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S_NAr Reaction/Claisen Rearrangement Approach to 2,4-Diisoprenylxanthones: Total Synthesis of Garcinone A

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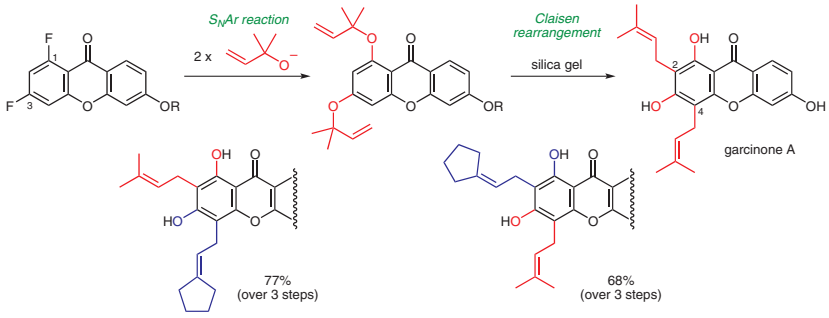

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Abstract A total synthesis of garcinone A, a natural xanthone possessing a 2,4-diisoprenylated structure, was accomplished by utilizing a readily available 1,3-difluoroxanthone derivative as the key intermediate through the installation of two isoprenyl side chains by an S_NAr reaction with the alkoxide of 1,1-dimethylallyl alcohol followed by a Claisen rearrangement. The strategy also permitted the selective installation of mutually different allylic moieties at the C2 and C4 positions.

Key words natural product synthesis, xanthones, isoprenylation, S_NAr reaction, Claisen rearrangement, garcinone A

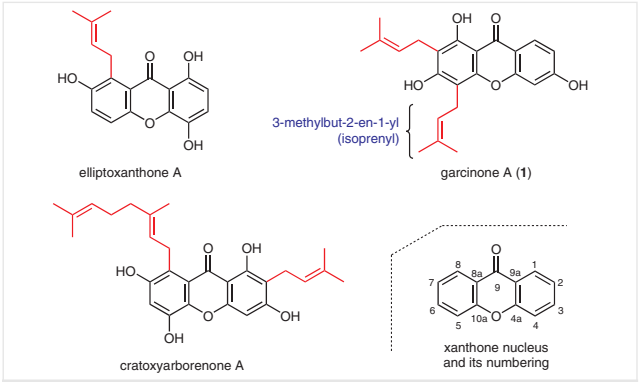
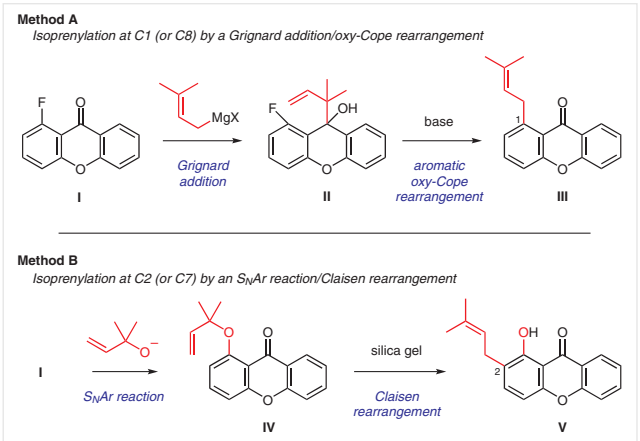


Figure 1 Examples of naturally occurring prenylated xanthones

Prenylated xanthones are widely distributed in the Clusiaceae, Gentianaceae, and Moraceae plant families, and constitute the most abundant group of naturally occurring xanthones (Figure 1).[1] These compounds display a vast range of pharmacological activities, including cytotoxic,[2a–c] antiinflammatory,[2d–f] antioxidant,[2g–i] antimalarial,[2j,k] antibacterial,[2l,m] and antifungal activities.[2n,o] The prenyl moieties exert a significant influence on these properties by their lipophilic nature and sterics.[2] In synthesis, a major problem to be solved is the late-stage selective and flexible installation of prenyl moieties onto existing xanthone cores.[3,4]

