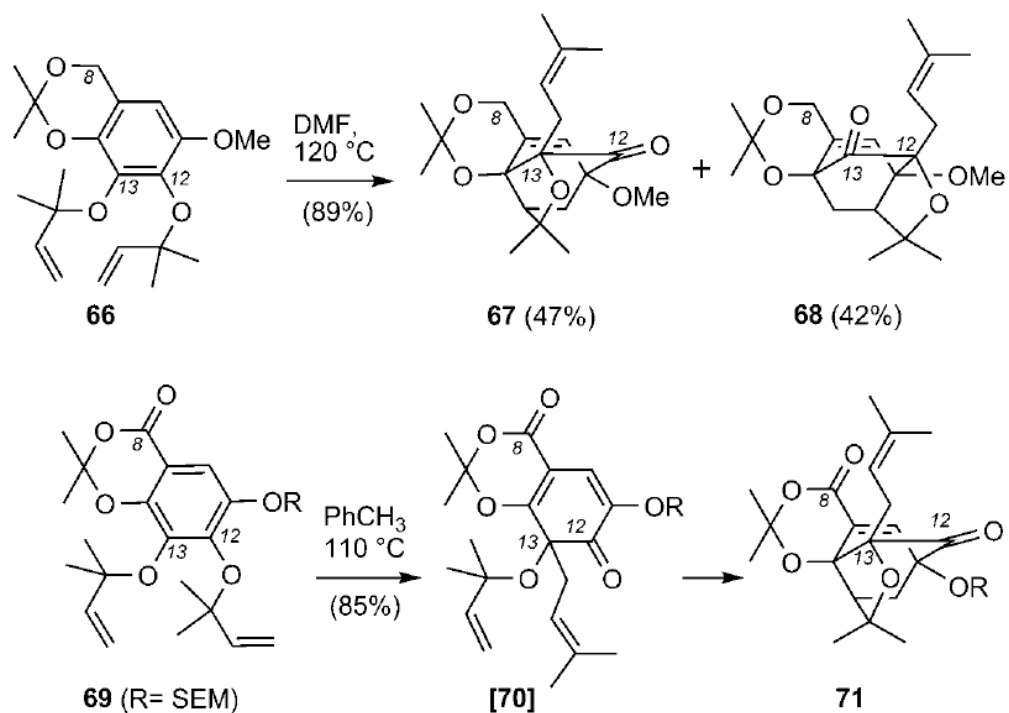
Scheme 5.
 Synthesis of caged structures **51** and **54**.



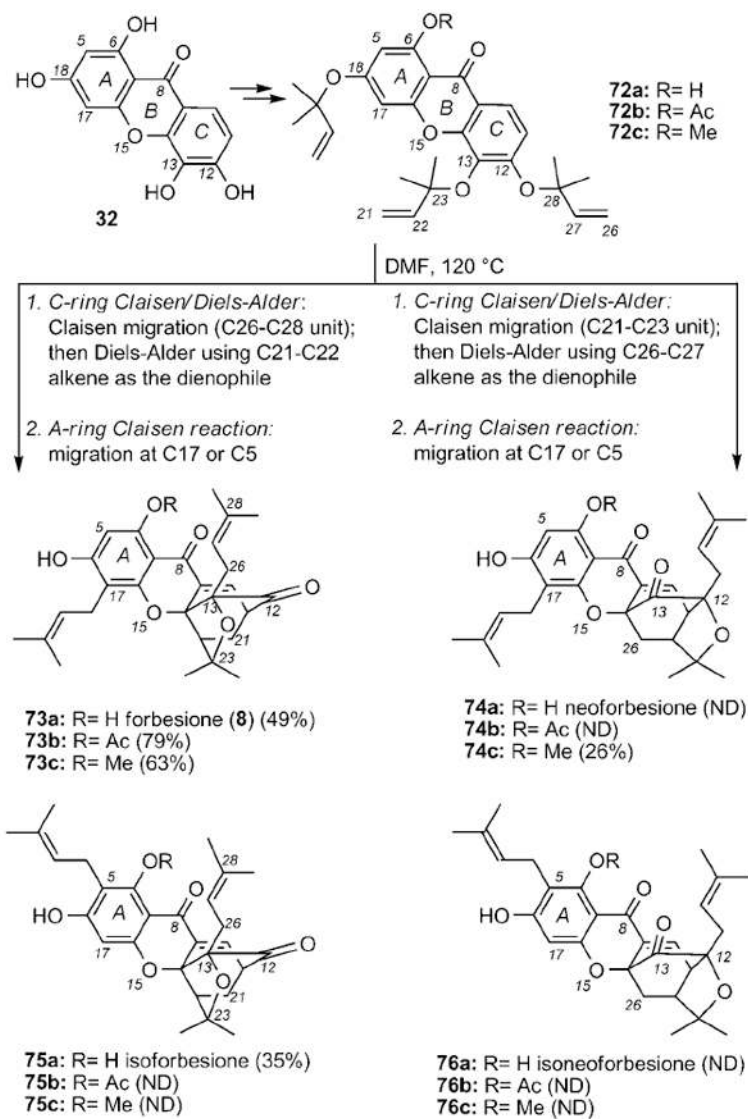
Scheme 6.
Synthesis of caged structures **56** and **57**.



