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Total synthesis of *seco*-lateriflorone

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Abstract—A convergent strategy toward the synthesis of lateriflorone (**5**) is described. Our approach is based on biosynthetic considerations and draws on a sequence of prenylation, oxygenation and Claisen reactions for the construction of chromenequinone **6**, and a tandem Claisen/Diels–Alder reaction cascade for the synthesis of caged tricycle **7**. Union of fragments **6** and **7** led to the synthesis of *seco*-lateriflorone (**49**).

1. Introduction and retrosynthetic analysis

The *Garcinia* species of plants provide a rich source of secondary metabolites that are characterized by interesting chemical architectures and diverse biological activities.[1] Among them is included a family of xanthone-based natural products exemplified by morellin (**1**),[2] desoxymorellin (**2**),[3] scortechinone A (**3**),[4] forbesione (**4**)[5] and lateriflorone (**5**)[6] (Fig. 1). The chemical structure of these compounds is highlighted by the fusion of a unique 4-oxa-tricyclo[4.3.1.0^{3,7}]decan-2-one scaffold onto a common xanthone motif. This unusual caged structure plays an essential role in the biological activity of the above metabolites and constitutes an intriguing synthetic target. An added level of architectural complexity is encountered in the structure of lateriflorone (**5**), in which the caged scaffold is connected to a chromenequinone fragment via an unprecedented spiroxalactone functionality.

From a biosynthetic point of view, all these natural products are postulated to derive from benzophenone or benzophenone-like intermediates that, upon an intramolecular oxidative coupling, produce a common xanthone scaffold.[7] A series of plant-specific oxygenations and prenylations could then set the stage for a tandem Claisen/Diels–Alder reaction thereby constructing the caged scaffold. This biosynthetic scenario was initially proposed by Quillinan and Scheinmann in 1971[8] and subsequently put to test by Nicolaou and Li during their pursuit of the total synthesis of forbesione (**4**).[9] Moreover, two related biosynthetic hypotheses were proposed for the unique spiroxalactone core of lateriflorone (**5**).[6] The first is based on an oxidative rearrangement of a xanthone precursor, while the second rests upon condensation of two fully functionalized fragments such as **6** and **7** (Fig. 2). In the synthetic direction, these two fragments are envisioned to combine at the C3′ center of **6** (lateriflorone numbering) through a biomimetic type of condensation, i.e. spirolactonization, to produce **5**. The chromenequinone functionality of **6** was projected to be formed via a double Claisen rearrangement[10] revealing phenolic ether **8** as the putative synthetic precursor. This type of disconnection suggested the use of pyrogallol (**9**), having three of the four needed hydroxyl groups at positions 3′, 4′ and 5′ (lateriflorone numbering), as the starting material of choice. On the other hand, the tricyclic motif of **7** was projected to be formed from benzodioxanone **10** via a biomimetic Claisen/Diels–Alder reaction.[11] The latter compound could be synthetically accessible from commercially available 4-hydroxysalicylic acid (**11**). Herein, we disclose the results of our studies based on such retrosynthetic considerations.[12]

2. Synthesis of the chromenequinone fragment 6

Our initial studies towards fragment **6** commenced with exhaustive benzylation of pyrogallol (**9**)[13] to produce the corresponding tris-benzyloxybenzene, which after oxidation with nitric acid,[14] led to 3′,5′-bis-benzyloxy-[1′,4′]benzoquinone (**12**) in 44% overall yield (Scheme 1). The other major product of this reaction, isolated in 39% yield, was found to be the 3′,4′,5′-tris-benzyloxy-1′-nitrobenzene. Clemmensen reduction of benzoquinone **12** using Zn dust in hot 25% H_2SO_4/EtOH afforded the intermediate hydroquinone which, without extensive purification, was alkylated with KOH and MeI in refluxing acetone to afford 3′,5′-bis-benzyloxy-1′,4′-dimethoxybenzene in 81% overall yield.[15] Exposure of the latter

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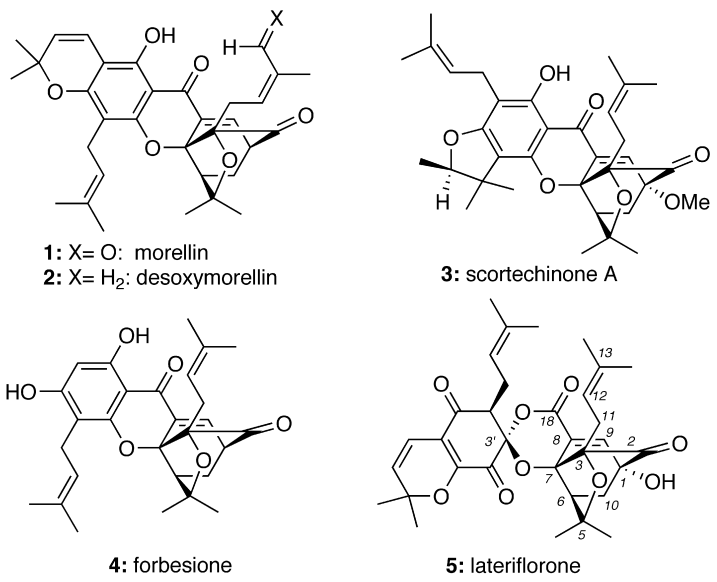


Figure 1. Selected xanthones from the *Garcinia* family of plants.

compound to hydrogenation under Pd (0) catalysis, gave rise to 2,5-dimethoxyresorcinol (**13**) in 94% yield.

Several methods were explored for an efficient conversion of **13** to **15**. Among them, alkylation with 1,1-dimethyl-prop-2-ynyl methyl carbonate (**14**) as the electrophile in combination with DBU as the base and $CuCl_2$ as the catalyst produced the best results.[16] After two successive rounds of alkylation under these conditions, propargyl ether **15** was formed in 81% yield, which, upon partial hydrogenation using Pd/$BaSO_4$ catalysis,[17] afforded the Claisen precursor **8** (80% yield) (Scheme 1).

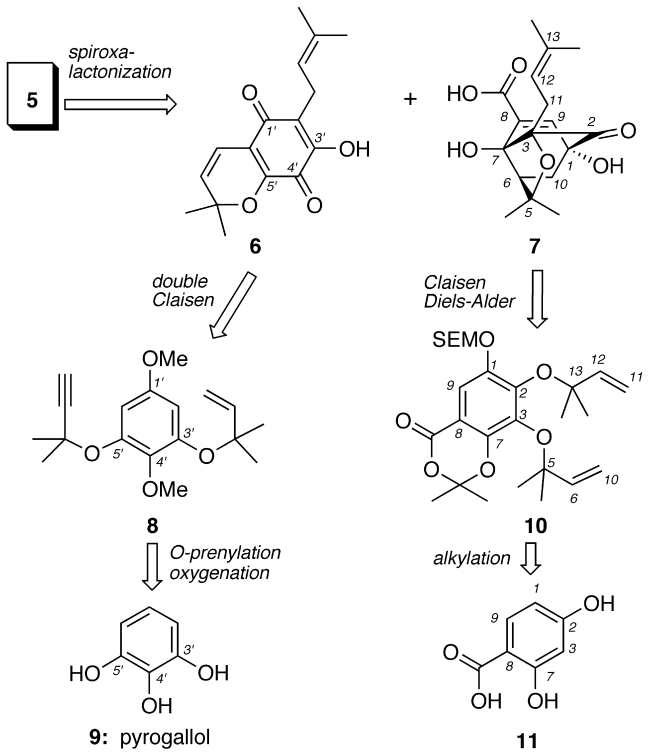
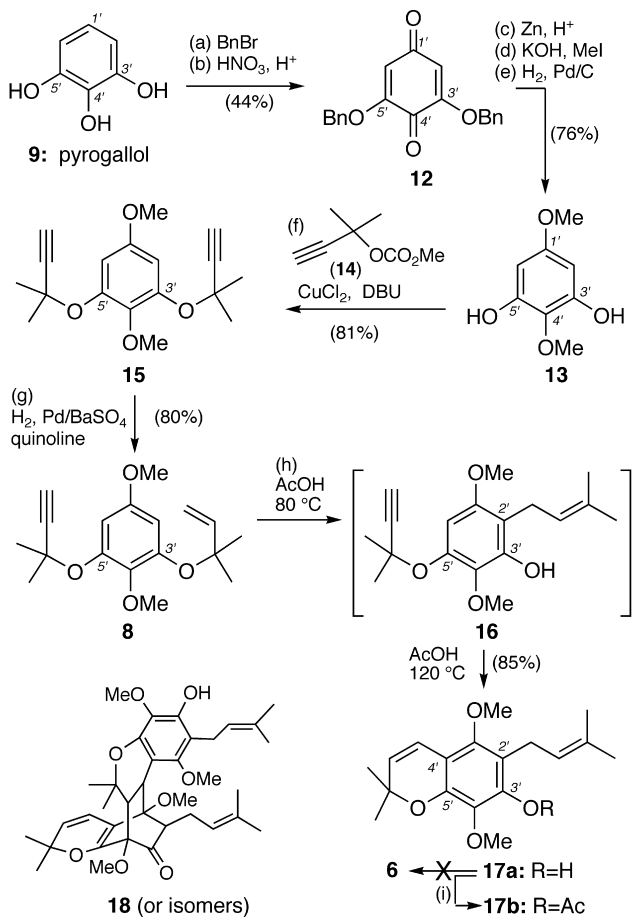


Figure 2. Proposed retrosynthetic analysis of lateriflorone (**5**).