We recently developed two new methods for the installation of an isoprenyl (3-methylbut-2-en-1-yl) group onto a xanthone, one for isoprenylation at the C1 (or C8) position (Scheme 1, Method A)[5] and the other for isoprenylation at the C2 (or C7) position (Scheme 1, Method B);[6] both methods use readily accessible fluoroxanthone derivatives as pivotal intermediates. With regard to the latter method,[6] the S_NAr reaction of a 1-fluoroxanthone **I** with the alkoxide of 1,1-dimethylallyl alcohol cleanly afforded the corresponding ether **IV**, which was previously unavailable because it could not be prepared by etherification of a 1-hydroxyxanthone derivative by the existing methods. A combination of the S_NAr reaction and a subsequent Claisen



Scheme 1 Rearrangement-based approaches to isoprenylated xanthones by using fluoroxanthone derivatives as intermediates

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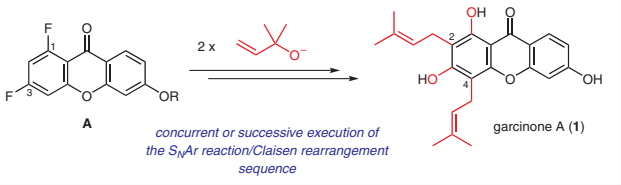
rearrangement provides a facile and selective method for the installation of an isoprenyl moiety at the C2 position of xanthone.[7]

In this communication, as an initial attempt to explore the utilities of Method B in the synthesis of polyisoprenylated xanthone derivatives, we report a total synthesis of garcinone A (**1**),[8,9] a minor constituent of the mangosteen, the fruit of *Garcinia mangostana*, known as 'the queen of fruit', and a rich source of xanthones with diverse biological activities.[10]

Our plan for the synthesis featured the use of 1,3-difluoroxanthone (**A**) as an intermediate and the execution of the S_NAr reaction/Claisen rearrangement sequence twice, either concurrently or successively (Scheme 2).

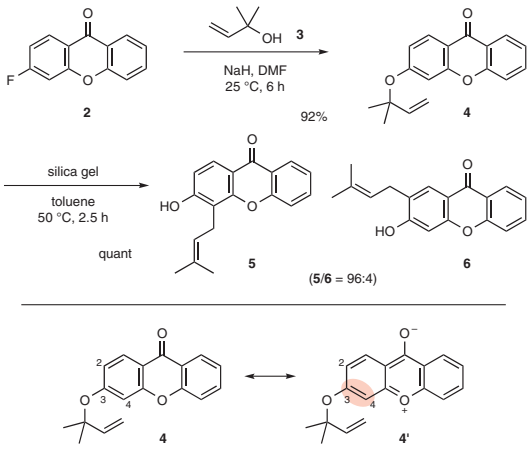


Scheme 2 Plan for the synthesis of garcinone A (**1**)

We hoped that the S_NAr reaction with the alkoxide of 1,1-dimethylallyl alcohol would work not only at C1, as we reported previously (Scheme 1, Method B),[6] but also at C3, thanks to the carbonyl group in the *para*-position. A major issue to be addressed was whether four reactions for the installation of two isoprenyl moieties [i.e., (i) the S_NAr reaction at C1, (ii) that at C3, (iii) the migration of a C_5 unit from C1–O to C2, and (iv) that from C3–O to C4] could all work effectively without conflicting with one another. Of particular concern was the regioselectivity in the migration from C3–O. As discussed later, the reaction proceeded for the most part so as to deliver the C_5 unit to C4. However, if delivery to C2 occurred, even slightly, it would be troublesome and we would need to complete the migration of the C_5 unit from C1–O to C2 before migration from C3–O. Otherwise, the preexisting isoprenyl moiety at C2, stemming from the migration from C3–O, would hinder the migration from C1–O to C2.[11]

We began our study by examining the viability of the S_NAr reaction/Claisen rearrangement sequence at the C3 position by employing 3-fluoroxanthone (**2**) as a model compound (Scheme 3). On using the sodium alkoxide of 1,1-dimethylallyl alcohol (2.0 equiv) in DMF, the S_NAr reaction of **2** proceeded cleanly, but somewhat more slowly than the corresponding reaction of 1-fluoroxanthone, which we reported previously.[6,12] However, the desired ether **4** was obtained in 92% yield after chromatographic purification on silica gel.[12]

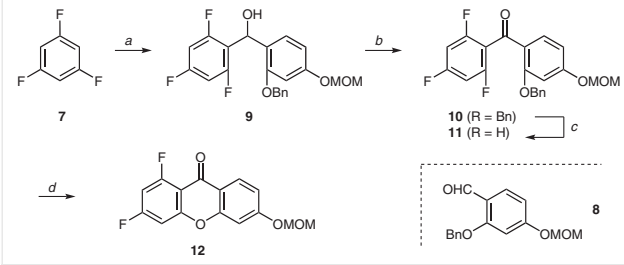
Claisen rearrangement of the resulting ether **4** was quite sluggish, even in refluxing toluene (<5% in 10 h), but was successfully accelerated by the addition of silica gel (100



