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# Regioselective Synthesis of the Bridged Tricyclic Core of *Garcinia* Natural Products via Intramolecular Aryl Acrylate Cycloadditions

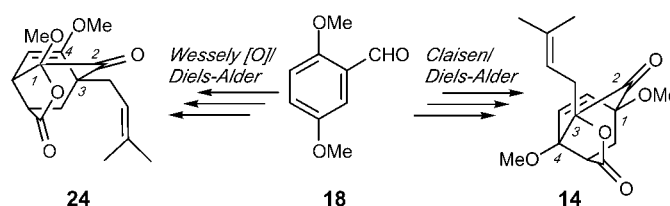
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## ABSTRACT



Two different routes to the tricyclic core of *Garcinia*-derived natural products are described. The first approach is based on a tandem Claisen/Diels–Alder rearrangement and delivers the desired lactone **14**. The second approach, employing a Wessely oxidation/Diels–Alder protocol, leads to the same caged heterocycle, albeit with modified constitution.

The Guttiferae family of tropical plants, specifically those of the genus *Garcinia*, has yielded an abundance of biologically active and structurally intriguing natural products.<sup>1</sup> Among them, morellin (**1**)<sup>2</sup> (Figure 1), produced by *Garcinia morella*, is the first known example of a xanthonoid natural product containing the 4-oxatricyclo[4.3.1.0<sup>3,7</sup>]decan-2-one scaffold. Since the initial disclosure of morellin's intriguing structure, many other natural products sharing the same caged skeleton have been reported, including morellic acid (**2**),<sup>3</sup>

scortechiones A and B<sup>4</sup> (**3**, **4**), forbesione<sup>5</sup> (**5**), and gaudichaudione H<sup>6</sup> (**6**) (Figure 1). In addition to their striking chemical architecture, most of these compounds exhibit interesting antibacterial activity and cytotoxicity. It has been postulated that such bioactivity results from the 4-oxatricyclo[4.3.1.0<sup>3,7</sup>]decan-2-one moiety as planar xanthenes alone do not show a marked biological profile.<sup>6</sup> Undoubtedly, the most exceptional example of structure and bioactivity in a *Garcinia* natural product is that of lateriflorone (**7**)<sup>7</sup> in which the familiar tricyclic scaffold is attached to an unprecedented spiroxalactone core.

From the biosynthetic standpoint, these natural products are presumed to derive from a common benzophenone intermediate of a mixed shikimate–acetate pathway that has

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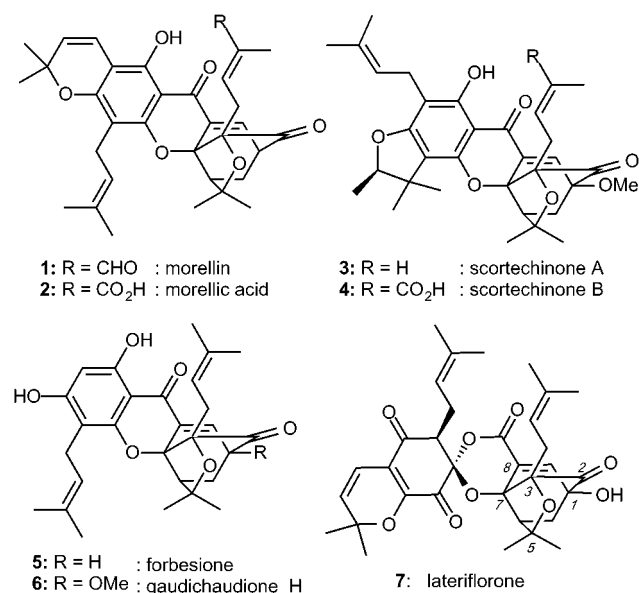
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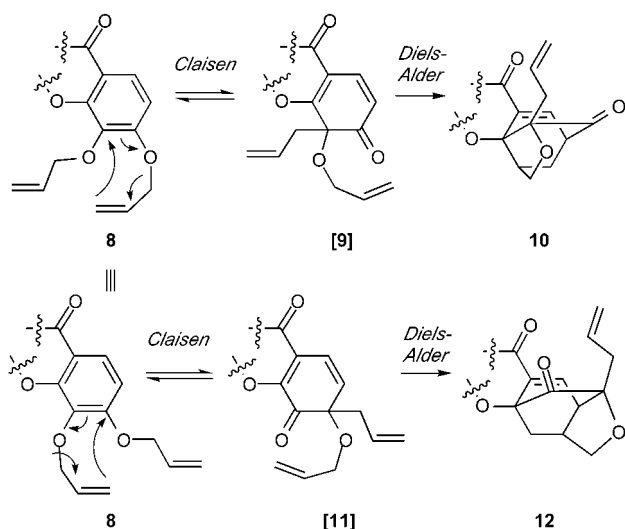
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**Figure 1.** Selected natural products from *Garcinia* plants.