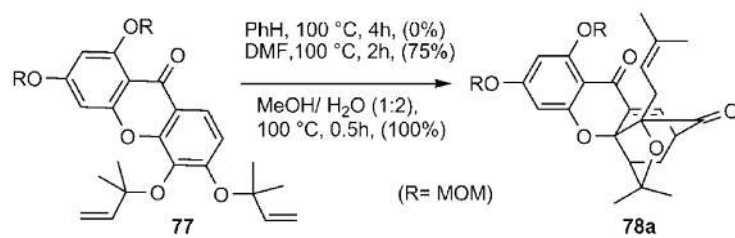
Scheme 7. Model studies on the Claisen/Diels–Alder reaction cascade with prenylated coumarin **59**.

**Scheme 8.**

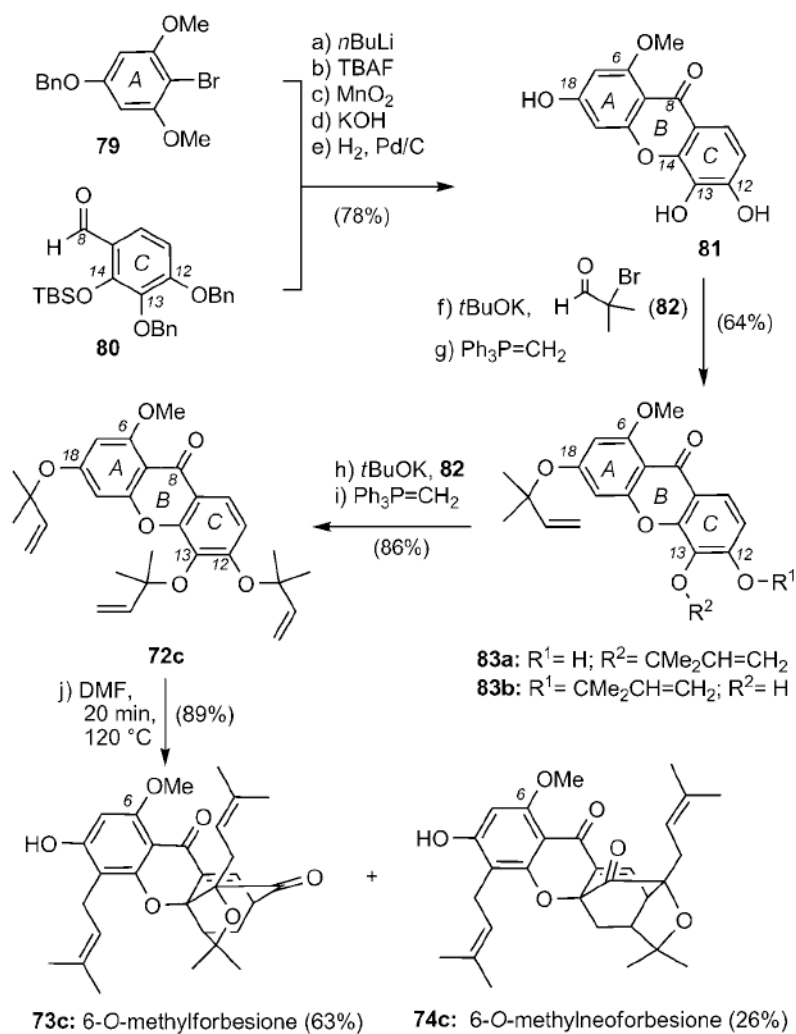
Construction of caged structures **67**, **68** and **71** through a biomimetic Claisen/Diels–Alder reaction cascade. SEM = [2-(trimethylsilyl)ethoxy]methyl.



