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Total syntheses of (±)-frondosin C and (±)-8-*epi*-frondosin C via a tandem anionic 5-*exo* dig cyclization–Claisen rearrangement sequence

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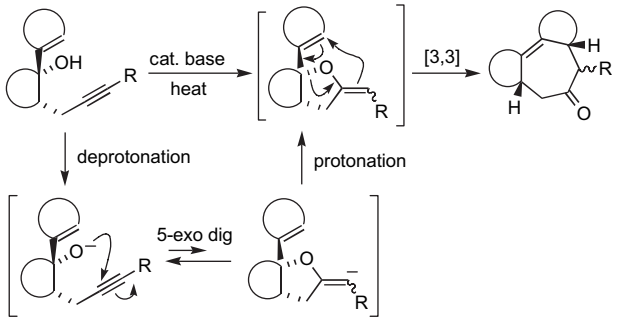
Abstract—Microwave-assisted anionic 5-*exo* dig cyclization–Claisen rearrangement sequence has been investigated as a convenient 'one-pot' route to fused cycloheptanoid ring systems. This process was used as the key transformation to construct the tetracyclic framework of frondosin C. Subsequent manipulation of the core allowed the first total syntheses of (±)-frondosin C and (±)-8-*epi*-frondosin C in a combined overall yield of 20.8% over 14 steps.

1. Introduction

We have recently demonstrated that a variety of cycloheptanoid fused ring systems may be prepared through a known[1] but largely ignored tandem reaction sequence that involves a base-catalyzed intramolecular cyclization of appropriately substituted 4-pentyn-1-ols, followed by in situ Claisen rearrangement of the intermediate 2-alkylidenetetrahydrofurans.[2–8] While Claisen rearrangements of analogous cyclic allyl vinyl ether systems, typically prepared from the corresponding lactones[9] or other cyclic precursors,[10,11] have been reported in the literature and the generation of various furanyl systems by transition metal catalyzed 5-*exo* dig cyclizations of acetylenic alcohols is well known,[12] the formation of 2-alkylidenetetrahydrofurans by intramolecular addition of an alkoxide moiety to proximal triple bonds is much less common. Although anionic 5-*exo* dig cyclizations involving oxygen nucleophiles have been known since the early 1950s,[13,14] these transformations are generally difficult to achieve due to the reversibility and unfavorable equilibria associated with such isomerizations particularly when the triple bond is unactivated. In addition, the initially formed 5-*exo* products are often unstable[15] and prone to undergo isomerization to form the corresponding endocyclic derivatives.[16]

These problems can be largely circumvented by using an acetylenic alcohol substrate that forms a transient 5-*exo* product, which does not have to be isolated. When such a reaction is conducted under high-temperature conditions, the intermediate 2-alkylidenetetrahydrofuran species may be trapped by way of a subsequent 3,3-sigmatropic rearrangement process, generating a seven-membered ring as the final product of the tandem sequence.[1–8] It is noteworthy that the initial intramolecular cyclization requires the use of a *catalytic* base that allows for rapid protonation of the intermediate vinyl anion species, in effect rendering the cycloisomerization process irreversible (Scheme 1).



R = H, Alkyl, Aryl, TMS, TES, TBS

Scheme 1. Sequential cyclization–Claisen rearrangement as a route to cycloheptane-containing polycycles.

In a typical case, the cyclization–Claisen rearrangement sequence is effected simply by treatment of an appropriately substituted acetylenic alcohol, dissolved in phenetole, diphenyl ether or DMF with approximately 10 mol % of MeLi and heating the mixture to 100–210 °C.[2,3] Although our initial experiments were conducted using conventional heating we recently found microwave irradiation (MWI) to

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be particularly well suited for these processes.[6] In general, the reactions conducted under MWI occur faster, give better yields and are more convenient to perform.[6]

The tandem process appears to be quite general although significant differences in reaction rates have been observed depending on the exact structure of the substrates and the nature of the substituent at the terminal acetylene carbon. In cases where the triple bond bears a trialkylsilyl group, the Claisen rearrangement is accompanied by the Brook rearrangement,[17] which allows the regiospecific generation of silyl enol ethers as the final products.[2,3]

So far, the tandem 5-*exo* cyclization–Claisen rearrangement reaction has been successfully employed for the straightforward construction of several cycloheptane-containing bi-,[5] tri-,[2,3,6] and tetracyclic structures.[4,6–8] In this article, we wish to report a further extension of this methodology to the first total syntheses of (±)-frondosin C and (±)-8-*epi*-frondosin C.

2. Results and discussion

2.1. The frondosins

Frondosin C is one of the five related novel sesquiterpene hydroquinone derivatives recently isolated from the Micronesian marine sponge *Dysidea frondosa* (Fig. 1).[18] All members of the frondosin family (A–E) are antagonists of interleukin-8 (IL-8) and inhibitors of protein kinase C (PKC) in the low micromolar range.[18] In addition to being involved in cellular inflammatory events,[19] IL-8 is now known to also play an important role in tumor progression and metastasis in several human cancers,[20] including lung cancers.[20b] It has also been reported that IL-8, along with growth-regulated oncogene alpha, is involved in chemoattraction, neovascularization, and stimulation of HIV-1 replication both in T-lymphocytes and macrophages.[21] Importantly, it was recently demonstrated that compounds which inhibit the actions of IL-8 also inhibit HIV-1 replication.[22] Overall, inhibitors of IL-8 action hold therapeutic potential as novel anti-inflammatory and antiviral agents, and may prove useful against cancer as inhibitors of tumorigenesis and proangiogenesis.[20]