Scheme 3 Application of the S_NAr reaction/Claisen rearrangement sequence to 3-fluoroxanthone (**2**)

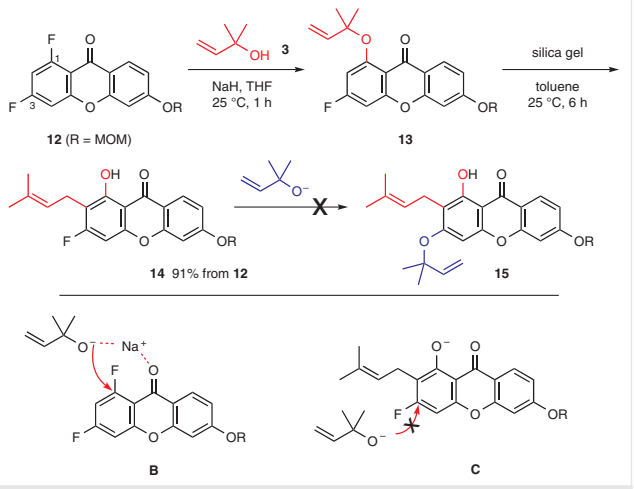
wt% based on **4**), going to completion within 2.5 hours at 50 °C.[6] The isomeric products 3-hydroxy-4-isoprenylxanthone (**5**) and 3-hydroxy-2-isoprenylxanthone (**6**) were obtained in a ratio of 96:4. The predominance of **5** can be reasonably attributed to the partial aromatic character of its central ring, as depicted by the resonance form **4′**, which enhances the double-bond character of the C3–C4 bond (shaded) rather than the C2–C3 bond.[13]

With these outcomes in mind, we attempted a synthesis of garcinone A (**1**). 1,3-Difluoroxanthone intermediate **12** was easily obtained by assembling two known fluorobenzene derivatives: 1,3,5-trifluorobenzene (**7**) and 2-benzyloxy-4-(methoxymethoxy)benzaldehyde (**8**)[14] (Scheme 4). Ortho lithiation of **7** with BuLi (THF, –78 °C, 2 h) and subsequent addition to aldehyde **8** (–78 °C, 50 min) gave alcohol **9** in 97% yield; this was then subjected to oxidation with 2-iodoxybenzoic acid (IBX) (DMSO, 25 °C, 8 h) and hydrogenolytic debenzylation (H_2, 10% Pd/C, EtOAc, 25 °C, 13.5 h). The resulting benzophenone **11** underwent an intramolecular S_NAr reaction on treatment with Cs_2CO_3 in DMF (25 °C, 25 min) to afford xanthone **12** in 94% yield.



Scheme 4 Synthesis of 1,3-difluoroxanthone **12**. *Reagents and conditions*: (a) BuLi, THF, –78 °C, 2 h, then **8**, THF, –78 °C, 50 min, 97%; (b) IBX, DMSO, 25 °C, 8 h, 92%; (c) H_2, 10% Pd/C (30 wt%), EtOAc, 25 °C, 13.5 h, quant; (d) Cs_2CO_3, DMF, 25 °C, 25 min, 94%.

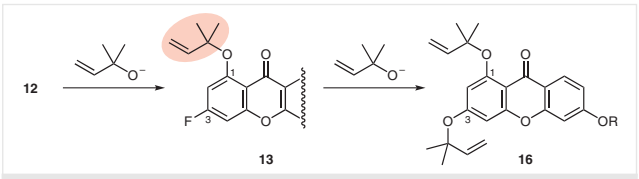
The S_NAr reaction of xanthone **12** with the sodium alkoxide of 1,1-dimethylallyl alcohol (**3**) (2.0 equiv) proceeded smoothly at 25 °C in THF, giving ether **13** as a single product (Scheme 5). The preference for the substitution at C1 rather than C3 was consistent with the difference in reactivity between 1-fluoroxanthone and 3-fluoroxanthone (as mentioned above),[12] and is presumed to be due to the coordination of the countercation of the alkoxide to the carbonyl oxygen (see **B** in Scheme 5).[15] The resulting ether **13**, upon treatment with silica gel (100 wt%) in toluene (25 °C, 6 h), underwent a clean Claisen rearrangement to give the 2-isoprenylated xanthone **14** in 91% yield. It turned out, however, that the C3-fluorine of xanthone **14** did not participate in an S_NAr reaction despite many trials with various solvent/base combinations. We speculate that the phenolate formation from the C1-hydroxy group enhances the electron density of the aromatic ring, thereby suppressing nucleophilic attack on C3 (**C** in Scheme 5).