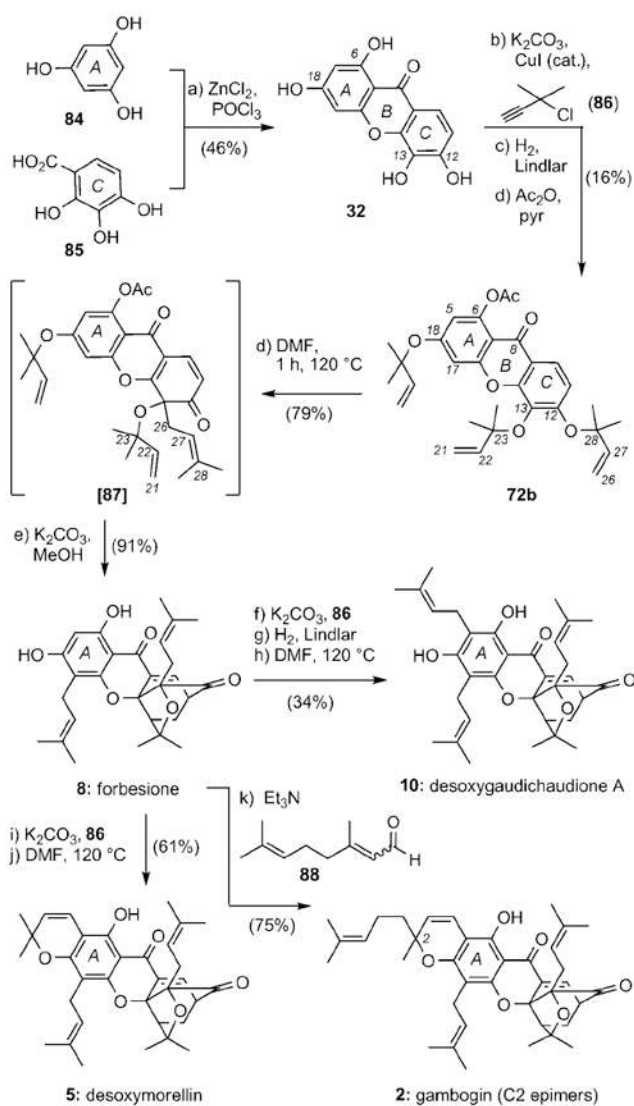
Scheme 9. Biomimetic synthesis of forbesione (**8**) and related structures through a Claisen/Diels-Alder/Claisen reaction cascade. ND = yield not determined.