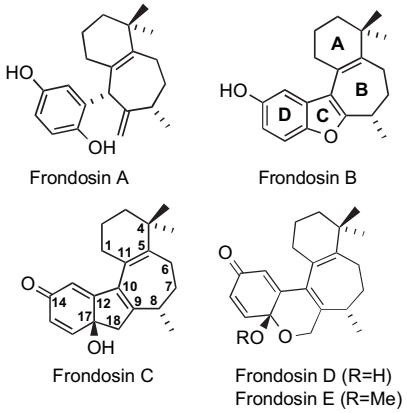
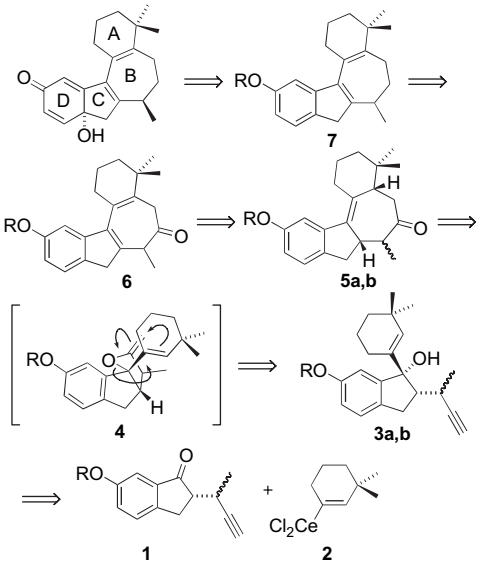


Figure 1. Structures of frondosins A–E.

Of the five naturally occurring frondosins, only frondosin B has been synthesized to date. The total synthesis of frondosin B was achieved first by Danishefsky et al.[23] in 2000 and, more recently, by the Trauner[24] and Flynn[25] groups.

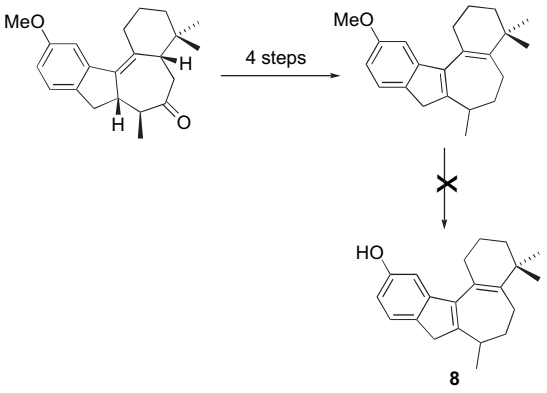
2.2. Synthetic strategy

At the outset of the current investigation, it was envisioned that frondosin C might be constructed according to the sequence depicted retrosynthetically in Scheme 2. The key transformations in the overall strategy include the preparation of acetylenic alcohol **3** by reacting vinyl cerium derivative **2** with indanone **1**, and the subsequent 'one-pot' generation of tetracyclic ketone **5** using our standard microwave-assisted tandem 5-*exo* cyclization–Claisen rearrangement protocol.[6] In two recent communications, we demonstrated that advanced tetracyclic intermediate **5** (R=Me) and its C8 desmethyl analogue were efficiently synthesized using this strategy.[7,8] We also found that ketone **5** (R=Me) could be readily oxidized with DDQ to install the requisite diene functionality in the **B** ring, and that the resulting product **6** could be manipulated further in a short sequence of steps to yield the methoxy indene derivative **7** (R=Me) (Scheme 2).[8]



Scheme 2. Retrosynthetic analysis for the construction of frondosin C.

With **7** (R=Me) in hand, it was anticipated that completion of the total synthesis of frondosin C could potentially be achieved in only two additional steps involving O-demethylation at C14 and oxidation of the resulting indenol derivative to the requisite *p*-quinol system. Unfortunately, exposure of **7** (R=Me) to a variety of conditions and reagents (EtSNa/DMF/reflux,[23a] $PhSH/K_2CO_3$/NMP/190 °C,[26] Ph_2S_2/CaH/NMP/190 °C,[27] $Me_3SiI/ClCH_2CH_2Cl$/reflux,[28] BBr_3/DCM[23b]) known to effect O-demethylation of analogous systems were largely unsuccessful, resulting in the formation of complex mixtures that were not amenable to purification by column chromatography (Scheme 3). While a small amount of the desired indenol product **8** could be detected when **7** (R=Me) was treated with BBr_3 in DCM, the ^1H NMR spectrum of the crude reaction mixture exhibited a distinct vinylic proton signal at 5.6 ppm, suggesting that

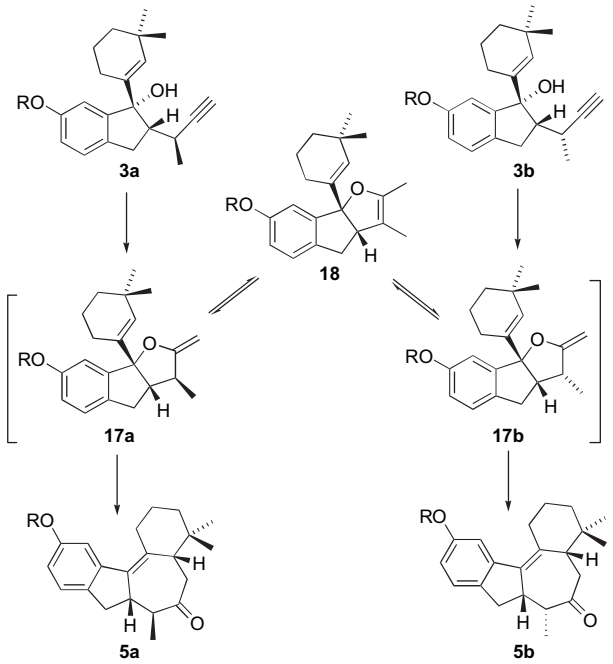


Scheme 3. Attempted preparation of **8**.

a double bond shift had occurred from the C5, C11 position to C1, C11. It is of interest to note that both EtSNa/DMF and BBr_3/DCM have been applied successfully by several investigators to effect O-demethylation as the final step in the synthesis of frondosin B.[23–25]

Having established that the aryl methyl ether **7** (R=Me) was not a suitable precursor to **8**, the use of alternative protecting groups was explored and the overall synthetic sequence was adjusted accordingly. Thus, the tetracyclic ketones **15** and **16** each bearing a TBS protecting group on the aromatic ring oxygen were prepared as a mixture of diastereomers (2.7:1 ratio) in seven steps starting with commercially available 6-hydroxyindanone as shown in Scheme 4.