undergone plant-specific prenylations, rearrangements, and/or oxidation reactions.<sup>8</sup> In 1971, Quillinan and Scheinmann suggested that the caged scaffold of these molecules arises in Nature from a tandem Claisen/Diels–Alder rearrangement (Figure 2).<sup>9</sup> Setting out to prove the feasibility of such a

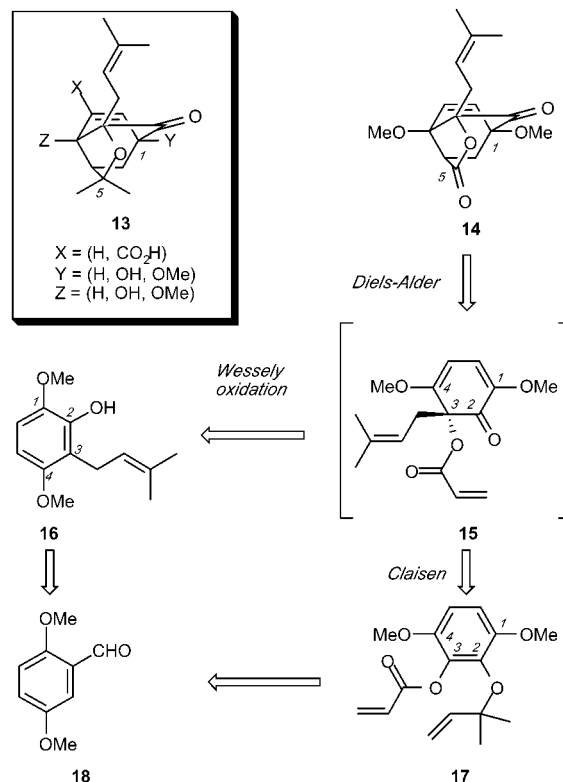


**Figure 2.** Proposed biosynthesis of the caged structures **10** and **12** starting from precursor **8** (see ref 9).

postulate, they heated compound **8** and obtained an isomeric mixture of Claisen/Diels–Alder adducts **10** and **12**. An initial nonregioselective Claisen rearrangement leads to the formation of intermediates **9** and **11** and, thus, the mixture of **10** and **12**. A similar mixture of isomers, produced via a Claisen/Diels–Alder reaction, was also reported by Nicolaou and

Li during their pursuit of the total synthesis of forbesione (**5**).<sup>10</sup>

Inspired by the unusual tricyclo[4.3.1.0<sup>3,7</sup>]decan-2-one scaffold and the biosynthetic issues mentioned above, we sought to design a general approach to these caged natural products (Figure 3). The strategy was envisioned to lead



**Figure 3.** Retrosynthetic analysis of tricyclic fragment **14**.

exclusively to the desired structure while allowing the flexibility to create analogues of the biologically active portion of the *Garcinia*-derived caged xanthonoids. With the C1-oxygenated *Garcinia* natural products in mind (lateriflorone numbering), we selected compound **14** because it mapped onto the variable retrosynthetic target **13** in a desirable manner. From a retrosynthetic standpoint, the *gem*-dimethyl group at the C5 carbon center of **13** was pictured to arise from an organometallic addition to lactone **14** followed by cyclodehydration.<sup>11</sup> The tricyclic structure of **14** could be formed via a Diels–Alder cycloaddition of intermediate **15**, which in turn could arise from either **16** or **17** after a Wessely oxidation<sup>12</sup> or a Claisen rearrangement,<sup>13</sup> respectively. Both **16** and **17** could be produced from readily available 2,5-dimethoxybenzaldehyde (**18**), thereby increas-

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(9) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1971**, 966–967.