**Scheme 10.**

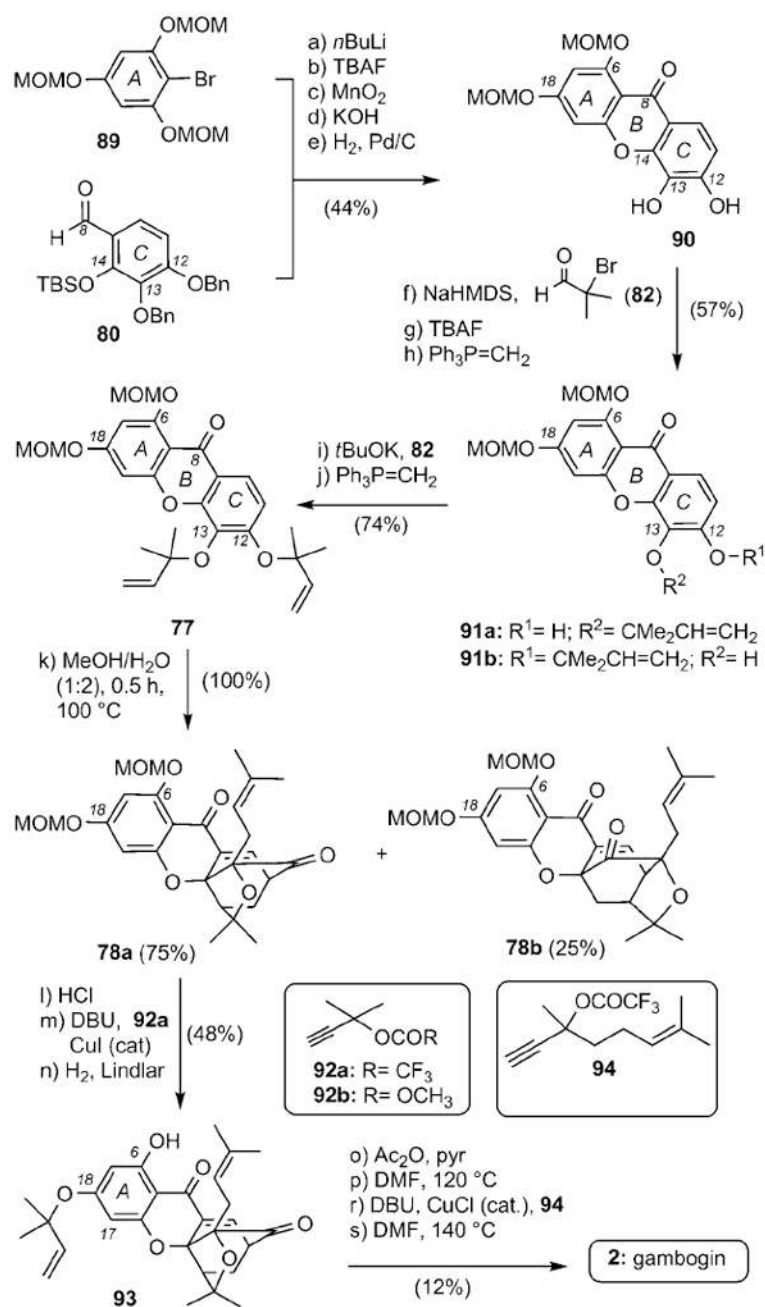
Solvent effect on the rate of the Claisen/Diels–Alder reaction cascade. MOM = methoxymethyl.

**Scheme 11.**

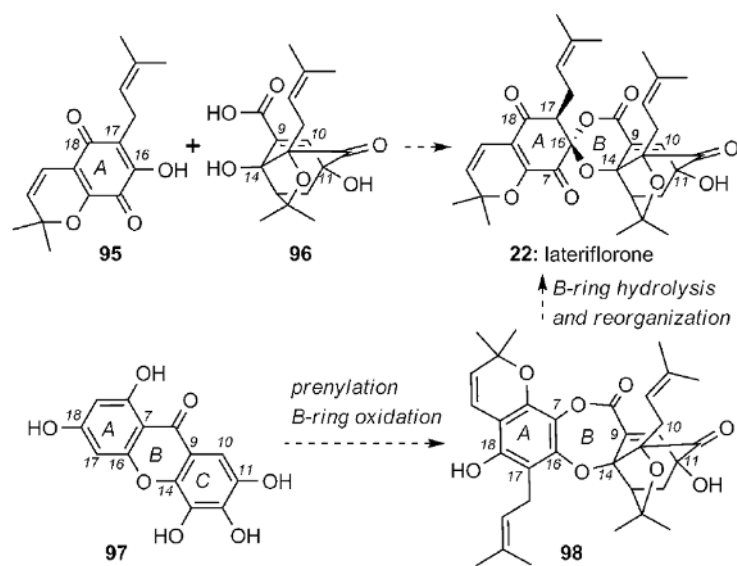
Biomimetic synthesis of 6-*O*-methylforbesione. TBAF = tetrabutylammonium fluoride, Bn = benzyl, TBS = *tert*-butyldimethylsilyl.