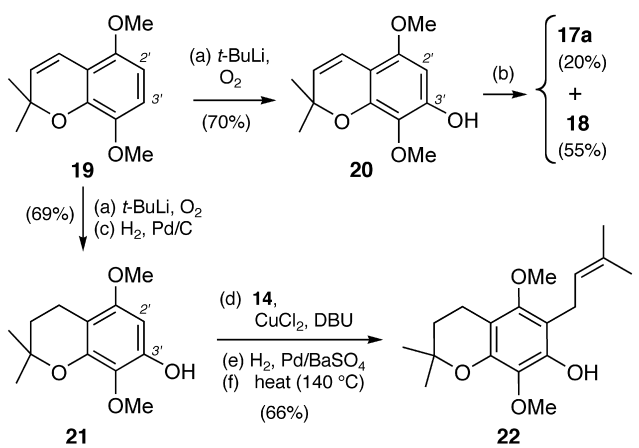
Having compound **8** in hand, the stage was set for the study of a double Claisen rearrangement. Based on similar examples from the literature we anticipated that the allylic ether at C3′ would undergo the [1,3] rearrangement at a lower temperature than that required for the cyclization of the propargylic ether appended at the C5′ center.[18] We were delighted to find that this was indeed the case. In fact, slow heating of **8** in CD_3CO_2D at 80°C led to a Claisen rearrangement of the pendant alkene and produced compound **16**, as evidenced by ^{1}H NMR studies. Gradual increase of the reaction temperature to 120°C (sealed tube) led to complete consumption of **16** and produced the desired bicyclic adduct **17a** in 85% isolated yield. Much to our surprise however, our attempts to demethylate hydroquinone **17a** met with failure. Deprotection attempts with $AlCl_3$/PhSH, PhSH/NMP, EtSNa, LiI/quinoline, TMSI and $AlBr_3$ gave back mainly starting material, while strong acidic/oxidative conditions (Ag_2O/HNO_3, CoF_3/H_2O, BBr_3, CAN/H_2O) led to decomposition of our substrate.

The choice of acetic acid as the solvent during the double Claisen rearrangement merits an additional comment.[19] Our initial studies were performed in refluxing *m*-xylene and led to isolation of compound **17a** in only 28% yield. Further investigation of this reaction indicated that the desired product was accompanied by substantial amounts of an inseparable mixture of dimeric species. Spectroscopic investigation of this mixture suggested that the aromatic ring and a chromene double bond had reacted together in a Diels–Alder reaction forming compound **18** and/or related isomers. This dimerization is, however, completely inhibited when the Claisen reaction is performed under acidic conditions.

To better understand the origins of the unusual reactivity of **17a** we attempted its construction at low temperature by C-alkylation of resorcinol adduct **20**[20] (Scheme 2). To this end, methylated hydroquinone **19** was initially oxygenated at the C3′ carbon center and subsequently subjected to alkylation with prenyl bromide at −30°C.[20] Despite the low temperature we still formed a mixture of compound **17a** (20%) and



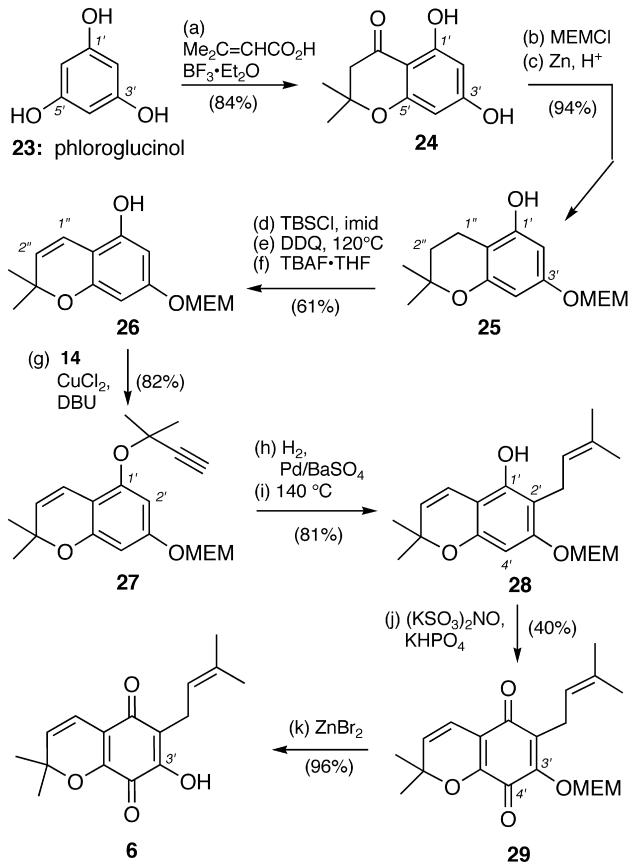
Scheme 1. *Reagents and conditions*: (a) 3.5 equiv. BnBr, 3.1 equiv. K_2CO_3, acetone, reflux, 15 h, 98%; (b) excess HNO_3, AcOH, 3 h, 45%; (c) 10.0 equiv. Zn dust, 25% H_2SO_4, EtOH, 80°C; (d) 5.0 equiv. KOH, 5.0 equiv. MeI, acetone, reflux, 81% (over two steps); (e) 10% Pd/C, H_2, EtOH/MeOH: 1:1, 3 h, 94%; (f) 2.4 equiv. **14**, 2.6 equiv. DBU, 0.03 equiv. $CuCl_2$, CH_3CN, 0°C, 8 h, 81%; (g) 3% Pd/$BaSO_4$, 3% quinoline, H_2, THF, 2 h, 80% (+13% recovered **15**); (h) AcOH, 80°C, 1 h then 120°C (sealed tube), 7 h, 85%; (i) 2.0 equiv. pyridine, Ac_2O, 25°C, 8 h, 97%.



Scheme 2. *Reagents and conditions*: (a) 3.0 equiv. *t*-BuLi, THF, 0°C, O_2 (excess), 30 min, 70%; (b) 1.1 equiv. NaH, toluene, 50°C, 4 h; 1.3 equiv. $Me_2C{=}CHCH_2Br$, −30°C, 12 h, 20% of **17a**, 55% of **18**; (c) 10% Pd/C, H_2, THF, 2 h, 98%; (d) 1.2 equiv. **14**, 1.3 equiv. DBU, 0.03 equiv. $CuCl_2$, CH_3CN, 0°C, 12 h, 89%; (e) 5% Pd/$BaSO_4$, 5% quinoline, H_2, THF, 30 min, 79%; (f) xylenes, 140°C, 8 h, 94%.

dimer(s) **18** (55%), together with some O-alkylation product (15%). These results suggested that the temperature does not play a significant role during the dimerization of **17a** to **18**. In addition, we observed that upon standing in Et_2O, compound **17a** was partially converted to **18**. It was also interesting to find that the reduced adduct **21** underwent the expected Claisen rearrangement producing exclusively **22**. This indicated that the chromene double bond is essential for dimerization. The above results indicted that dimerization of compound **17a** is due to both the presence of the chromene double bond and the highly oxygenated aromatic ring. It is also interesting to note that acid conditions (CH_3CO_2H) and/or protection of the C3′ phenol (such as **17b**) prevent dimerization. Based on these observations, we propose that a phenol–keto tautomerization at the C3′ center of **17a** triggers dearomatization, thereby revealing a very reactive diene unit. In the presence of the chromene double bond, a Diels–Alder reaction takes place consuming, at least partially, the desired product.