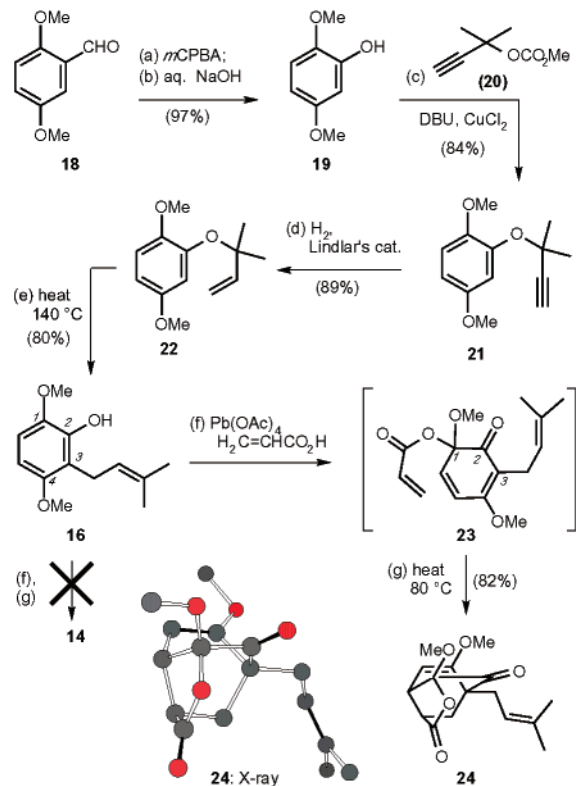
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ing the convergency of both strategies. Herein, we disclose the results of our studies based on these retrosynthetic considerations.

The synthesis of the Wessely oxidation/Diels–Alder precursor **16** is shown in Scheme 1. Commercially available

**Scheme 1.** Synthesis of Lactone **24**<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) 1.3 equiv of *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 4 h, 25 °C; (b) 10% NaOH (aq)/MeOH (1:1), 25 °C, 30 min, 97%; (c) 1.2 equiv of **20**, 1.3 equiv of DBU, 0.3 mol % of CuCl<sub>2</sub>, CH<sub>3</sub>CN, 0 °C, 24 h, 84%; (d) 10% Pd/BaSO<sub>4</sub> (3.2%/weight), quinoline (3.2%/weight), H<sub>2</sub>, EtOH, 0.5 h, 89%; (e) *m*-xylene, 140 °C; 2 h, 80%; (f) 1.2 equiv of Pb(OAc)<sub>4</sub>, acrylic acid (excess), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 10 min; (g) PhH, 80 °C, 2 h, 82% (over two steps).

2,5-dimethoxybenzaldehyde (**18**) was subjected to Baeyer–Villiger oxidation, and the resulting formate ester was hydrolyzed under basic conditions to produce phenol **19** in 97% yield.<sup>14</sup> Various propargylating reagents and conditions were used to alkylate alcohol **19**, among which carbonate **20** was found to give optimum results when used in