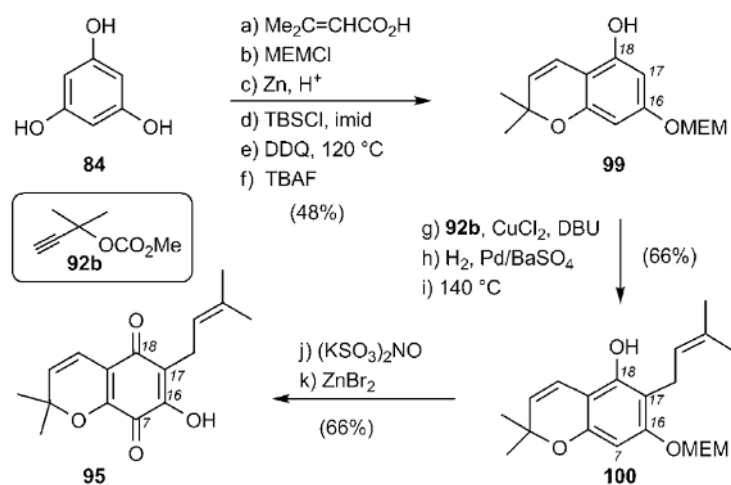
Scheme 12.
 Unified biomimetic synthesis of caged *Garcinia* xanthenes.

**Scheme 13.**

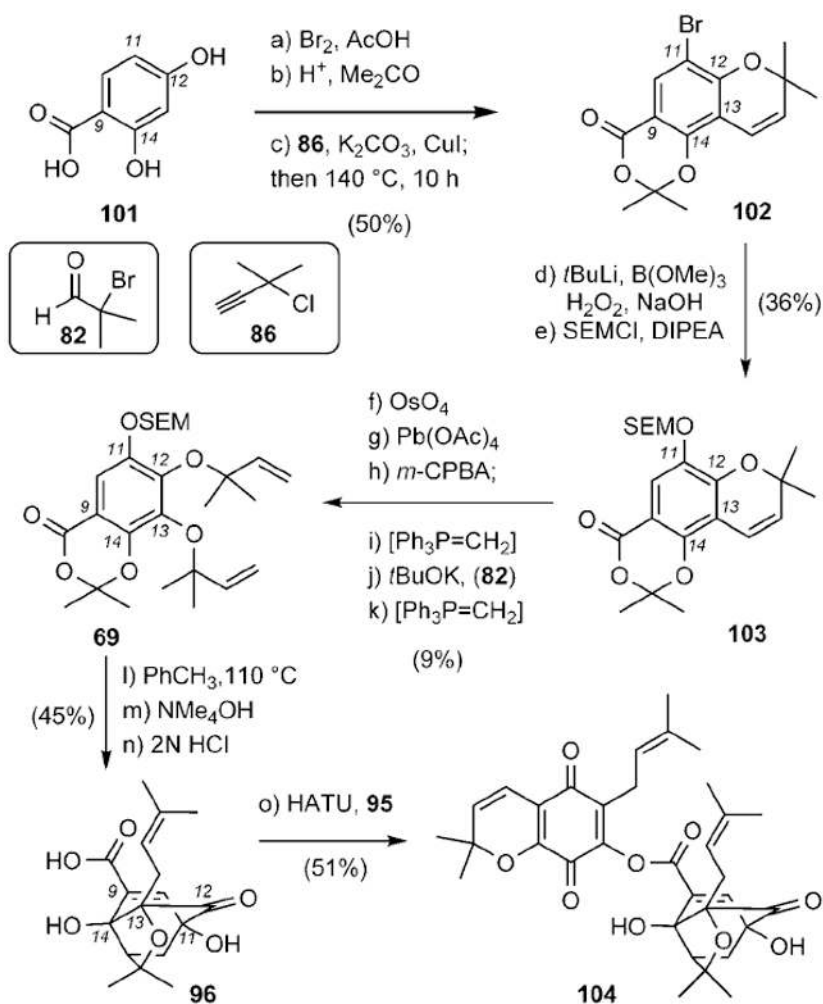
Biomimetic synthesis of gambogin (**2**). HMDS = hexamethyldisilazane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