According to our strategy recently described for the synthesis of the analogous methoxy derivative, installation of the C8 methyl group of frondosin C was conveniently achieved early on in the sequence through alkylation of hydrazone **9** with 3-iodo-1-trimethylsilyl-1-butyne.[8] Since an additional stereogenic center is introduced in this step, a mixture of diastereomeric indanone derivatives (**10a** and **10b**) is produced in the reaction (Scheme 4). However, the configuration at the propargyl carbon is inconsequential as it will not control the ultimate stereochemical course or the ratio of the two isomeric tetracyclic ketones produced in the cyclization–Claisen rearrangement step. In fact, we have recently demonstrated that either diastereomerically pure acetylenic alcohol **3a** or **3b** by themselves or any mixture of the two invariably provide the same ca. 2.5:1 ratio of **5a** and **5b** (R=Me), respectively, presumably through a mechanism that involves the interconversion of two diastereomeric

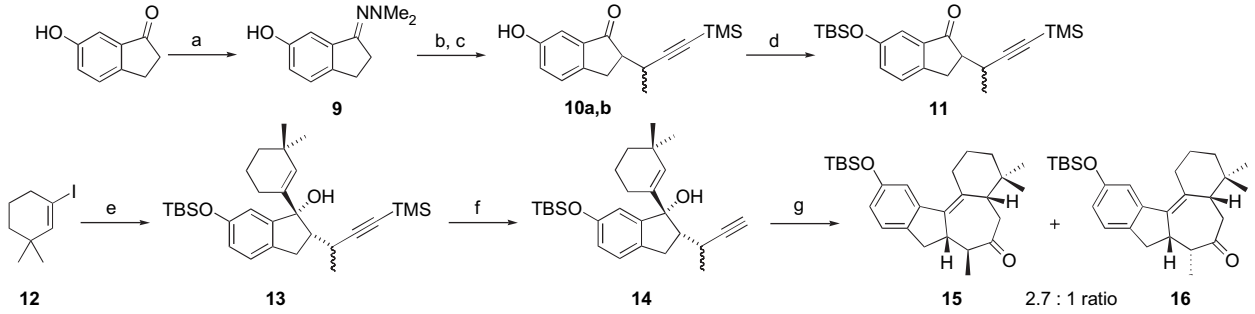


Scheme 5. Proposed mechanism for the interconversion of 5-*exo* intermediates **17a** and **17b**.

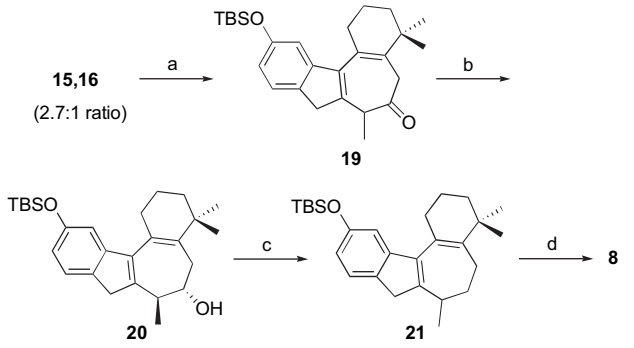
exocyclic 2-alkylidenetetrahydrofuran intermediates (**17a**,**b**) via a common endocyclic intermediate **18** (Scheme 5).[8] We have also shown that the minor product is easily isomerized in the presence of *t*-BuOH/*t*-BuOK or several other bases to provide a diastereomer ratio of up to 15:1 in favor of **5a** (R=Me).[8]

2.3. Synthesis of frondosin C and 8-*epi*-frondosin C

The requisite B ring diene functionality was introduced efficiently and in an excellent yield by treating a mixture of ketones **15** and **16** with DDQ at 0 °C (Scheme 6). Subsequent removal of the carbonyl functionality was achieved through a three-step sequence involving borohydride reduction of **19** to afford alcohol **20**, in situ elimination of the mesylate prepared from **20** and selective diimide reduction[29] of the resulting triene. Whereas our attempted O-demethylation reactions involving the methoxy derivative of **7** (R=Me) gave mainly complex mixtures of inseparable isomeric products, deprotection of the corresponding TBS analogue **21** with TBAF proceeded cleanly to provide the desired indenol **8** in nearly quantitative yield (Scheme 6).



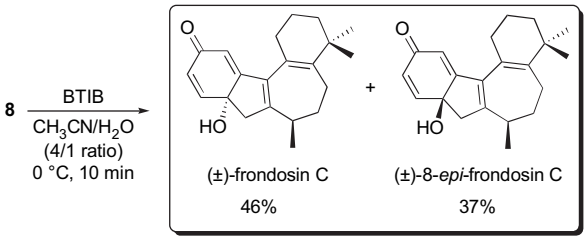
Scheme 4. Synthesis of tetracyclic ketones **15** and **16**. Reagents and conditions: (a) NH_2NMe_2, MWI, 140 °C, 30 min, quant; (b) 2.5 equiv LDA, THF, −40 °C, then 3-iodo-1-trimethyl-silyl-1-butyne; (c) $(COOH)_2$, THF/H_2O, reflux 6 h, 72% (two steps); (d) TBSCl, imidazole, DMF, rt, 97%; (e) *t*-BuLi, −78 °C, Et_2O, $CeCl_3$, THF, −78 °C then **11**, 86%; (f) (i) TBAF, THF, (ii) TBSCl, imidazole, DMF, 90% (two steps); (g) 10 mol %, MeLi, MWI, 210 °C, phenetole, 40 min, 80%.



Scheme 6. Preparation of **8**. Reagents and conditions: (a) DDQ, DCM, 0 °C, 89%; (b) $NaBH_4$, MeOH, 0 °C, 97% (85% de); (c) (i) MsCl, TEA, DCM, (ii) $TsNHNH_2$, TEA, 70% (two steps); (d) TBAF, THF, rt, 96%.