The unsuccessful conversion of **17a** to chromenequinone **6** led us to consider an alternative synthetic approach. The revised strategy departs from phloroglucinol (**23**) which contains three of the four phenolic oxygens at positions 1′, 3′



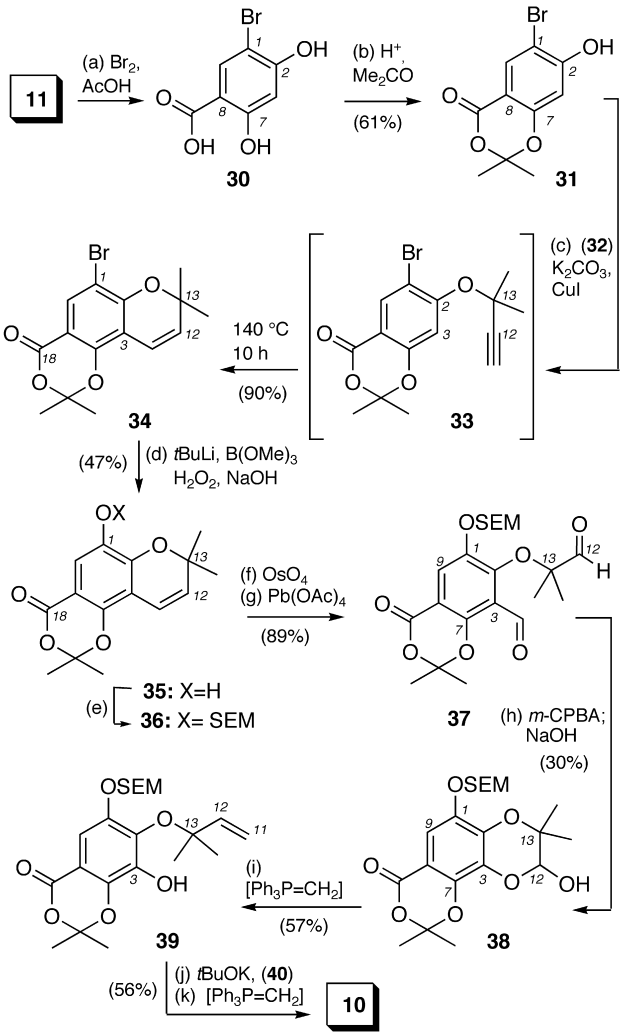
Scheme 3. *Reagents and conditions*: (a) 1.2 equiv. $Me_2C{=}CHCO_2H$, $BF_3{\cdot}OEt_2$, 80°C for 10 min, 25°C for 12 h, 84%; (b) 1.2 equiv. MEMCl, 1.4 equiv. *i*Pr_2EtN, CH_2Cl_2, 0°C, 2 h; (c) 10 equiv. Zn dust, excess HCl, MeOH, 0°C, 1 h, 94% (over two steps); (d) 1.3 equiv. TBSCl, 1.4 equiv. imid, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 8 h, 92%; (e) 2.1 equiv. DDQ, toluene, 120°C, 1 h, 72%; (f) 2.1 equiv. TBAF·THF, THF, 25°C, 30 min, 92%; (g) 1.2 equiv. **14**, 1.3 equiv. DBU, 0.03 equiv. $CuCl_2$, CH_3CN, 0°C, 12 h, 82%; (h) 5% Pd/$BaSO_4$, 5% quinoline, H_2, THF, 30 min, 82%; (i) xylenes, 140°C, 8 h, 99%; (j) 2.2 equiv. $(KSO_3)_2NO$, 2.4 equiv. KH_2PO_4, H_2O/acetone: 12:1, 6 h, 40%; (k) 3.0 equiv. $ZnBr_2$, CH_2Cl_2, 1 h, 96%.

and 5′, respectively (Scheme 3). Treatment of **23** with β,β-dimethylacrylic acid under Friedel–Crafts conditions produced chromanone **24** in 84% yield.[21] Selective protection of the more reactive C3′ phenol of **24** as the corresponding MEM ether[22] followed by reductive decarbonylation using Clemmensen conditions, furnished compound **25** in 94% combined yield. Introduction of unsaturation at the C1″–C2″ centers was expected to be accomplished using DDQ oxidation in refluxing toluene.[23,24] Surprisingly, this oxidation was unsuccessful when unprotected phenol **25** was used as the starting material and led to several non-identified degradation products. This problem was circumvented by transiently protecting **25** as the corresponding TBS ether. The latter compound underwent a smooth oxidation in the presence of DDQ and generated, after fluoride-induced desilylation, chromanol **26** in a combined yield of 61% (over three steps). Treatment of **26** with DBU, $CuCl_2$ (catalytic) and 1,1-dimethyl-prop-2-ynyl methyl carbonate (**14**) under previously described conditions gave rise to propargyl ether **27** in 82% yield. This compound was then reduced using Lindlar catalyst and subsequently heated in refluxing *m*-xylene to produce Claisen adduct **28** in 81% combined yield. Oxidation of **28** to **29** was accomplished using Fremy's salt.[25] Although the isolated yields of the purple quinone **29** were modest (ca. 40%), there was little decomposition and the remaining starting material was readily removed from the reaction mixture and recycled, bringing the cumulative yield of this oxidation to 69%. Finally, treatment of quinone **29** with an excess of $ZnBr_2$ in CH_2Cl_2 gave rise to chromenequinone **6** in 96% yield.[22]

3. Synthesis of the caged tricyclic fragment 7

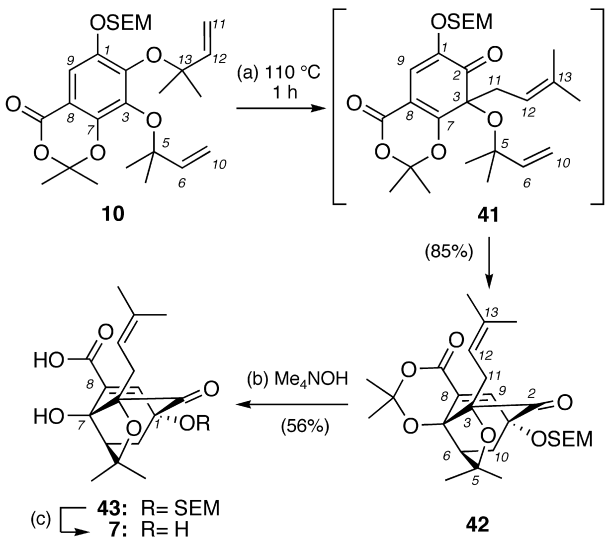
The synthesis of the caged fragment **7** of lateriflorone commenced with commercially available 4-hydroxysalicylic acid (**11**) and proceeded as shown in Schemes 4–6. Regioselective bromination of **11** afforded 5-bromo-4-hydroxysalicylic acid (**30**) in 91% yield (Scheme 4). Under these conditions, we also observed the formation of 3,5-dibromo-2-hydroxysalicylic acid as a minor byproduct (5% yield) that was easily separated from the desired adduct **30** using column chromatography. Selective protection of bromide **30** in the presence of acetone and TFAA/TFA furnished dioxanone **31** in 61% yield.[26] Phenol **31** was O-alkylated using 3-chloro-3-methylbutyne (**32**)[15] to produce alkyne **33** that, upon heating at 140°C overnight, was transformed to benzopyran **34** in 90% combined yield. Conversion of **34** to phenol **35** was achieved via treatment with *t*-BuLi and quenching of the resulting anion with trimethyl borate.[27] After aqueous extraction, the resulting boronic acid derivative was oxidized with aqueous 30% H_2O_2 to furnish **35** in 47% yield. The latter compound was then treated with SEMCl and DIPEA to afford SEM ether **36** in 77% yield.[28]

With compound **36** in hand, the focus was shifted to a strategy for the introduction of the remaining oxygen at the C3 position of the aromatic ring. To achieve this task, the chromene double bond was dihydroxylated[29] and subsequently oxidatively cleaved[30] to produce dialdehyde **37** in 89% combined yield. Our strategy was to introduce the oxygen at the C3 center of benzaldehyde derivative **37** via a



Scheme 4. *Reagents and conditions*: (a) 1.1 equiv. Br_2, HOAc, 5 h, 25°C, 91%; (b) 5.0 equiv. $(CH_3)_2CO$, 3.0 equiv. TFAA, TFA, 10 h, 0 to 25°C, 61%; (c) 2.5 equiv. 3-chloro-3-methyl-1-butyne (**32**), 1.3 equiv. K_2CO_3, 1.1 equiv. KI, 1 mol% CuI, $(CH_3)_2CO$, 0.5 h, reflux; then DMF, 10 h, 140°C, 90%; (d) 2.0 equiv. *t*-BuLi, 3.0 equiv. $B(OMe)_3$, THF, 0.5 h, −78 to −30°C; then excess 30% H_2O_2 (aq), 1N NaOH (aq), 10 h, −30 to 25°C, 47%; (e) 3.0 equiv. SEMCl, 4.0 equiv. DIPEA, 10 h, 0 to 25°C, 77%; (f) 1.6 equiv. NMO, 0.3 mol% OsO_4, H_2O/THF/*t*-BuOH, 12 h, 25°C; (g) 1.2 equiv. $Pb(OAc)_4$, CH_2Cl_2, 0.3 h, 25°C, 89% (over two steps); (h) 0.5 equiv. *m*-CPBA per 0.5 h, CH_2Cl_2, 6 h, 0°C; then 0.3 equiv. 1N NaOH (aq) per 0.2 h, MeOH, 1 h, 25°C, 30%; (i) 3.0 equiv. methyltriphenylphosphonium bromide, 2.5 equiv. NaHMDS, THF, 1 h, 0 to 25°C, 57%; (j) 1.1 equiv. *t*-BuOK, THF, 0.5 h, 0 to 25°C; then 1.5 equiv. α-bromoisobutyraldehyde (**40**), 1.0 equiv. 18-C-6, CH_3CN, 1.0 h, 0 to 60°C, 80%; (k) 2.1 equiv. methyltriphenylphosphonium bromide, 1.6 equiv. NaHMDS, THF, 1 h, 0 to 25°C, 70%.