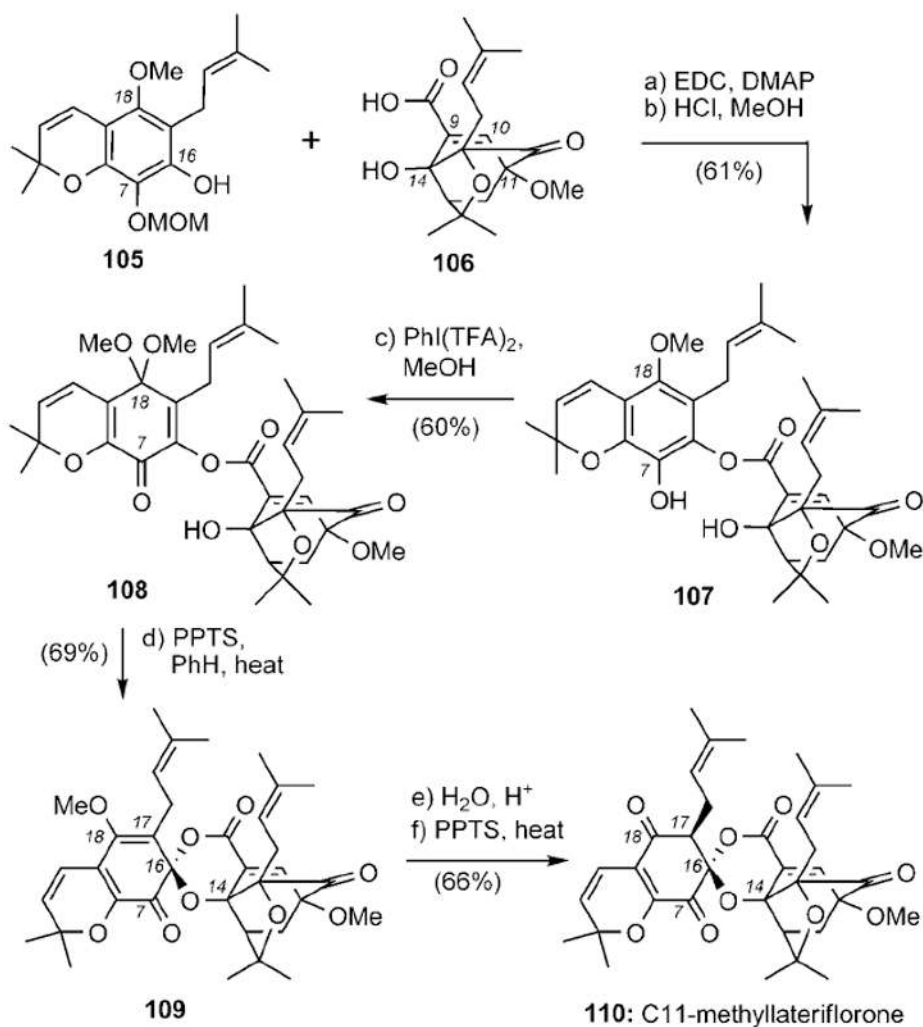
Scheme 14.
Synthetic plans toward lateriflorone (**22**) based on biogenetic scenarios.