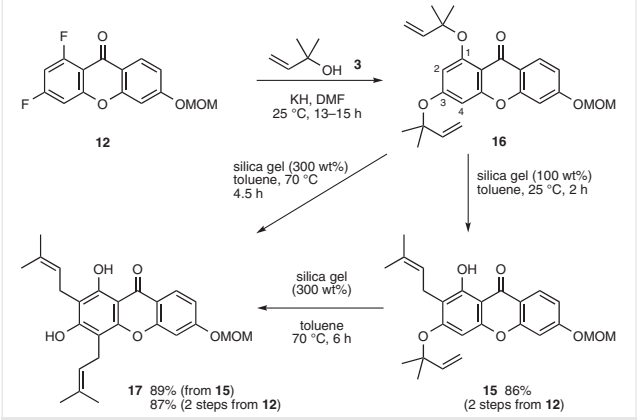
Scheme 5 Dead end in our initial attempt at 2,4-diisopropenylation

We therefore envisioned a one-pot conversion of difluoroxanthone **12** into diether **16** (Scheme 6) with a subsequent Claisen rearrangement. Our hope was that the 1,1-dimethylallyl group on the C1-oxygen (shaded) might serve as a protection against phenolate formation, eliminating suppression of the attack at C3.

Although our initial attempts using the sodium alkoxide of **3** in a large excess and/or at elevated temperatures resulted in failure, the use of the potassium alkoxide of **3** in DMF proved quite successful (Scheme 7). The S_NAr reaction at C1 progressed rapidly at 25 °C, and the subsequent reaction at C3 proceeded slowly but steadily to completion after 13–15 hours, giving the desired diether **16**.



Scheme 6 'Protection' of the C1-OH by a 1,1-dimethylallyl group to facilitate the S_NAr reaction at C3

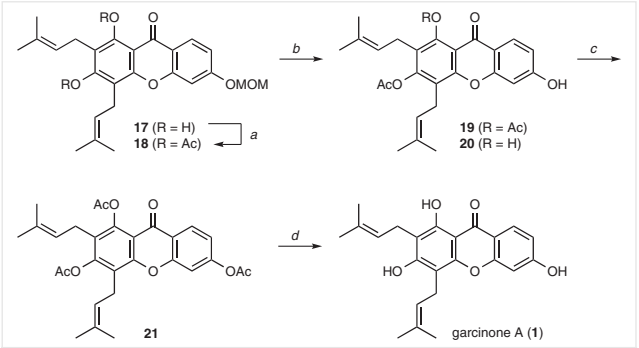


Scheme 7 Successful installation of two isoprenyl moieties

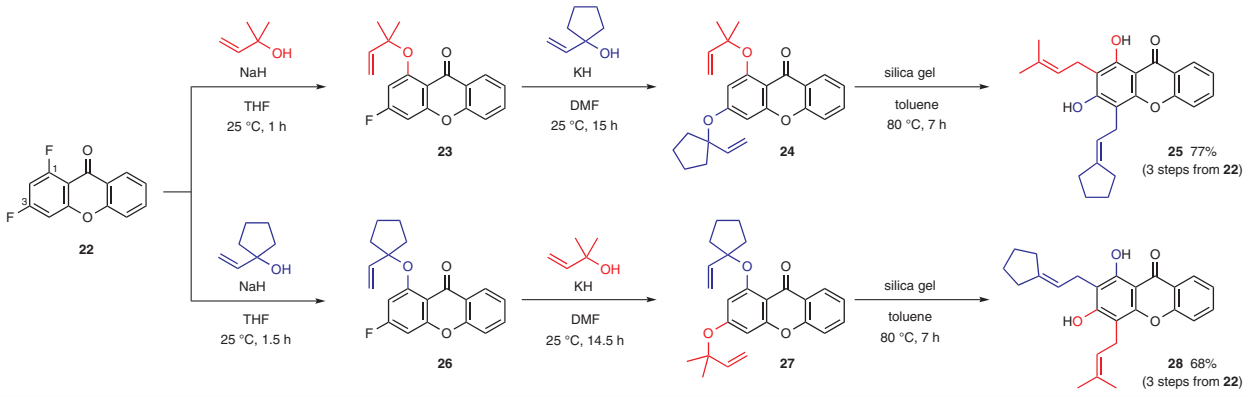
The Claisen rearrangement of diether **16** proceeded stepwise in the presence of silica gel in toluene. The reaction at 25 °C (100 wt% of silica gel) afforded the 2-isoprenylated xanthone **15** in 86% yield over two steps from **12**.[16] Treatment of **15** with a higher loading of silica gel (300 wt%) at 70 °C led to clean conversion into the 2,4-diisoprenylated product **17** in 89% yield. Moreover, a one-pot conversion of **16** into **17** was effected by applying the latter conditions (87% yield over two steps from **12**).[17]