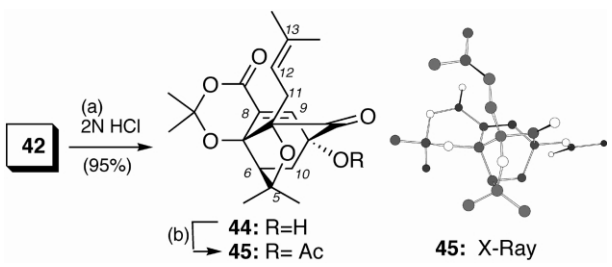
Baeyer–Villiger oxidation.[31] Although this transformation was successfully applied by our laboratories in related systems,[32] in this case it proved to be rather problematic, presumably due to the steric hindrance around the benzaldehyde center. A variety of oxidants including *m*-CPBA, MMPP and TFPA, were used over a range of temperatures in reaction mixtures of different concentrations. Among them, we found that treatment of a dilute solution of dialdehyde **37** at 0°C with 0.5 equiv. of *m*-CPBA in CH_2Cl_2 every 0.5 h was the key to success. Careful saponification of the resulting formate ester with 1N NaOH in MeOH gave lactol **38**, albeit in only 30% yield. This compound was subjected to a Wittig olefination reaction to



Scheme 5. *Reagents and conditions*: (a) $PhCH_3$, 1 h, 110°C, 85%; (b) excess 5% NMe_4OH (aq), MeOH, 2.5 h, 25°C, 56%; (c) excess 2N HCl (aq), MeOH, 0.5 h, 25°C, 95%.

form alkene **39** in 57% yield. It is interesting to note at this point that protecting phenol **35** as its corresponding SEM ether was critical to the success of this strategy. The related TBS ether was found to be labile during the described manipulations and, in fact, it could not survive the olefination conditions. Treatment of the potassium salt of **39** with α-bromoisobutyraldehyde (**40**)[9] in the presence of 18-C-6 produced the corresponding α-phenoxy carboxaldehyde that was subsequently converted to alkene **10** using a second Wittig olefination (56% combined yield).

With alkene **10** available, attention was turned to the final steps required for the synthesis of lateriflorone's proposed biosynthetic precursor **7**. To implement the biomimetic Claisen/Diels–Alder cascade, we heated bis-(α,α-dimethylallyl) aryl ether **10** in toluene at 110°C and observed the formation of a single product **42** in 85% yield (Scheme 5). The structure and composition of **42** were ultimately confirmed by crystallographic analysis of derivative **45**, which proved that the tandem rearrangement produced exclusively the desired tricyclic scaffold (Scheme 6). It is also worth mentioning that compound **10** can be converted to **42**, in comparable yield, simply upon standing at room temperature for a number of days. Such facile rearrangement could be attributed to the cumulative electron donating effect of the four oxygens attached to the aromatic ring of **10** prompting its dearomatization through a tandem Claisen/Diels–Alder reaction cascade.



Scheme 6. *Reagents and conditions*: (a) excess 2N HCl (aq), MeOH, 0.5 h, 25°C, 95%; (b) 10 equiv. pyridine, 10 equiv. CH_3COCl, 10 equiv. Ac_2O, 0.1 equiv. DMAP, $CHCl_3$, 80°C (sealed tube), 10 h, 92%.

Having confirmed the structure of **42**, we sought to develop appropriate deprotection conditions for the sequential removal of the silyl ether and the acetonide units. To this end, exposure of **42** to 5% NMe_4OH (aq) in MeOH was found to provide the optimum saponification conditions and produced the desired β-hydroxy carboxylic acid **43** in 56% yield.[36] Desilylation of the O1-silyl ether was best accomplished in the presence of 2N HCl in MeOH and gave rise to desired fragment **7** in 94% yield (Scheme 5).[37]

Of particular interest was the excellent regioselectivity observed during the tandem Claisen/Diels–Alder reaction. In principle, compound **10** can undergo two different *ortho*-Claisen rearrangements to produce structures **41** and **46** that, after the tandem Diels–Alder reaction, are expected to furnish adducts **42** and **47**, respectively (Fig. 3).[33] Exclusive conversion of compound **10** to desired regioisomer **42** could be attributed to the electronic effects of the substituents on the aromatic ring, that elicit the formation of Claisen adduct **41**.[19,34] With this in mind, it appears that having preinstalled all functionalities at the correct oxidation state in compound **10** triggers the desired rearrangement producing exclusively tricycle **42**.[35] Such regiochemical preference during this tandem rearrangement is also manifested in Nature, since the vast majority of the caged *Garcinia* natural products are highlighted by the same tricyclic scaffold (Fig. 1).

4. Coupling of fragments 6 and 7 and synthesis of *seco*-lateriflorone

With both fragments **6** and **7** in hand we were able to examine several biomimetic scenarios for the construction of the spiroxalactone functionality of lateriflorone. Our initial attempts were focused on developing conditions for an one-step spiroxalactonization reaction. Consequently, compounds **6** and **7** were treated with a variety of acids or Lewis acids (such as PPTS, TsOH, Ac_2O, TFA/TFAA, $ZnCl_2$, $AlCl_3$ and $TiCl_4$) under several reaction conditions. Unfortunately, all these reactions led to decomposition of

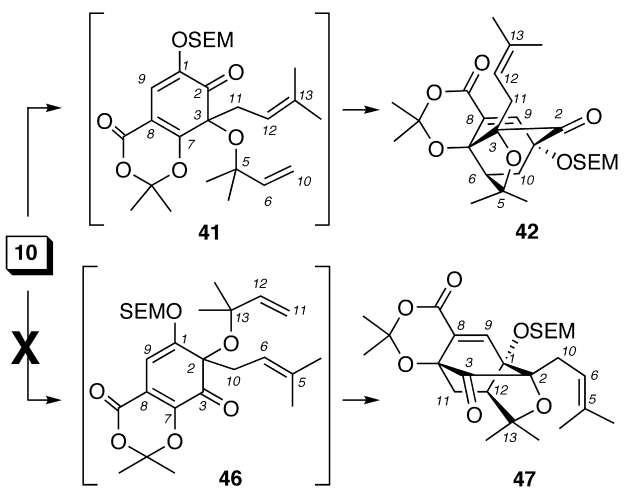
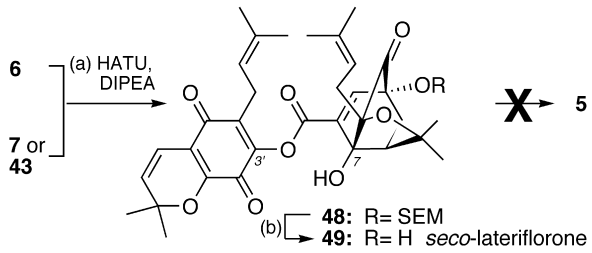


Figure 3. Possible isomers anticipated from the tandem Claisen/Diels–Alder reaction of compound **10**.



Scheme 7. *Reagents and conditions*: (a) 2.0 equiv. DIPEA, 1.2 equiv. HATU, CH_3CN, 25°C, 30 min, 51% (**6**+**7**) and 62% (**6**+**43**); (b) excess 2N HCl (aq), MeOH, 1 h, 25°C, 93%.

the fragments and showed no evidence that the desired spiroxalactone structure had been formed. Similar studies were also performed using partially protected adduct **43** as the right hand coupling partner, but proved to be equally unsuccessful.

Faced with such results we examined a stepwise approach to the spiroxalactone core initiated by connecting the two fragments via an ester linkage (Scheme 7). Along these lines, the standard DCC-mediated coupling of **6** and **7** produced the coupling product **48** in only 14% yield. To further optimize the coupling yield we examined the use of several reagents, such as HATU, HBTU, BOP-Cl and BOP reagent. In a typical condensation involving one of these reagents, the starting materials were dissolved in acetonitrile containing DIPEA and treated with the coupling reagent. Among them, condensation with HATU was found to be the most efficient, both in terms of product yield and reaction times. Under the above reaction conditions, use of HATU led to a 51% yield of *seco*-lateriflorone (**49**), while a 62% yield of compound **48** was obtained using the semiprotected partner **43** for the coupling. Compound **48** could then converted to **49** by acid-induced desilylation as previously described (93% yield).

Having secured a route to *seco*-lateriflorone (**49**) and its SEM protected analog **48** we turned our attention to form the ether linkage between centers C3′ and C7. Unfortunately, acid conditions (PPTS, TsOH, TFA/TFAA, $CeCl_3$, $TiCl_4$) were ineffective while basic conditions (DIPEA, DBU, *t*-BuOK/*t*-BuOH, $CsCO_3$) led to a slow decomposition of the coupling partners.[38] We also attempted to form lateriflorone via reduction/oxidation of either *seco*-lateriflorone (**49**) or its SEM protected analog **48**. These compounds were reduced with $NaBH_4$ in AcOH/THF to yield the respective hydroquinones,[39] which after isolation, were treated with periodine-based reagents, such as IBX,[40] [bis(trifluoroacetoxy)iodo]benzene (BTIB)[41] or $PhI(OAc)_2$,[42] hoping to effect the spirolactonization and concomitant oxidation to lateriflorone. Unfortunately, such redox treatment gave back the non-cyclized starting materials.