At this stage, it was anticipated that completion of the total synthesis of frondosin C could potentially be achieved in a single operation involving a straightforward oxidation reaction. Although a number of oxidizing agents have been employed to effect dearomatization of *para*-substituted phenols to produce the corresponding *p*-quinol derivatives,[30] the use of hypervalent iodine reagents appeared particularly promising in this context.[31] For example, Taylor et al.[32] have reported the use of [bis-(trifluoroacetoxy)iodo]benzene (BTIB) for the efficient oxidation of a number of 4-substituted phenols and Mal et al.[33] have utilized phenyliodonium diacetate (PIDA) for analogous transformations.

Gratifyingly, we found that treatment of **8** with BTIB in CH_3CN/H_2O at 0 °C resulted in rapid formation (ca. 10 min) of (±)-frondosin C and (±)-8-*epi*-frondosin C as a 1.3:1 mixture of separable epimers in 83% overall yield (Scheme 7). Analysis of the ^1H NMR, ^{13}C NMR and MS spectra of synthetic frondosin C and side by side comparison of these data with those reported for the isolated natural product[18] confirmed that (±)-frondosin C was indeed successfully synthesized.



Scheme 7. Synthesis of (±)-frondosin C and (±)-8-*epi*-frondosin C.

Although no extensive optimization of the final step was undertaken, it was found that PIDA in CH_3CN/H_2O may be used interchangeably with BTIB to effect facile oxidation of **8** to (±)-frondosin C and (±)-8-*epi*-frondosin C. However, PIDA in *t*-BuOH/H_2O[34] (1:3 ratio) had a negative effect on both the yield and stereoselectivity of the reaction, providing an equal mixture of the epimers in approximately 65% overall yield. Given the nearly planar geometry of **8**, particularly in the immediate vicinity of the reactive site at C17, and the absence of any obvious proximate stereodirecting groups, it is not surprising that the reaction occurs with little stereochemical bias. Be that as it may, the formation of both the natural product and its epimer through the same sequence may be considered advantageous in that it allows for the creation of more diverse analogues of frondosin C, thereby permitting further biological studies and the potential development of novel IL-8 inhibitors based on this class of compounds.

3. Conclusions

The total syntheses of (±)-frondosin C and (±)-8-*epi*-frondosin C were achieved in 14 steps and in 20.8% overall yield. The anionic tandem cyclization–Claisen rearrangement sequence was successfully applied to the construction of the requisite tetracyclic core of frondosin C in eight steps, and subsequent manipulation of the core to the natural product was completed in six steps. The total syntheses of other members of the frondosin family are currently being pursued in our laboratories. The results from these investigations will be reported in due course.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were obtained using a Varian INOVA NMR 500 MHz spectrometer. Chemical shifts are reported in units of parts per million (ppm), relative to tetramethylsilane at δ=0.00 ppm. Coupling constants J are reported in hertz (Hz).

Infrared spectra were recorded on a Perkin–Elmer 1600 series FTIR and reported in cm^{-1}. Melting points were observed using a Mel-Temp in an open Pyrex capillary tube and are uncorrected. High-resolution mass spectra were analyzed by the Mass Spectrometry Laboratory at the University of Illinois, Urbana Champaign, Illinois.

All microwave experiments were conducted in a CEM Focused Microwave™ Synthesis System, Model Discover microwave oven, equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL microwave vials.

Tetrahydrofuran and diethyl ether were freshly distilled under N_2 from dark blue solutions of sodium benzophenone ketyl. Phenetole (PhOEt), CH_2Cl_2, TMSCl, and Et_3N were freshly distilled under N_2 from calcium hydride. Bulk solvents were purchased from Fisher or VWR.

All starting reagents were purchased from Sigma–Aldrich, Acros or Strem. The concentrations of solutions of *n*-BuLi, *t*-BuLi, and MeLi were determined by titrations with *sec*-butyl alcohol using 1,10-phenanthroline as the indicator following the method of Watson and Eastham.[35] All glassware was flame dried under an inert atmosphere and all reactions were performed under an atmosphere of dry argon or nitrogen.

4.1.1. 6-Hydroxyindan-1-one dimethylhydrazone (9). 6-Hydroxy-1-indanone (0.500 g, 3.38 mmol) and *N*,*N*-dimethylhydrazine (1.5 mL) were placed in a sealed reaction vial equipped with a magnetic stir bar and heated under

microwave irradiation at 140 °C for 30 min. The reaction mixture was then concentrated under reduced pressure to remove excess *N*,*N*-dimethylhydrazine to yield 0.642 g of the crude hydrazone (quant) as a yellow solid, which was used without purification for the subsequent step: mp 171–172 °C; IR (neat) 3745, 2927, 1650, 1049, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 10.38 (br s, 1H), 7.19 (d, J=2.5 Hz, 1H), 7.02 (d, J=8.5 Hz, 1H), 6.83 (dd, J=8.5, 2.5 Hz, 1H), 2.80–2.75 (m, 4H), 2.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.2, 156.3, 140.2, 137.5, 125.7, 120.8, 107.7, 46.7, 46.7, 29.1, 27.5; HRMS (EI) calcd for $C_{11}H_{14}N_2O$ (M^+) *m*/*z* 190.1106, found 190.1107.