To achieve a synthesis of garcinone A (**1**),[8] we needed a bit of contrivance because of the acid lability of the product. In fact, all our efforts to remove the MOM group from **17** by exposure to various acid conditions were fruitless, giving intractable mixtures of products. The effective solution, which we eventually discovered, is shown in Scheme 8.

After acetylation of the two hydroxy groups of **17**, the MOM group was hydrolyzed by treatment with 3 M aque-



Scheme 8 Completion of the total synthesis of garcinone A. *Reagents and conditions*: (a) Ac_2O, DMAP (15 mol%), $(i\text{-Pr})_2NEt$, CH_2Cl_2, 25 °C, 8.5 h, 95%; (b) 3 M aq H_2SO_4, EtOH, 60 °C, 2 h; (c) Ac_2O, DMAP (17 mol%), py, 25 °C, 30 min, 98% (2 steps); (d) NaOMe, MeOH, 50 °C, 2.5 h, 96%.



Scheme 9 Synthesis of isomeric xanthones **25** and **28**

ous H_2SO_4 in EtOH. The reaction proceeded smoothly at 60 °C to give the expected hydroxyxanthone **19** as the major product, accompanied by a considerable amount of diol **20** (17%). The resulting crude mixture was subjected to acetylation once more to converge **19** and **20** to the triacetate **21** (98% over two steps).[18] Deacetylation of triacetate **21** with NaOMe (MeOH, 50 °C, 2.5 h) followed by careful workup with 1 M aqueous HCl at 0 °C gave, after purification by silica-gel chromatography, garcinone A (**1**) in 96% yield. The spectral and physical data of our synthetic **1** (^{1}H and ^{13}C NMR, IR, combustion analysis) were fully consistent with the reported structures for garcinone A.[18]

Finally, we examined the possibility of synthesizing xanthone derivatives possessing mutually different allylic moieties at C2 and C4 by employing 1,3-difluoroxanthone (**22**) as a model compound. As shown by the reactions with 1,1-dimethylallyl alcohol (**3**) and 1-vinylcyclopentanol (Scheme 9), changing the order of treatment by the alcohols permitted selective access to each of the isomeric xanthones **25** and **28** in high yield. These results show that the present method should permit the synthesis of a broad range of 1,3-dihydroxy-2,4-diisoprenylxanthone derivatives and their analogues containing other isoprenoids and related allylic side chains, paving the way to an extensive structure–activity relationship study.

In summary, a total synthesis of garcinone A (**1**), a natural xanthone possessing a 2,4-diisoprenylated structure, was successfully accomplished by iteratively applying an S_NAr reaction/Claisen rearrangement sequence to a readily available 1,3-difluoroxanthone derivative. The strategy also permitted the selective installation of mutually different allylic moieties at the C2 and C4 positions, showing promising prospects for biological studies of related compounds.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707819.

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(11) The model reaction with **4** (Scheme 3) was not completely regioselective (96:4). Fortunately, however, this was not a problem in the actual reaction of **16** (Scheme 7), because migration of the C_5 unit from C1–O to C2 took place easily at 25 °C and was completed before the migration from C3–O (70 °C) began; see also ref. 16.

(12) The reaction of 1-fluoroxanthone under the same conditions went to completion within 1.75 h (see ref. 6). The product ether **29** (Figure 2) was quite susceptible to the Claisen rearrangement and partly underwent the reaction on exposure to silica gel, even in the short time required for TLC analysis. For isolation, we had to perform chromatographic purification quickly with a column of neutral alumina.