5. Conclusion

In conclusion we have presented herein an efficient and convergent strategy toward the synthesis of lateriflorone (**5**). Our synthetic approach was inspired by biosynthetic considerations and is highlighted by the implementation of a Claisen/Diels–Alder cascade reaction that produced, in an efficient and regioselective fashion, the tricyclic fragment **7** of lateriflorone. Variations of the aromatic Claisen rearrangement were also implemented for the synthesis of the chromenequinone adduct **6**, which represents the left hemisphere of lateriflorone. Specifically, a double Claisen reaction was employed for the conversion of adduct **8** to benzopyran structure **17** while a sequence of Claisen rearrangement and Fremy's oxidation allowed the construction of adduct **29**, a precursor of fragment **6**. Our strategy yielded the first total synthesis of *seco*-lateriflorone **49** which could not be converted to lateriflorone (**5**).

6. Experimental

6.1. General techniques

All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45°C at approximately 20 mm Hg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (ether, Et_2O), dichloromethane (CH_2Cl_2), toluene ($PhCH_3$) and benzene (PhH) were purified by passage through a bed of activated alumina. Pyridine, *N*,*N*-diisopropylethylamine, triethylamine and boron trifluoride etherate were distilled from calcium hydride prior to use. Pyrogallol (**9**), 4-hydroxysalicylic acid (**11**) and phloroglucinol (**23**) were commercially available and used without any additional purification. Yields refer to chromatographically and spectroscopically (^1H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. X-Ray data were recorded on a Bruker SMART APEX 3kW Sealed Tube X-ray diffraction system.

6.1.1. 2,6-Bis-benzyloxy-[1,4]benzoquinone (12). To a stirring solution of pyrogallol (**9**) (60.0 g, 0.48 mol) in

acetone (1 L) was added K_2CO_3 (197.3 g, 1.47 mol) and benzyl bromide (284.8 g, 1.67 mol). The reaction mixture was then put under argon and refluxed for 15 h with vigorous stirring. Potassium carbonate was removed by gravity filtration and the filtrate concentrated to a brown oil. Treatment of the crude material with hexane precipitated the product and allowed the excess benzyl bromide to be washed away. The product was then recrystallized from hot methanol to yield 1,2,3-tris-benzyloxybenzene (184.9 g, 0.47 mol, 98%). R_f=0.6 (30% Et_2O/hexane). IR (film) ν_{max} 3029, 1596, 1456, 1099, 738; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.29 (m, 15H), 6.96 (t, J=8.4 Hz, 1H), 6.67 (d, J=8.4 Hz, 2H), 5.14 (s, 4H), 5.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 138.3, 137.7, 137.0, 128.4, 128.3, 128.0, 127.6, 127.64, 127.60, 123.5, 107.8, 75.1, 71.1; HRMS calcd for $C_{27}H_{24}O_3$ (M+Na^+) 419.1618, found 419.1634. A solution of 1,2,3-tris-benzyloxybenzene (101.1 g, 0.25 mol) in acetic acid (1 L) was stirred and gradually brought to 40°C. To this solution was added 30% HNO_3 dropwise until a precipitate persisted. At this point, both heating and stirring were discontinued and the reaction mixture was allowed to stand for 15 h. The reaction mixture was then filtered and the crystals washed with hexane. The crude material was column chromatographed (CH_2Cl_2 then 25% Et_2O/CH_2Cl_2) to yield 1,2,3-tris-benzyloxy-5-nitro-benzene (61.9 g, 0.14 mol, 51%) and 2,6-bis-benzyloxy-[1,4]benzoquinone (**12**) (36.8 g, 0.11 mol, 45%). 1,2,3-tris-benzyloxy-5-nitro-benzene: R_f=0.5 (30% Et_2O/hexane). IR (nujol) ν_{max} 1522, 1348, 1126, 862, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 2H), 7.44–7.24 (m, 15H), 5.16 (s, 2H), 5.15 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 143.5, 143.1, 136.7, 135.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.4, 103.1, 75.2, 71.3; HRMS calcd for $C_{27}H_{23}NO_5$ (M+Na^+) 464.1468, found 464.1467.

Compound **12**. R_f=0.15 (50% Et_2O/hexane). IR (nujol) ν_{max} 1643, 1588, 1254, 1091, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 10H), 5.87 (s, 2H), 5.03 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 156.0, 133.9, 128.73, 128.72, 128.6, 127.4, 108.5, 71.2; HRMS calcd for $C_{20}H_{16}O_4$ (M+H^+) 321.1121, found 321.1132.

6.1.2. 2,5-Dimethoxy resorcinol (13). To a solution of **12** (27.8 g, 86.7 mmol) in ethanol (900 mL) was added Zn dust (55.5 g, 0.85 mol). After reaching reflux, 25% H_2SO_4 (41.7 mL) was added dropwise by means of an addition funnel. After the yellow solution became colorless, the reaction mixture was filtered through celite. The filtrate was diluted with a large amount of ether and separated from the aqueous layer. The aqueous layer was back-extracted and the combined ether layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude 2,6-bis-benzyloxy-benzene-1,4-diol was dissolved in acetone (300 mL). To this solution was added KOH (24.3 g, 0.43 mol) and methyl iodide (27.0 mL, 0.35 mol) and the resulting reaction mixture was heated at reflux for 4 h. The reaction mixture was diluted with a large amount of ether and water. The ether layer was separated, dried over $MgSO_4$, filtered and concentrated. The crude material was column chromatographed (CH_2Cl_2) to yield 1,3-bis-benzyloxy-2,5-dimethoxybenzene (24.6 g, 70.3 mmol, 81%). R_f=0.45 (30% Et_2O/hexane); IR (film) ν_{max} 2936, 1592, 1507, 1150, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.30 (m, 10H), 6.20 (s, 2H), 5.13 (s, 4H), 3.86 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 152.7, 137.0, 128.4, 127.7, 127.1, 94.4, 71.1, 61.1, 55.5. HRMS calcd for $C_{22}H_{22}O_4$ (M+Na^+) 373.1410, found 373.1423. To a solution of 1,3-bis-benzyloxy-2,5-dimethoxybenzene (24.7 g, 70.5 mmol) partially dissolved in ethanol (700 mL) was added 10% Pd/C (2.48 g) with vigorous stirring. The reaction vessel was then evacuated and the atmosphere replaced with hydrogen. After 6 h, the reaction mixture was filtered through celite and the filtrate concentrated. The crude material was then chromatographed over silica gel (50% Et_2O/hexane) to yield 2,5-dimethoxyresorcinol (**13**) (11.3 g, 66.4 mmol, 94%). R_f=0.7 (Et_2O). IR (film) ν_{max} 3487, 3153, 1627, 1332, 1064; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 2H), 5.66 (br s, 2H), 3.80 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 149.1, 128.7, 94.2, 61.5, 55.5. HRMS calcd for $C_8H_{10}O_4$ (M+H^+) 171.0652, found 171.0658.

6.1.3. 1,1-Dimethyl-prop-2-ynyl methyl carbonate (14). To a solution of commercially available 2-methyl-but-3-yn-2-ol (48.0 g, 0.57 mol) in THF (600 mL) under argon at 0°C was added dropwise 2.5 M *n*-BuLi in hexane (228 mL, 0.57 mol). After complete addition and an additional 0.5 h of stirring, methyl chloroformate (53.9 g, 0.57 mol) was added dropwise. The reaction mixture was allowed to warm to 25°C and allowed to stir an additional hour. The reaction mixture was then partitioned between dichloromethane and water. The water layer was extracted once more with ether (2×100 mL) and the combined organic layers dried with $MgSO_4$, filtered and concentrated. The crude material was distilled under vacuum to yield 1,1-dimethylprop-2-ynyl methyl carbonate (**14**) (75.4 g, 0.53 mol, 93%).

Compound **14**. Bp 182–184°C/760 mm Hg; IR (neat) ν_{max} 3289, 2959, 2124, 1757, 1277.^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 2.57 (s, 1H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 83.9, 72.8, 67.8, 54.3, 28.7.

6.1.4. Alkyne 15. To a solution of compound **13** (3.4 g, 0.020 mol) in anhydrous acetonitrile (250 mL) was added anhydrous $CuCl_2$ (100 mg, 6 μmol) at 0°C. DBU (3.9 mL, 26.3 mmol) was next added dropwise and the yellow solution became green. After 15 min of stirring, the carbonate **14** (7.53 mL, 0.06 mol) was added dropwise and the reaction mixture was stirred overnight at 0°C. The reaction was quenched with water and extracted with ether (3×100 mL). The organic solution was washed with 10% aqueous $CuSO_4$ solution and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (1:20 ether/hexane) afforded alkyne **15** (4.89 g, 81%).

Compound **15**. Yellow oil; R_f=0.6 (silica, 25% ether in hexanes); IR (film) ν_{max} 3284, 2988, 2937, 1603, 1588, 1492, 1466, 1432, 1230, 1195, 1136, 1064; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.55 (s, 2H), 1.65 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 149.4, 140.4, 103.7, 86.5, 73.7, 73.3, 60.7, 55.4, 29.4; HRMS calcd for $C_{18}H_{22}O_4$ (M+Na^+) 303.1596, found 303.1599.