4.1.2. 6-Hydroxy-2-[1-methyl-3-(trimethylsilyl)prop-2-yn-1-yl]indan-1-one (10a,b). To a solution of diisopropylamine (3.37 g, 33.3 mmol) in 100 mL of THF at 0 °C was added *n*-BuLi (1.6 M in hexane, 20.0 mL, 32.0 mmol) and the resulting mixture was stirred at 0 °C for 1 h and then cooled to −40 °C. A solution of hydrazone **9** (2.44 g, 12.8 mmol) in THF (20 mL), which had been dried over activated molecular sieves for 15 min, was then added in a dropwise fashion via Teflon cannula and the reaction mixture was allowed to stir at −40 °C for 3 h. A solution of 3-iodo-1-trimethyl-silyl-1-butyne (4.84 g, 19.2 mmol) in THF (20 mL), which had been dried over activated molecular sieves for 15 min, was added to the reaction vessel in a dropwise fashion via Teflon cannula. The reaction mixture was allowed to stir at −40 °C overnight. The reaction was quenched with water (3 mL) and the mixture was concentrated under reduced pressure. The residue was then dissolved in diethyl ether (150 mL) and the solution was washed successively with water (2×50 mL) and brine (2×50 mL). Drying over $MgSO_4$, filtration, and solvent evaporation under reduced pressure afforded the crude product, which was then mixed with THF (50 mL) and aqueous oxalic acid solution (4.55 g in 25 mL H_2O, 50.5 mmol). The resulting heterogeneous mixture was heated at reflux for 6 h. The solvents were then removed under reduced pressure and the aqueous solution was extracted with ether (2×100 mL). The combined organic layers were then washed successively with water and brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by column chromatography (15–25% EtOAc in hexane) to give two diastereomers **10a** and **10b** in a 1.26:1 ratio as a yellow amorphous solid (2.51 g, 72%). IR (neat) 3220, 2929, 2164, 1680, 1458, 1049, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35 (br s, 1H, minor), 7.34 (br s, 1H, major), 7.30 (d, J=2.5 Hz, 1H, minor), 7.28 (d, J=2.5 Hz, 1H, major), 7.21 (d, J=2.5 Hz, 1H, major), 7.20 (d, J=2.5 Hz, 1H, minor), 3.25–3.17 (m, 3H), 3.12–3.03 (m, 2H), 3.03 (d, J=2.5 Hz, 1H), 2.99–2.97 (m, 1H), 2.70–2.67 (m, 1H), 1.31 (d, J=7.0 Hz, 3H, minor), 1.04 (d, J=7.0 Hz, 3H, major), 0.08 (s, 9H, major), −0.14 (s, 9H, minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.6, 208.0, 156.0, 155.9, 147.3, 146.9, 138.3, 137.9, 127.3, 127.2, 124.2, 124.2, 109.1, 108.8, 108.7, 106.9, 86.2, 85.2, 52.7, 51.6, 28.8, 28.6 (two peaks), 27.7, 19.8, 15.7, 0.0, −0.3; HRMS (EI) calcd for $C_{16}H_{20}O_2Si$ (M^+) *m*/*z* 272.1233, found 272.1229.

4.1.3. 6-(*tert*-Butyldimethylsilyloxy)-2-(1-methyl-3-trimethylsilylprop-2-yn-1-yl)indan-1-one (11). To a solution of **10** (1.20 g, 4.40 mmol) in DMF (3 mL) were added imidazole (718 mg, 10.6 mmol) and TBSCl (796 mg, 5.30 mmol) at room temperature and the resulting solution was stirred for 6 h. Water (50 mL) was added and the mixture was extracted with ether (2×100 mL). The combined organic layers were then washed successively with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (10% EtOAc in hexane) to give **11** as a pale yellow oil (1.65 g, 97%). IR (neat) 2932, 2167, 1713, 1489, 1049, 842; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32–7.30 (m, 2H), 7.14 (d, J=2.0 Hz, 1H, minor), 7.11–7.07 (m, 3H), 3.24–3.15 (m, 3H), 3.10 (d, J=7.0 Hz, 2H), 3.00–2.91 (m, 2H), 2.64 (dd, J=6.0, 10.0 Hz, 1H, major), 1.30 (d, J=7.0 Hz, 3H, minor), 1.05 (d, J=7.0 Hz, 3H, major), 0.96 (s, 18H), 0.18 (s, 6H), 0.17 (s, 6H), 0.07 (s, 9H, major), −0.15 (s, 9H, minor); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.8, 206.1, 155.2, 155.1, 147.6, 147.1, 138.6, 138.2, 127.9, 127.9, 127.0, 126.9, 113.3, 113.2, 109.3, 107.1, 85.9, 85.0, 52.5, 51.4, 28.7, 28.6, 28.5, 27.6, 25.6 (two peaks), 19.8, 15.7, 0.0, −0.2, −4.6; HRMS (EI) calcd for $C_{22}H_{34}O_2Si_2$ (M^+) *m*/*z* 386.2097, found 386.2091.

4.1.4. (1*S,2*S**)-6-(*tert*-Butyldimethylsilyloxy)-1-(3,3-dimethylcyclohex-1-enyl)-2-(1-methyl-3-trimethylsilylprop-2-yn-1-yl)indan-1-ol (13).** *t*-BuLi (1.27 M in pentane, 6.86 mL, 5.40 mmol) was added dropwise to a solution of 1-iodo-3,3-dimethylcyclohexene[7] (0.700 g, 2.96 mmol) in Et_2O (10 mL) at −78 °C. The resulting solution was first stirred at −78 °C for 30 min, then at 0 °C for an additional 15 min to destroy excess *t*-BuLi and finally re-cooled to −78 °C. In a separate flask, a slurry of anhydrous $CeCl_3$ (740 mg, 3.00 mmol) in THF (20 mL) was stirred for 1 h at room temperature and then cooled to −78 °C. To the slurry at −78 °C was then rapidly added the vinyllithium solution via cannula and the resulting solution was stirred for 1 h at this temperature. A solution of ketone **11** (385 mg, 0.998 mmol) in THF (5 mL) was then added dropwise via cannula to the resulting vinyl cerium species at −78 °C. The resulting solution was stirred for 2 h at −78 °C and then quenched with water (3 mL). The solvents were removed under reduced pressure, the residue was diluted with ether and H_2O, and the aqueous layer was extracted with ether (3×40 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5–10% EtOAc in hexane) to give compound **13** as a mixture of diastereomers (426 mg, 86%). IR (neat) 3548, 2931, 2162, 1609, 1489, 1260, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, J=8.5 Hz, 1H, major), 7.05 (d, J=8.5 Hz, 1H, minor), 6.75–6.71 (m, 2H), 6.58 (d, J=2.5 Hz, 1H, minor), 6.54 (d, J=2.5 Hz, 1H, major), 5.78 (s, 1H, major), 5.72 (s, 1H, minor), 3.04–2.87 (m, 5H), 2.85–2.80 (m, 3H), 2.63 (dd, J=16, 8.0 Hz, 1H, minor), 2.52 (dd, J=16, 8.0 Hz, 1H, major), 2.40 (s, 1H), 2.07–2.02 (m, 2H), 1.90–1.85 (m, 1H), 1.64–1.42 (m, 5H), 1.32–1.27 (m, 3H), 1.32 (d, J=7.0 Hz, 3H, minor), 1.26 (d, J=7.0 Hz, 3H, major), 1.06 (s, 6H), 1.05 (s, 3H), 1.03 (s, 3H), 0.97 (s, 18H), 0.17 (s, 6H), 0.16 (s, 6H), 0.13 (s, 9H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.7, 154.7, 148.8, 148.5, 137.7, 137.0, 135.5, 134.9, 132.2, 131.7, 125.3, 124.9, 120.6 (two peaks), 114.4 (two peaks), 111.2,