**Scheme 15.**

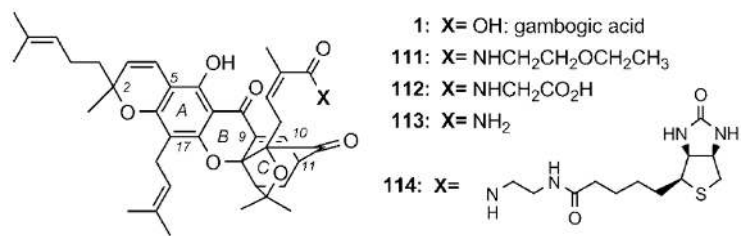
Synthesis of chromenequinone **95**. MEMCl = 2-methoxyethoxymethyl chloride, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

**Scheme 16.**

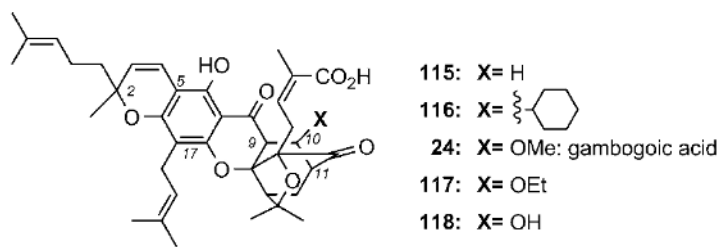
Synthesis of secolateriflorone (**104**). DIPEA = *N,N*-diisopropylethylamine, *m*-CPBA = *m*-chloroperoxybenzoic acid, HATU = 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

**Scheme 17.**

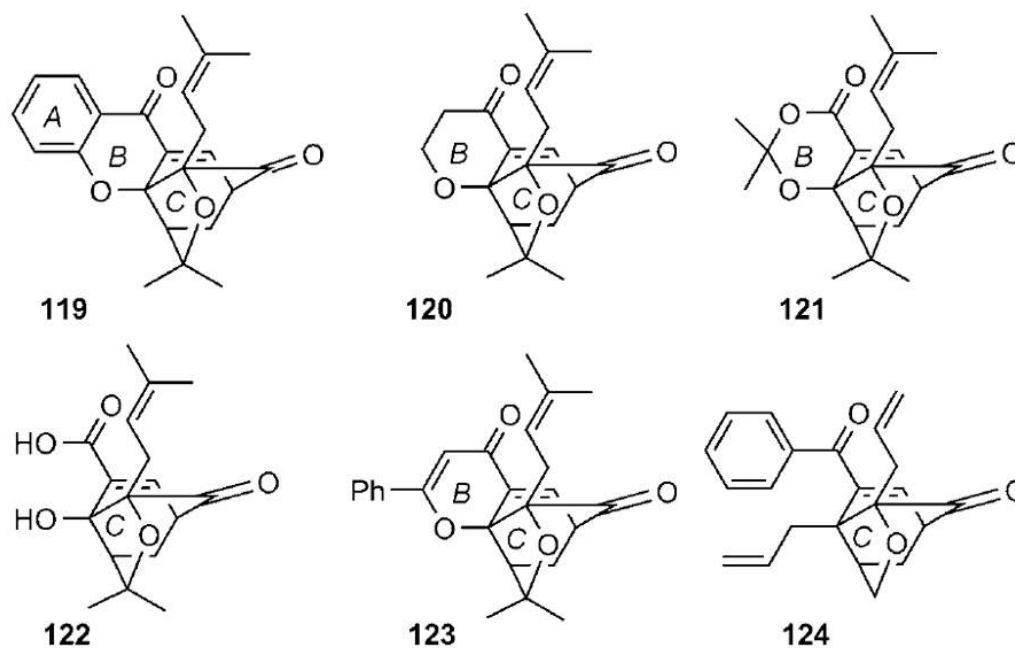
Synthesis of C11-methylateriflorone (**110**). EDC = *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide, DMAP = 4-(*N,N*-dimethylamino)pyridine, TFA = trifluoroacetate, PPTS = pyridinium *p*-toluenesulfonate.