6.1.5. Allyl ether 8. To a solution of alkyne **15** (540 mg, 1.79 mmol) in THF (15 mL) was added Lindlar's catalyst,

Pd $CaCO_3$ (16 mg) and quinoline (5 μL) and the mixture was subjected to hydrogenation. The reaction was monitored by TLC to prevent over-reduction. After most of the starting material was consumed (2 h), the reaction was filtered through celite, concentrated and subjected to a silica gel chromatography (1:20 ether/hexane) to afford allyl ether **8** (348 mg, 80%) plus recovered **15** (13%).

Compound **8**. Colorless liquid; R_f=0.63 (silica, 25% ether in hexanes); IR (film) ν_{max} 3282, 2984, 2936, 1601, 1586, 1490, 1430, 1230, 1133, 1065 1011; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J=3.2 Hz, 1H), 6.39 (d, J=3.2 Hz, 1H), 6.16 (dd, J=17.2, 10.8 Hz, 1H), 5.18 (dd, J=17.2, 0.8 Hz, 1H), 5.10 (dd, J=10.8, 0.8 Hz, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 2.54 (s, 1H), 1.64 (s, 6H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ154.1, 144.4, 140.6, 127.4, 113.1, 86.6, 80.9, 73.7, 73.3, 60.6, 55.4, 29.4, 26.7; HRMS calcd for $C_{18}H_{24}O_4$ ($M+H^+$) 305.1752, found 305.1769.

6.1.6. Chromene 17a. A solution of compound **8** (900 mg, 2.96 mmol) in AcOH (50 mL) was heated to 80°C for 1 h and for 7 h at 120°C. The solution was diluted with water and extracted with ether. The organic layers were washed with aqueous saturated $NaHCO_3$, collected and concentrated. The residue was chromatographed on silica gel (ether/hexane: 1:15) to afford product **17a** (765 mg, 2.51 mmol, 85%).

Compound **17a**. Yellow oil; R_f=0.71 (silica, 50% ether in hexanes); IR (film) ν_{max} 3407 (br), 2973, 2929, 1604, 1470, 1435, 1166, 1052, 981; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (d, J=10.0 Hz, 1H), 5.90 (s, 1H), 5.48 (d, J=10.0 Hz, 1H), 5.23 (t, J=7.2 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 3.28 (d, J=7.2 Hz, 2H), 1.78 (s, 3H), 1.69 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 147.6, 143.5, 131.8, 131.3, 127.0, 123.1, 117.5, 113.1, 108.1, 76.1, 62.4, 61.1, 27.8, 27.7, 25.8, 22.8, 17.8; HRMS calcd for $C_{18}H_{24}O_4$ ($M+H^+$) 305.1752, found 305.1771.

6.1.7. Acetate 17b. To a solution of chromene **17a** (600 mg, 1.97 mmol) in Ac_2O (3 mL) was added pyridine (0.32 mL, 3.94 mmol) and the mixture was stirred for 8 h at 25°C. The reaction was quenched with H_2O (10 mL) and worked up with ether (3×10 mL). The aqueous layers were washed with brine, collected, dried with $MgSO_4$, and chromatographed to give acetate **17b** (662 mL, 97%).

Compound **17b**. Yellow oil; R_f=0.55 (silica, 50% ether in hexanes); IR (film) ν_{max} 2973, 2935, 1766, 1469, 1375, 1203, 1130, 1097, 1055; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, J=10.5 Hz, 1H), 5.60 (d, J=10.5 Hz, 1H), 5.07 (t, J=6.5 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.17 (d, J=6.5 Hz, 2H), 2.27 (s, 3H), 1.77 (s, 3H), 1.62 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 149.5, 144.6, 142.6, 137.2, 131.3, 129.7, 122.8, 119.5, 117.1, 113.8, 76.2, 62.5, 60.5, 27.6, 25.6, 23.4, 20.5, 17.8; HRMS calcd for $C_{20}H_{26}O_5$ ($M+Na^+$) 369.1678, found 369.1689.

6.1.8. Phenol 20. A solution of compound **19** (100 mg, 0.45 mmol) in THF was cooled to 0° C and treated under stirring with *t*BuLi (0.80 mL of 1.7 M in pentane) added dropwise over a period of 20 min. Next, excess O_2 was bubbled through the reaction. The dark yellow solution was quenched with aqueous $Na_2S_2O_3$ (10 mL) and extracted with ether (3×10 mL). The collected organic fractions were washed with brine, dried ($MgSO_4$), concentrated and chromatographed on silica to afford phenol **20** (74 mg, 70%, plus 20% of recovered **19**).

Compound **20**. Red solid; R_f=0.4 (silica, 50% ether in hexanes); IR (film) ν_{max} 3416 (br), 2926, 2852, 1608, 1501, 1465, 1124, 1098, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J=10.0 Hz, 1H), 6.08 (s, 1H), 5.81 (s, 1H), 5.42 (d, J=10.0 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 149.2, 145.6, 129.2, 125.5, 116.8, 104.2, 90.7, 61.3, 55.8, 29.8, 27.8; HRMS calcd for $C_{13}H_{16}O_4$ ($M+H^+$) 237.1121, found 237.1123.

6.1.9. Phenol 21. To a solution of compound **20** (224 mg, 0.95 mmol) in THF was added 10% Pd/C (25 mg) and the mixture was hydrogenated for 2 h under an atmosphere of H_2 (balloon). Filtration over celite afforded compound **21** that was directly used in the next step. A purified sample was used for analysis.

Compound **21**. Yellow solids; R_f=0.4 (silica, 50% ether in hexanes); IR (film) ν_{max} 3425 (br), 2973, 2936, 1613, 1499, 1466, 1194, 1161, 1101, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.56 (t, J=6.8 Hz, 2H), 1.74 (t, J=6.8 Hz, 2H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 147.1, 147.0, 129.1, 102.4, 89.6, 74.4, 60.8, 55.3, 32.1, 26.5, 16.7; HRMS calcd for $C_{13}H_{18}O_4$ ($M+H^+$) 239.1283, found 239.1291.

6.1.10. Phenol 22. To a solution of crude **21** (222 mg, 0.93 mmol) in anhydrous acetonitrile (3 mL) was added anhydrous $CuCl_2$ (5 mg, 0.028 mmol) at 0°C. DBU (0.18 mL, 1.21 mmol) was next added dropwise and the yellow solution became green. After 15 min of stirring, carbonate **14** (0.14 mL, 1.11 mmol) was added dropwise and the reaction mixture was stirred overnight at 0°C. The reaction was quenched with water (20 mL) and extracted with ether (3×20 mL). The organic solutions were washed with 10% aqueous $CuSO_4$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting alkyne was purified by chromatography on silica gel (251 mg, 89%) as a yellow oil. A solution of this alkyne in THF (3 mL) was treated with Pd/$BaSO_4$ (10 mg) and quinoline (5 μL) and the mixture was hydrogenated under an atmosphere of H_2 (balloon). The reaction was monitored by TLC to minimize over-reduction. Once most of the starting material was consumed (ca. 30 min), the reaction was filtered through celite and concentrated for use directly in the Claisen rearrangement. Xylenes (5 mL) was added directly to the crude mixture above and the mixture heated at 140°C for 8 h. The yellow solution was condensed and directly purified by column chromatography (1:10 ether/hexane) to yield **22** (189 mg, 74% over 2 steps).

Compound **22**. Light yellow oil; R_f=0.5 (silica, 50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (br s, 1H), 4.88–4.84 (m, 1H), 3.75 (s, 3H), 3.09 (s, 3H), 2.58 (d, J=7.6 Hz, 2H), 2.36–2.20 (m, 2H), 1.74–1.57 (m, 2H), 1.58 (s, 3H), 1.53 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 175.2, 160.6, 136.2, 117.1, 105.7, 96.8, 77.9, 57.5, 54.4, 40.2, 33.4, 28.4, 27.3, 27.2, 19.5, 17.6;

HRMS calcd for $C_{18}H_{26}O_4$ ($M+H^+$) 307.1909, found 307.1930.