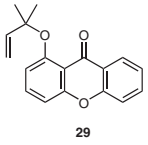

Figure 2 The structure of ether **29**

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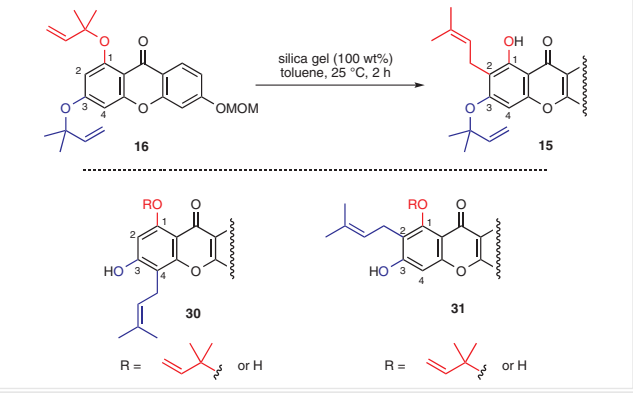
(16) At this stage, neither of the byproducts **30** nor **31** that might possibly arise through prenyl migration from C3–O was detected (Scheme 10).



Scheme 10 Possible byproducts **30** and **31** from the Claisen rearrangement of **16**

(17) **S_NAr Reaction/Claisen Rearrangement for the Synthesis of 17; Typical Procedure**

A 1.0 M solution of the potassium alkoxide of 1,1-dimethylallyl alcohol **3** in DMF (0.74 mL, 0.74 mmol) was added dropwise to a solution of 1,3-difluoroxanthone **12** (103 mg, 352 μmol) in DMF (1.0 mL), and stirring was continued for 13 h at 25 °C. The reaction was quenched with phosphate buffer (0.1 M, pH 7), and the products were extracted with Et_2O (×3). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was azeotropically dried with toluene and the crude product **16** was used for the next step without further purification.

Silica gel (452 mg, 300 wt% based on the theoretical yield of **16**), in a two-necked round-bottomed flask, was dried in vacuo by heating it with a heating gun and then suspended in toluene (0.5 mL). To this suspension was added a solution of the crude product **16** in toluene (1.2 mL) at 0 °C, and the mixture was stirred for 4.5 h at 70 °C. After removal of the silica gel by filtration through a sintered glass filter, the filtrate was concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (20:1)] to give xanthone **17** as a yellow solid; yield: 130 mg (87%, 2 steps). Crystallization from hexane–EtOAc gave **17** as yellow needles; mp 125.6–126.1 °C.

IR (ATR): 2986, 2911, 1647, 1618, 1604, 1566, 1487, 1446, 1416, 1390, 1307, 1289, 1258, 1236, 1218, 1208, 1166, 1154, 1134, 1115, 1079, 1003, 978, 949, 919, 864, 833, 816, 792, 701, 663, 626, 607, 563, 524, 500, 468, 455, 442, 421, 404 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.63 (s, 6 H), 1.67 (s, 3 H), 1.80 (s, 3 H), 3.35 (d, *J* = 7.2 Hz, 2 H), 3.50 (s, 3 H), 5.27 (br t, *J* = 7.2 Hz, 1 H), 5.31 (d, *J* = 11.2 Hz, 1 H), 5.395 (d, *J* = 17.6 Hz, 1 H), 5.396 (s, 2 H), 6.26 (dd, *J* = 17.6, 11.2 Hz, 1 H), 6.71 (s, 1 H), 7.09 (d, *J* = 9.6 Hz, 1 H), 7.10 (s, 1 H), 8.12 (d, *J* = 9.6 Hz, 1 H), 13.13 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 22.1, 25.6, 27.5 (2 C), 56.4, 82.0, 95.1, 96.2, 103.4, 103.6, 114.47, 114.55, 114.9, 115.4, 123.2, 127.7, 131.3, 144.7, 155.7, 158.3, 160.3, 162.2, 163.6, 180.7. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.83; H, 6.66.

(18) The original papers on isolation of garcinone A (**1**) by Sen et al.[8a,b] did not record any NMR data for the natural product, but instead gave spectral data for the natural product-derived triacetate **21** (IR, ^1H NMR). We identified **1** and **21**, which we synthesized, by comparing their data with those of the respective synthetic materials reported by Sen et al.[8a,b] and Ahluwalia et al.[9a] (for **21**) and by Ahluwalia et al.[9a], Zhang et al.[9b] and Lim et al.[9d] (for **1**). Furthermore, the structures were fully characterized by an extensive NMR study. See the Supporting Information for details.