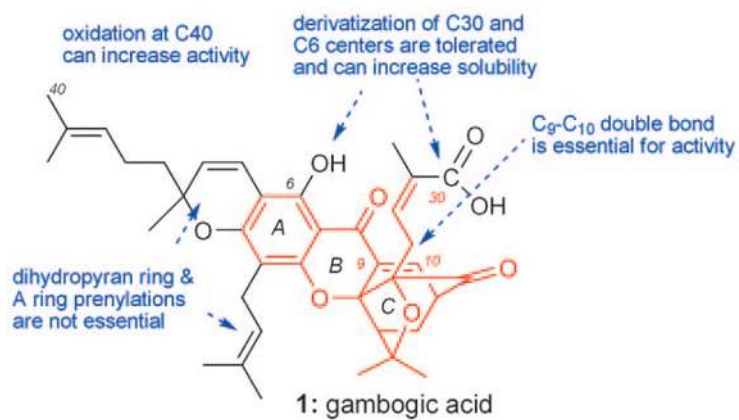
Scheme 18.
Selected structures of gambogic acid conjugates.



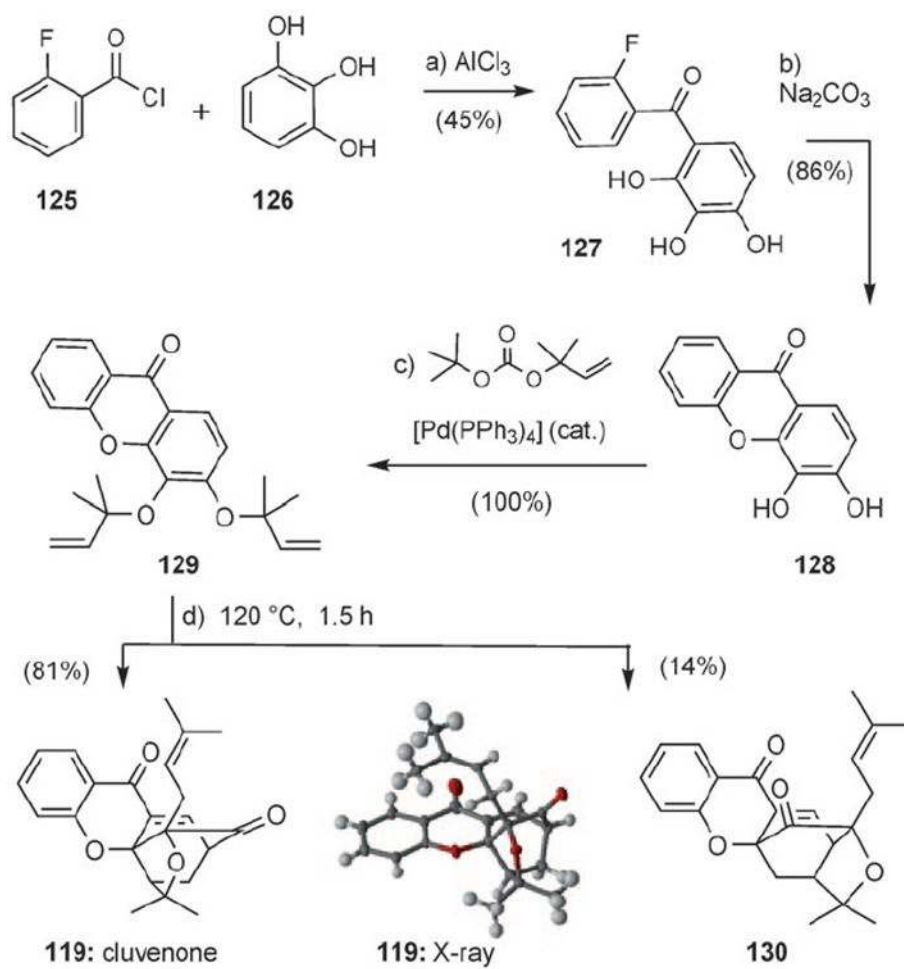
Scheme 19.
Selected structures of gambogic acid derivatives containing functionalities at the C9–C10 bond.



Scheme 20.
Selected caged structures used to evaluate the minimum pharmacophore of the caged *Garcinia* xanthones.



Scheme 21.
Summary of SAR studies with **1** and related analogues.



Scheme 22. Optimized synthesis of cluvenone (**119**) by using a Pd⁰-catalyzed reverse prenylation reaction.