6.1.11. Phenol 25. A solution of compound **24** (27.0 g, 0.120 mol) in CH_2Cl_2 (50 mL) at 0°C was treated under argon with diisopropylethylamine (29.3 mL, 0.168 mol) followed by dropwise addition of MEMCl (16.4 mL, 0.144 mol). After 2 h at 0°C, the reaction was quenched with a saturated solution of NH_4Cl (100 mL), and extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated and subjected to silica chromatography (1:7 ether/hexane) to give the semiprotected chromanone (33.1 g, 98%) as a light yellow oil. R_f=0.4 (silica, 50% ether in hexanes); IR (film) ν_{max} 2977, 2930, 1642 (str), 1575, 1315, 1202, 1089, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 6.07, (d, J=2.4 Hz, 1H), 6.01 (d, J=2.4 Hz, 1H), 5.20 (s, 2H) 3.76–3.73 (m, 2H), 3.51–3.49 (m, 2H), 3.32 (s, 3H), 2.63 (s, 2H), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 165.3, 163.4, 161.2, 102.8, 96.1, 95.7, 92.8, 78.8, 71.3, 68.0, 58.8, 47.5, 26.5; HRMS calcd for $C_{15}H_{20}O_6$ ($M+Na^+$) 319.1158, found 319.1165. To a slurry of zinc dust (28.9 g, 0.45 mol) and semiprotected chromanone (14.0 g, 0.045 mol) in methanol (160 mL) was added concentrated hydrochloric acid (64 mL) dropwise at 0°C via an additional funnel. After 2 h of slow addition and vigorous stirring, the yellow solution was decanted away from the solid zinc and partitioned between ether (2×80 mL) and brine (80 mL). The combined ethereal extracts were washed with water, dried ($MgSO_4$), concentrated and purified on a silica gel column (1:10 ether/hexane) to give phenol **25** (12.8 g, 96%).

Compound **25**. Light yellow oil; R_f=0.2 (silica, 50% ether in hexanes); IR (film) ν_{max} 3377, 2973, 2931, 1625, 1594, 1512, 1434, 1156, 1120, 1065, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (d, J=2.0 Hz, 1H), 6.10 (d, J=2.0 Hz, 1H), 5.15 (s, 2H), 3.81–3.79 (m, 2H), 3.59–3.56 (m, 2H), 3.38 (s, 3H), 2.58 (t, J=7.2 Hz, 2H), 1.76 (t, J=7.2 Hz, 2H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.3, 154.7, 102.5, 97.2, 95.4, 93.5, 74.2, 71.5, 67.4, 58.8, 32.2, 26.6, 16.5; HRMS calcd for $C_{15}H_{22}O_5$ ($M+H^+$) 283.1545, found 283.1562.

6.1.12. Phenol 26. A solution of phenol **25** (14.0 g, 47.2 mmol) in CH_2Cl_2 at 25°C was treated under argon with imidazole (4.50 g, 66.1 mmol), DMAP (0.577 g, 4.72 mmol) and TBSCl (9.25 g, 61.4 mmol). After stirring for 8 h, the yellow solution was filtered, concentrated and directly purified by silica gel chromatography (1:20 ether/hexane) to afford the silylated adduct as a colorless liquid (17.8 g, 92%). R_f=0.6 (silica, 33% ether in hexane); IR (film) ν_{max} 2931, 2890, 2858, 1614, 1587, 1157, 1087, 1028, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J=2.8 Hz, 1H), 6.11 (d, J=2.8 Hz, 1H), 5.17 (s, 2H), 3.80–3.77 (m, 2H), 3.56–3.53 (m, 2H), 3.36 (s, 3H), 2.56 (t, J=6.8 Hz, 2H), 1.72 (t, J=6.8, 2H), 1.29 (s, 6H), 1.00 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.2, 154.2, 106.4, 99.2, 97.7, 93.5, 73.9, 71.5, 67.4, 58.9, 32.4, 26.6, 25.7, 18.2, 17.5; HRMS calcd for $C_{21}H_{36}O_5Si$ ($M+H^+$) 397.2410, found 397.2406. DDQ (3.44 g, 1.46 mmol) was added to a diluted solution of the above compound (3.0 g, 0.73 mmol) in toluene (1000 mL) at 25°C. The red solution was then heated at 120°C for 1 h. The resulting brown solution was filtered through celite and washed with $NaHCO_3$ (2×100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), concentrated and chromatographed (silica gel, 1:20 ether/hexane) to afford the desired chromene as a light yellow oil (2.15 g, 72%). R_f=0.5 (silica, 33 % ether in hexanes); IR (film) ν_{max} 2956, 2931, 2889, 2859, 1611, 1573, 1432, 1150, 1120, 1023, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (d, J=9.6 Hz, 1H), 6.18 (d, J=2.0 Hz, 1H), 6.09 (d, J=2.0 Hz, 1H), 5.43 (d, J=9.6 Hz, 1H), 5.18 (s, 2H), 3.80–3.78 (m, 2H), 3.56–3.54 (m, 2H), 3.37 (s, 3H), 1.39 (s, 6H), 0.97 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 154.7, 152.0, 126.6, 117.3, 108.0, 100.4, 98.0, 93.4, 76.0, 71.6, 67.6, 59.0, 27.8, 25.8, 18.3, −4.3; HRMS calcd for $C_{21}H_{34}O_5Si$ ($M+Na^+$) 417.2073, found 417.2090. TBAF (0.5mL of 1M solution in THF, 0.535 mmol) was added to a THF solution of the chromene (75 mg, 0.27 mmol) above at 25°C. After 30 min, the reddish reaction was quenched with NH_4Cl and extracted with ether (3×10 mL). The combined organic extracts were washed with brine (2×10 mL), dried over $MgSO_4$ and purified with silica gel (1:7 ether/hexane) to produce phenol **26** (69.6 mg, 92%).

Compound **26**. Light yellow oil; R_f=0.3 (silica, 50% ether in hexanes); IR (film) ν_{max} 3356 (br), 2973, 2929, 1622, 1586, 1437, 1149, 1117, 1072, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J=10.0 Hz, 1H), 6.11 (d, J=2.0 Hz, 1H), 6.09 (d, J=2.0 Hz, 1H), 5.45 (d, J=10.0 Hz, 1H), 3.8–3.79 (m, 2H), 3.59–3.57 (m, 2H), 3.38 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 154.8, 152.4, 126.7, 116.3, 104.3, 97.4, 97.4, 96.2, 93.3, 76.2, 71.6, 67.5, 58.9, 27.8; HRMS calcd for $C_{15}H_{20}O_5$ ($M+Na^+$) 303.1209, found 303.1217.

6.1.13. Alkyne 27. To a solution of chromene **26** (1.2 g, 4.28 mmol) in anhydrous acetonitrile (50 mL) was added anhydrous $CuCl_2$ (22.1 mg, 0.0128 mmol) at 0°C. DBU (0.7 mL, 5.56 mmol) was next added dropwise and the yellow solution became green. After 15 min of stirring, the carbonate **14** (0.645 mL, 5.14 mmol) was added dropwise and the reaction mixture was stirred for 12 h at 0°C. The reaction was quenched with water (50 mL) and extracted with ether (3×30 mL). The organic layers were washed with 10% aqueous $CuSO_4$ solution (2×30 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed with silica gel (1:10 ether/hexane) to afford alkyne **27** (1.22 g, 82%).

Compound **27**. Light yellow oil; R_f=0.5 (silica, 50% ether in hexanes); IR (film) ν_{max} 3281, 2979, 2933, 1612, 1574, 1488, 1433, 1148, 1117, 1082, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J=2.4 Hz, 1H), 6.53 (d, J=9.6 Hz, 1H), 6.26 (d, J=2.4 Hz, 1H), 5.42 (d, J=9.6 Hz, 1H), 5.19 (s, 2H), 3.80–3.78 (m, 2H), 3.55–3.53 (m, 2H), 3.36 (s, 3H), 2.57 (s, 1H), 1.64 (s, 6H), 1.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 154.3, 152.0, 126.8, 117.6, 109.2, 101.2, 99.3, 93.4, 85.9, 75.9, 73.9, 72.8, 71.5, 67.6, 59.0, 29.4, 27.6; HRMS calcd for $C_{20}H_{26}O_5$ ($M+H^+$) 347.1858, found 347.1870.

6.1.14. Phenol 28. A solution of alkyne **27** (2.0 g, 5.78 mmol) in THF (10mL) was treated with Pd/$BaSO_4$ (60 mg) and quinoline (20 μL) and the mixture was

hydrogenated (1 atm) over 30 min (the reaction was monitored every 10 min by TLC and ^{1}H NMR and stopped once the starting material was consumed). The reaction mixture was filtered through celite, concentrated and submitted directly to the Claisen rearrangement. A purified sample (colorless liquid) was used for analytical purposes. R_f=0.55 (silica, 33% ether in hexanes); IR (film) ν_{max} 2977, 2930, 1610, 1574, 1487, 1432, 1168, 1117, 1083, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J=10.0 Hz, 1H), 6.33 (d, J=2.0 Hz, 1H), 6.20 (d, J=2.0 Hz, 1H), 6.10 (dd, J=17.6, 11.2 Hz, 1H), 5.42 (d, J=9.6 Hz, 1H), 5.18 (d, J=17.6, 1H), 5.14 (s, 2H), 5.12 (dd, J=11.2, 1.2 Hz, 1H), 3.78–3.75 (m, 2H), 3.54–3.51 (m, 2H), 3.35 (s, 3H), 1.44 (s, 6H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 154.3, 152.5, 144.2, 126.6, 117.7, 113.3, 109.1, 101.3, 98.5, 93.3, 80.2, 75.8, 71.5, 67.5, 58.9, 27.6, 26.9; HRMS calcd for $C_{20}H_{28}O_5$ (M+Na^+) 371.1835, found 371.1842. The crude alkene was dissolved in xylenes (20 mL) and heated at 140°C for 8 h. The yellow solution was concentrated and purified by column chromatography on silica gel (1:10 ether/hexane) to yield a phenol **28** (1.89 g, 94% over 2 steps).