conjunction with DBU and catalytic copper(II) chloride.<sup>15</sup> Under these conditions, ether **21** was produced in consistent yields of 84%. Lindlar-catalyzed partial hydrogenation<sup>16</sup> of alkyne **21** gave rise to alkene **22**, which upon heating at 140 °C produced Claisen adduct **16**<sup>17</sup> (71% combined yield), thereby setting the stage for a tandem Wessely oxidation/Diels–Alder reaction.<sup>18</sup> To this end, compound **16** was treated with Pb(OAc)<sub>4</sub> in acrylic acid/dichloromethane and the resulting intermediate heated in refluxing benzene to produce tricyclic lactone **24** in 82% combined yield. Crystallographic studies established that **24** was a constitutional isomer of desired structure **14**. The connectivity of compound **24** suggested that during the Wessely oxidation the acrylate unit was attached exclusively at the C1 center of **16**, instead of the anticipated C3 carbon. This produced diene **23**, which subsequently underwent Diels–Alder cycloaddition with the pendant dienophile. The outcome of the Wessely oxidation can be rationalized if we consider that addition at the C1 center is preferred due to the electron-donating effect of the attached methoxy group. Despite the discrepancy in connectivity, lactone **24** assured us an entry point to the tricyclo-[4.3.1.0<sup>3,7</sup>]decan-2-one caged system and suggests that the outcome of the reaction can be altered by decreasing the electron-donating effect of the substituent at the C1 carbon center.

Concurrent with the above studies, we examined the feasibility of the tandem Claisen/Diels–Alder rearrangement as an entry point to the 4-oxatricyclo[4.3.1.0<sup>3,7</sup>]decan-2-one scaffold (Scheme 2). To this end, 2,5-dimethoxybenzaldehyde (**18**) was transformed to alkyne **21**, which after a subsequent Claisen rearrangement in refluxing *m*-xylene, produced benzopyran **25** (61% combined yield). Lactol **26** was acquired from pyran **25** in 22% yield by a fairly consistent three-step protocol involving ozonolysis, a chemo-selective Baeyer–Villiger oxidation, and basic hydrolysis. Each step in this string of reactions was carried out on crude material as purification of the intermediates proved to be difficult.<sup>19</sup> After purification, compound **26** was subjected to a Wittig olefination protocol to afford phenolic ether **27**,<sup>20</sup> which upon a straightforward acryloylation produced the Claisen/Diels–Alder precursor **17** in 93% yield. Heating of

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(18) The tandem Wessely oxidation/Diels–Alder reaction has been utilized extensively by Yates and co-workers. For selected examples on this work, see: Bhamare, N. K.; Granger, T.; John, C. R.; Yates, P. *Tetrahedron Lett.* **1991**, 32, 4439–4442. Bhamare, N. K.; Granger, T.; Macas, T. S.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1990**, 739–740. Bichan, D. J.; Yates, P. *J. Am. Chem. Soc.* **1972**, 94, 4773–4774. Yates, P.; Kaldas, M. *Can J. Chem.* **1992**, 70, 2491–2501. Yates, P.; Langford, G. E. *Can J. Chem.* **1981**, 59, 344–355. Yates, P.; Auksi, H. *J. Chem. Soc., Chem. Commun.* **1976**, 1016–1017. Yates, P.; Auksi, H. *Can. J. Chem.* **1979**, 57, 2853–2863.

(19) Both the ozonolysis and the Baeyer–Villiger oxidation reactions tended to be clean. This led to the conclusion that hydrolysis of the intermediate formate ester to lactol **26** was the bottleneck of this protocol. Attempts were made to optimize the reaction sequence, particularly the hydrolysis, but little ground could be gained.

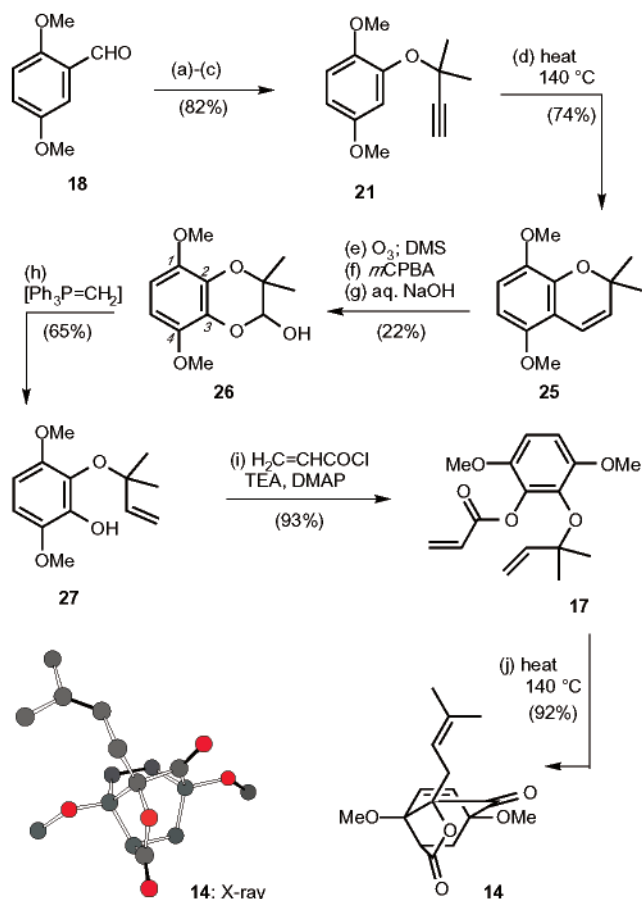
(20) Wittig olefination of the pendant aldehyde was also attempted prior to hydrolysis of the formate ester. This change in reaction sequence, however, did not change overall product yields.