111.1, 86.0, 85.8, 85.3, 85.2, 51.3, 50.6, 37.3, 37.1, 34.6, 34.0, 31.8 (two peaks), 31.6, 30.5, 30.4, 30.1 (two peaks), 27.2, 27.1, 26.3, 25.7 (two peaks), 20.3, 20.2, 18.2, 14.0, 0.2, 0.1, −4.4 (two peaks), −4.5 (two peaks); HRMS (EI) calcd for $C_{30}H_{48}O_2Si_2$ (M^+) *m/z* 496.3193, found 496.3191.

4.1.5. 6-(*tert*-Butyldimethylsilyloxy)-1-(3,3-dimethylcyclohex-1-enyl)-2-(1-methylprop-2-yn-1-yl)indan-1-ol (14). To a solution of **13** (401 mg, 0.810 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 2.03 mL, 2.03 mmol) at room temperature and the resulting solution was stirred for 30 min. Water (5 mL) was then added to quench the reaction and the aqueous solution was extracted with ether (2×40 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was dissolved in DMF (3 mL) followed by the addition of imidazole (132 mg, 1.94 mmol) and TBSCl (146 mg, 0.970 mmol). The resulting mixture was stirred at room temperature for 5 h. Water (20 mL) was then added and the mixture was extracted with ether (2×40 mL). The combined organic layers were washed successively with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography (5–10% EtOAc in hexane) to give compound **14** as a mixture of diastereomers (309 mg, 90%). Less polar isomer: IR (neat) 3553, 2930, 1609, 1487, 1269, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.10 (d, *J*=8.5 Hz, 1H), 6.75 (dd, *J*=8.5, 2.5 Hz, 1H), 6.52 (d, *J*=2.5 Hz, 1H), 5.84 (s, 1H), 3.09–2.90 (m, 3H), 2.54 (dd, *J*=16, 8.0 Hz, 1H), 2.07 (d, *J*=2.0 Hz, 1H), 1.88–1.83 (m, 1H), 1.77 (s, 1H), 1.65–1.49 (m, 4H), 1.42–1.37 (m, 1H), 1.29 (d, *J*=7.0 Hz, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 0.96 (s, 9H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 148.7, 136.7, 135.5, 132.5, 125.4, 120.8, 114.0, 88.6, 85.0, 69.0, 51.0, 37.3, 34.2, 31.8, 30.4, 30.1, 26.5, 25.9, 25.7, 20.2, 19.9, −4.4, −4.5; HRMS (EI) calcd for $C_{27}H_{40}O_2Si$ (M^+) *m/z* 424.2798, found 424.2798 (HRMS was obtained for a mixture of **15** and **16**).

More polar isomer: IR (neat) 3566, 2930, 1612, 1491, 1269, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.06 (d, *J*=8.5 Hz, 1H), 6.73 (dd, *J*=8.5, 2.5 Hz, 1H), 6.55 (d, *J*=2.5 Hz, 1H), 5.81 (s, 1H), 2.94 (dd, *J*=15, 7.5 Hz, 1H), 2.81–2.71 (m, 2H), 2.63–2.58 (m, 1H), 2.07–2.01 (m, 2H), 1.98 (d, *J*=2.0 Hz, 1H), 1.95 (s, 1H), 1.56–1.49 (m, 2H), 1.42–1.37 (m, 2H), 1.29 (d, *J*=7.0 Hz, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.95 (s, 9H), 0.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 148.3, 137.4, 135.1, 131.5, 125.1, 120.8, 114.1, 87.7, 85.4, 69.6, 50.5, 37.2, 34.7, 31.8, 30.2, 30.0, 26.7, 25.5, 25.7, 20.3, 20.1, −4.5, −4.4; HRMS (EI) calcd for $C_{27}H_{40}O_2Si$ (M^+) *m/z* 424.2798, found 424.2798 (HRMS was obtained for a mixture of **15** and **16**).

4.1.6. (4a*S,7*S**,7a*S**)- and (4a*S**,7*R**,7a*S**)-11-(*tert*-Butyldimethylsilyloxy)-4,4,7-trimethyl-1,2,3,4,4a,5,7a,8-octahydrodibenzo-[*a*,*h*]azulen-6(2*H*)-one (15 and 16).** Compound **14** (300 mg, 0.706 mmol) was transferred to a 10 mL flame dried microwave vial with anhydrous phenetole (1.5 mL). A ca. 10 mol % MeLi in Et_2O was added and the solution was heated at 210 °C for 40 min in the microwave oven. Excess phenetole was then removed under reduced pressure and the resulting mixture was directly purified by column chromatography (5–10% EtOAc in hexane) to give compounds **15** and **16** as a 2.7:1 mixture of inseparable diastereomers (240 mg, 80%). IR (neat) 2929, 1700, 1602, 1457, 1050, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.11 (d, *J*=2.0 Hz, 1H, major), 7.07–7.04 (m, 2H), 7.02 (d, *J*=2.0 Hz, 1H, minor), 6.68 (dd, *J*=8.0, 2.0 Hz, 1H, major), 6.66 (dd, *J*=8.0, 2.0 Hz, 1H, minor), 3.50–3.48 (m, 1H), 3.26–3.21 (m, 2H), 3.11–3.01 (m, 2H), 2.91 (dd, *J*=15, 10 Hz, 1H), 2.76–2.72 (m, 2H), 2.69–2.61 (m, 5H), 2.57–2.51 (m, 2H), 2.44–2.37 (m, 3H), 1.78–1.71(m, 2H), 1.68–1.61 (m, 2H), 1.50–1.41 (m, 2H), 1.38–1.31 (m, 2H), 1.25 (d, *J*=7.0 Hz, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 1.00 (s, 9H), 0.99 (s, 9H), 0.98 (s, 3H), 0.92 (s, 3H), 0.75 (d, *J*=7.0 Hz, 3H), 0.21 (s, 3H), 0.21 (s, 3H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.5, 214.3, 154.1, 154.0, 142.8, 142.5, 139.7, 138.9, 137.9, 137.7, 137.2, 136.2, 125.1, 124.8, 118.8, 118.8, 117.0, 116.3, 52.9, 52.8, 48.2, 47.4, 47.3, 43.0, 42.4, 42.3, 37.7, 37.5, 35.4, 35.0, 34.0, 33.2, 30.3, 29.2, 28.9, 26.0, 25.7, 25.5, 24.9, 21.5, 19.4, 18.2, 18.1, 15.6, −4.4 (two peaks); HRMS (EI) calcd for $C_{27}H_{40}O_2Si$ (M^+) *m/z* 424.2798, found 424.2802.

4.1.7. 11-(*tert*-Butyldimethylsilyloxy)-4,4,7-trimethyl-1,2,3,4,5,8-hexahydrodibenzo[*a*,*h*]azulen-6(2*H*)-one (19). To a solution of compounds **15** and **16** (240 mg, 0.565 mmol) in CH_2Cl_2 (10 mL) was added DDQ (194 mg, 0.855 mmol) and the mixture was stirred at 0 °C for 30 min. The reaction mixture was then filtered through Celite, eluting with diethyl ether. The filtrate was diluted further with more diethyl ether, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% EtOAc in hexane) to give compound **19** as a colorless oil (214 mg, 89%). IR (neat) 2930, 1716, 1610, 1472, 1049, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, *J*=8.5 Hz, 1H), 6.97 (d, *J*=2.0 Hz, 1H), 6.69 (dd, *J*=8.5, 2.0 Hz, 1H), 3.36 (br s, 2H), 3.18–3.16 (m, 2H), 2.93 (br s, 1H), 2.24 (br s, 2H), 1.88–1.80 (m, 2H), 1.73–1.62 (m, 2H), 1.40 (d, *J*=7.0 Hz, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 1.03 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.2, 154.4, 145.6, 143.9, 140.8, 138.6, 135.2, 129.8, 124.0, 115.8, 112.9, 47.6, 44.8, 39.6, 37.6, 35.6, 28.9, 28.1, 25.7, 19.8, 18.2, 11.0, −4.4 (two peaks); HRMS (EI) calcd for $C_{27}H_{38}O_2Si$ (M^+) *m/z* 422.2641, found 422.2638.

4.1.8. (6*S,7*S**)-11-(*tert*-Butyldimethylsilyloxy)-4,4,7-trimethyl-1,2,3,4,5,6,7,8-octahydrodibenzo-[*a*,*h*]azulen-6-ol (20).** To a solution of compound **19** (200 mg, 0.473 mmol) in MeOH (8 mL) was added $NaBH_4$ (27.0 mg, 0.710 mmol) at 0 °C. After 30 min, water (1 mL) was added to quench the reaction. Most of the methanol was then evaporated under reduced pressure, the residue was diluted with water (4 mL) and the aqueous layer was extracted with ether (2×40 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexane) to give compound **20** as a colorless oil (193 mg, 97%, 85% de). IR (neat) 3396, 2930, 1608, 1466, 1281, 1050, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) major isomer δ 7.26 (d, *J*=8.5 Hz, 1H), 6.90 (d, *J*=2.0 Hz, 1H), 6.65 (dd, *J*=8.5, 2.0 Hz, 1H), 3.90 (br s, 1H), 3.46 (d,

J=23 Hz, 1H), 3.34 (d, J=23 Hz, 1H), 2.57–2.49 (m, 2H), 2.35–2.29 (m, 1H), 2.24 (d, J=4.0 Hz, 2H), 1.80–1.75 (m, 3H), 1.68–1.64 (m, 2H), 1.31 (d, J=7.0 Hz, 3H), 1.21 (s, 3H), 1.12 (s, 3H), 1.03 (s, 9H), 0.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 148.3, 146.4, 141.5, 139.8, 135.6, 129.8, 123.7, 115.1, 112.6, 86.0, 42.1, 39.8, 38.9, 36.3, 34.6, 29.1, 28.8 (two peaks), 25.8, 20.0, 18.2, −4.4 (two peaks); HRMS (EI) calcd for $C_{27}H_{40}O_2Si$ (M^+) m/z 424.2798, found 424.2799.