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**Scheme 2.** Synthesis of Tricyclic Lactone **14**<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) 1.3 equiv of *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 4 h, 25 °C; (b) 10% NaOH (aq)/MeOH (1:1), 25 °C, 30 min, 97%; (c) 1.2 equiv of **20**, 1.3 equiv of DBU, 0.3 mol % of CuCl<sub>2</sub>, CH<sub>3</sub>CN, 0 °C, 24 h, 84%; (d) *m*-xylene, 140 °C, 2 h, 74%; (e) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 30 min, then DMS, 30 min; (f) 1.3 equiv of *m*CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 4 h; (g) 10% NaOH (aq)/MeOH (1:1) 30 min, 25 °C, 22% (over three steps); (h) 5.0 equiv of H<sub>3</sub>CPPh<sub>3</sub>Br, 4.6 equiv of NaHMDS, THF (inverse addition), 25 °C, 2 h, 65%; (i) 1.1 equiv of acryloyl chloride, 1.2 equiv of TEA, 0.1 equiv of DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, 93%; (j) *m*-xylene, 140 °C, 45 min, 92%.

**17** in boiling *m*-xylene allowed the tandem Claisen/Diels–Alder to take place, thereby producing tricyclic structure **14** in a remarkably efficient process (92% overall yield).

Compound **14** was crystalline, and X-ray diffraction studies revealed that it possessed the desired connectivity across the central tetrahydrofuran core. The remarkably efficient and regioselective Claisen/Diels–Alder process owes much of its success to the reversibility of the Claisen rearrangement. While the α,α-dimethylallyl substituent of **17** can migrate and, thus, prenylate either of two adjacent positions, only the desired isomeric intermediate **15** (see Figure 3) adopts a geometry that allows it to be trapped as the Diels–Alder adduct. Consequently, all the available starting material eventually funnels through the desired mechanistic pathway to generate the preferred adduct **14**.

In conclusion, we have demonstrated, using two different methods, the ability to access the 4-oxatricyclo[4.3.1.0<sup>3,7</sup>]-decan-2-one scaffold encountered in many of the *Garcinia*-derived natural products. Both strategies are very efficient and afford the tricyclic structures with excellent regiocontrol. The tandem Claisen/Diels–Alder strategy proceeds in 10 steps (from aldehyde **18**) and produces the desired tricyclic scaffold **14**. The efficiency of the Claisen/Diels–Alder rearrangement presented here allows access to the desired natural product scaffold in a high-yielding and predictable process. In contrast, the alternative sequence of Wessely oxidation/Diels–Alder reaction gives rise to isomeric structure **24**, whose application to the synthesis of the above natural products should await some fine-tuning, especially as related to the electronic effects of the substituents of the aromatic ring. Nonetheless, adduct **24** may be useful for the preparation and biological investigation of nonnatural analogues of the above natural products.

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**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C NMR spectra available for compounds **14**, **16**, **17**, **22**, **24**, **26**, and **27**. Experimental procedures, spectroscopic, and analytical and X-ray data for compounds **14** and **24**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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