4.1.9. 11-(*tert*-Butyldimethylsilyloxy)-4,4,7-trimethyl-1,2,3,4,5,6,7,8-octahydrodibenzo-[*a*,*h*]azulene (21). To a solution of **20** (180 mg, 0.42 mmol) and NEt_3 (215 mg, 2.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added MsCl (144 mg, 1.26 mmol), and the reaction mixture was stirred at this temperature for 1 h. The solution was then filtered through Celite and the solvent was evaporated under reduced pressure. The residue was then diluted with water (10 mL), the aqueous layer was extracted with ether (2×40 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then dissolved in anhydrous MeOH (8 mL) followed by the addition of NEt_3 (850 mg, 8.41 mmol) and $TsNHNH_2$ (782 mg, 4.20 mmol). The resulting solution was heated at reflux for 16 h. Upon cooling, the methanol solvent was evaporated under reduced pressure and the residue was taken up in water (10 mL). The aqueous mixture was extracted with ether (2×30 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (1% EtOAc in hexanes) to give compound **21** as a colorless oil (120 mg, 70%). IR (neat) 2928, 1461, 1049, 829 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (d, J=8.5 Hz, 1H), 6.84 (d, J=2.0 Hz, 1H), 6.61 (dd, J=8.5, 2.0 Hz, 1H), 3.43 (d, J=23 Hz, 1H), 3.33 (d, J=23 Hz, 1H), 2.71–2.61 (m, 2H), 2.26–2.18 (m, 1H), 2.07–1.97 (m, 2H), 1.91–1.84 (m, 1H), 1.79–1.65 (m, 3H), 1.60–1.56 (m, 2H), 1.19 (d, J=7.0 Hz, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.00 (s, 9H), 0.21 (s, 3H), 0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 151.0, 146.8, 145.4, 139.5, 135.7, 128.5, 123.7, 114.7, 112.2, 46.7, 39.8, 37.4, 35.2, 32.1, 30.4, 28.3, 28.3, 26.5, 25.8, 19.8, 18.2, −4.3, −4.4; HRMS (EI) calcd for $C_{27}H_{40}OSi$ (M^+) m/z 408.2848, found 408.2850.

4.1.10. 4,4,7-Trimethyl-1,2,3,4,5,6,7,8-octahydrodibenzo-[*a*,*h*]azulen-11-ol (8). To a solution of **21** (101 mg, 0.247 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.380 mL, 0.380 mmol) at room temperature and the resulting solution was stirred for 30 min. The reaction was then quenched by the addition of water (5 mL). The aqueous layer was extracted with ether (3×30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in hexane) to give compound **8** as a colorless oil (70 mg, 96%). IR (neat) 3395, 2927, 1457, 1049, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J=8.5 Hz, 1H), 6.87 (d, J=2.0 Hz, 1H), 6.59 (dd, J=8.5, 2.0 Hz, 1H), 4.68 (br s, 1H), 3.43 (d, J=23 Hz, 1H), 3.34 (d, J=23 Hz, 1H), 2.71–2.63 (m, 2H), 2.26–2.19 (m, 1H), 2.06–1.96 (m, 2H), 1.89–1.82 (m, 1H), 1.78–1.65 (m, 3H), 1.61–1.56 (m, 2H), 1.19 (d, J=7.0 Hz, 3H), 1.16 (s, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 151.6, 147.0, 145.6, 139.3, 135.2, 128.3, 124.0, 109.9, 107.4, 46.7, 39.7, 37.3, 35.2, 32.0, 30.3, 28.3 (two peaks), 26.5, 19.8, 18.2; HRMS (EI) calcd for $C_{21}H_{26}O$ (M^+) m/z 294.1984, found 294.1983.

4.1.11. (±)-Frondosin C and (±)-8-*epi*-frondosin C. Compound **8** (50.0 mg, 0.170 mmol) was dissolved in acetonitrile/water (5 mL, 4:1) and the resulting solution was cooled at 0 °C. Bis(trifluoroacetoxy)iodobenzene (BTIB, 88.0 mg, 0.205 mmol) was added and the resulting mixture was stirred at 0 °C for 10 min. Saturated aqueous $NaHCO_3$ (5 mL) was then added and the resulting heterogeneous mixture was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc in benzene) to give frondosin C as a pale yellow oil (24 mg, 46%) and 8-*epi*-frondosin C as a pale yellow oil (19 mg, 37%). Frondosin C: IR (neat) 3421, 2928, 1651, 1494, 1050, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.08 (dd, J=9.5, 2.0 Hz, 1H), 6.12 (dd, J=9.5, 2.0 Hz, 1H), 5.85 (d, J=2.0 Hz, 1H), 2.80 (dd, J=16.5, 1.9 Hz, 1H), 2.75 (d, J=16.5 Hz, 1H), 2.72–2.70 (m, 1H), 2.33 (dt, J=16.5, 4.5 Hz, 1H), 2.20–2.15 (m, 2H), 2.02–1.99 (m, 1H), 1.93–1.89 (m, 1H), 1.79–1.73 (m, 2H), 1.65–1.63 (m, 2H), 1.56–1.49 (m, 2H), 1.12 (s, 3H), 1.11 (d, J=7.0 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.5, 167.6, 161.1, 148.1, 145.9, 138.3, 129.7, 126.0, 116.4, 72.8, 45.4, 43.0, 39.3, 35.3, 33.5, 29.8, 27.9, 27.6, 26.3, 19.4, 17.7 (lit.[18] 186.5, 167.6, 161.0, 148.1, 145.9, 138.3, 129.6, 125.9, 116.3, 72.7, 45.4, 43.0, 39.3, 35.3, 33.4, 29.7, 27.8, 27.5, 26.3, 19.3, 17.7); HRMS (EI) calcd for $C_{21}H_{26}O_2$ (M^+) m/z 310.1933, found 310.1936.

8-*epi*-Frondosin C: IR (neat) 3397, 2927, 1651, 1494, 1049, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07 (d, J=9.5 Hz, 1H), 6.13 (dd, J=9.5, 1.5 Hz, 1H), 6.03 (d, J=1.5 Hz, 1H), 2.78 (d, J=16.5 Hz, 1H), 2.67 (d, J=16.5 Hz, 1H), 2.58–2.53 (m, 1H), 2.27–2.18 (m, 2H), 2.14–2.00 (m, 3H), 1.70–1.60 (m, 2H), 1.58–1.46 (m, 4H), 1.15 (d, J=7.0 Hz, 3H), 1.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.7, 168.4, 160.4, 147.8, 146.1, 137.1, 129.3, 125.5, 117.4, 72.6, 44.7, 42.2, 39.4, 35.9, 35.4, 29.1, 28.9, 27.9, 26.6, 19.7, 18.5; HRMS (EI) calcd for $C_{21}H_{26}O_2$ (M^+) m/z 310.1933, found 310.1935.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for compounds **8–11**, **13–16**, **19–21**, (±)-frondosin C, and (±)-8-*epi*-frondosin C.

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.057.

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