Compound **28**. Light yellow oil; R_f=0.5 (silica, 33% ether in hexanes); IR (film) ν_{max} 3422 (br), 2973, 2924, 1620, 1579, 1484, 1444, 1197, 1166, 1128, 1054; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, J=10.0 Hz, 1H), 6.23 (s, 1H), 5.58 (s, 1H), 5.44 (d, J=10.0 Hz, 1H), 5.19 (s, 3H), 3.80–3.77 (m, 2H), 3.56–3.54 (m, 2H), 3.37 (s, 3H), 3.33 (d, J=7.2 Hz, 2H), 1.80 (s, 3H), 1.74 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 152.4, 151.1, 134.7, 126.7, 122.3, 116.4, 107.7, 104.4, 95.9, 93.7, 75.8, 71.5, 67.8, 58.9, 27.7, 25.7, 22.2, 17.7; HRMS calcd for $C_{20}H_{28}O_5$ (M+Na^+) 371.1835, found 371.1853.

6.1.15. Quinone 29. A fresh solution of Fremy's salt was prepared by adding $(KSO_3)_2NO$ (34 mg, 0.126 mmol) and KH_2PO_4 (19 mg, 0.138 mmol) to a solution of H_2O (10 mL). To this purple solution was added a solution of **28** (20 mg, 0.057 mmol) in H_2O/acetone (12:1) dropwise at 25°C. Note that if the purple color disappears, more water should be added. After a vigorous stirring for 6 h, the solution became red with insoluble red oily droplets. The reaction was extracted with ether (3×30 mL), washed with brine (2 x 30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel (1:15 ether/hexane) provided quinone **29** (13.4 mg, 40%) together with unreacted starting material **28** (53% yield).

Compound **29**. Red solid; R_f=0.3 (silica, 33% ether in hexanes); IR (film) ν_{max} 2976, 2924, 1674, 1647, 1299, 1132, 1046; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J=10.4 Hz, 1H), 5.57 (d, J=10.4 Hz, 1H), 5.33 (s, 2H), 5.04 (t, J=1.2 Hz, 1H), 3.89–3.87 (m, 2H), 3.55–3.53 (m, 2H), 3.38 (s, 3H), 3.17 (d, J=7.2 Hz, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 178.3, 151.5, 149.0, 133.7, 132.2, 129.9, 119.9, 115.1, 97.2, 80.5, 71.4, 69.1, 59.0, 28.2, 25.7, 22.8, 17.9; HRMS calcd for $C_{20}H_{26}O_6$ (M+H^+) 363.1807, found 363.1821.

6.1.16. Chromenequinone 6. A solution of quinone **29** (81 mg, 0.224 mmol) in CH_2Cl_2 (5 mL) was treated at 25°C under argon with anhydrous $ZnBr_2$ (151 mg, 0.672 mmol). After stirring for 1 h the mixture was quenched with aqueous saturated $NaHCO_3$ (10 mL) and extracted with ether (3×10 mL). The organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The mixture was subjected to silica gel chromatography (1:20 ether/hexane) to furnish chromenequinone **6** (59 mg, 96%).

Compound **6**. Purple solid; R_f=0.6 (silica, 50% ether in hexanes); IR (film) ν_{max} 3363 (br), 2977, 2925, 1655 (str), 1626 (str), 1334, 1311; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.47 (s, J=10.4 Hz, 1H), 5.63 (d, J=10.4 Hz, 1H), 5.12 (t, J=1.6 Hz, 1H), 3.13 (d, J=7.6 Hz, 2H), 1.74 (s, 3H), 1.67 (s, 3H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 178.4, 149.6, 147.6, 133.7, 130.9, 119.7, 118.6, 116.7, 115.5, 80.3, 28.2, 25.7, 22.0, 17.8; HRMS calcd for $C_{16}H_{18}O_4$ (M+H^+) 275.1278, found 275.1278.

6.1.17. Aryl bromide 30. To a magnetically stirred solution of 2,4-dihydroxybenzoic acid (**11**) (5.00 g, 32.4 mmol) in acetic acid (35.0 mL) was added dropwise a solution of bromine (1.83 mL, 35.7 mmol) in acetic acid (30.0 mL). After 4 h, the reaction mixture was poured into a separatory funnel, diluted with water and quenched with aqueous saturated $Na_2S_2O_3$ (aq). The reaction mixture was then extracted successively with ethyl acetate until the extracts showed no sign of product. The combined ethyl acetate layers were dried over $MgSO_4$, filtered and concentrated. The crude solids were then recrystallized from a hot solution of 50% acetonitrile/toluene to yield 5-bromo-2,4-dihydroxybenzoic acid (**30**) (6.88 g, 29.5 mmol, 91%).

Compound **30**. R_f=0.55 (Et_2O with 2 drops AcOH); IR (film), ν_{max} 3565, 3060, 1657, 1404, 1250; ^{1}H NMR (400 MHz, d_6-acetone) δ 7.97 (s, 1H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, d_6-acetone) δ 171.1, 163.7, 160.7, 135.0, 106.7, 104.2, 100.4; HRMS calcd for $C_7H_5O_4Br$ (M−H^+) 230.9298, found 230.9302.

6.1.18. Acetonide 31. To a suspension of 5-bromo-2,4-dihydroxybenzoic acid (**30**) (23.3 g, 0.10 mol) in TFA (125 mL) was added TFAA (42.4 mL, 0.30 mol) and dry acetone (36.7 mL, 0.50 mmol) at 0°C. The heterogenous reaction mixture was then allowed to warm to 25°C. After 10 h, the homogeneous reaction mixture was concentrated under reduced pressure to half its volume and subsequently stirred with ethyl acetate and aqueous saturated $NaHCO_3$ in a large Erlenmeyer flask. The aqueous and ethyl acetate layers were then separated and the aqueous layer was back-extracted. The combined ethyl acetate layers were dried over $MgSO_4$, filtered and concentrated. The crude material was column chromatographed (silica, 30% Et_2O/hexane) to give **31** as a white solid (16.7 g, 61.0 mmol, 61%).

Compound **31**. R_f=0.31 (50% Et_2O/hexane); IR (film) ν_{max} 3084, 1684, 1602, 1452, 1268; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 6.61 (s, 1H), 6.38 (s, broad, 1H), 1.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 158.7, 157.0, 133.0, 107.8, 106.8, 104.0, 76.4, 25.9; HRMS calcd for $C_{10}H_9O_4Br$ (M−H^+) 270.9611, found 270.9618.

6.1.19. 3-Chloro-3-methyl-but-1-yne (32). To neat 2-methyl-3-butyn-2-ol (173.6 g, 2.06 mol) at 0°C was added dropwise 37% HCl (850 mL, 10.4 mol). The solution was

then brought to 25°C and stirred for a total of 3 h. The reaction mixture was diluted with dichloromethane and separated from the aqueous layer. After drying over $MgSO_4$ and filtering, the crude material was purified by fractional distillation to afford pure 3-chloro-3-methyl-1-butyne (**32**) as a colorless liquid (52.9 g, 0.52 mol, 25% yield).

Compound **32**. Bp 75–76°C/760 mm Hg); IR (neat) ν_{max} 3299, 2985, 2120, 1227, 1119; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 1H), 1.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5, 71.9, 56.9, 34.6.

6.1.20. Bromide 34. To a solution of phenol **31** (10.4 g, 38.1 mmol) in dry acetone (40 mL) at 25°C was added under argon K_2CO_3 (5.79 g, 49.9 mmol), KI (6.95 g, 41.9 mmol), CuI (72.5 mg, 0.38 mmol) and 3-chloro-3-methyl-1-butyne (**32**) (10.7 mL, 95.2 mmol). The reaction mixture was then brought to reflux. After 1 h, DMF (40.0 mL) was added and the temperature raised to 150°C. After 15 h, the reaction mixture was partitioned between ether and water. The aqueous layer was back-extracted and the combined ether layers dried over $MgSO_4$, filtered and concentrated. The crude material was column chromatographed (silica, 10% ether/hexane) to yield **34** (11.6 g, 34.3 mmol, 90%).

Compound **34**. R_f=0.7 (50% Et_2O/hexane); IR (film) ν_{max} 2981, 2921, 1737, 1601, 1574, 1442, 1375, 1303, 1290, 1204, 1171, 1125; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.50 (d, J=10.0 Hz, 1H), 5.67 (d, J=10.0 Hz, 1H), 1.73 (s, 6H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 155.7, 150.8, 132.5, 130.1, 114.7, 110.6, 106.9, 106.6, 104.4, 79.3, 28.4, 26.0; HRMS calcd for $C_{15}H_{15}O_4Br$ (M+Na^+) 361.0046, found 361.0056.

6.1.21. Phenol 35. To the reaction vessel containing the vacuum dried bromide **34** (47.3 mg, 0.14 mmol) was added dry THF (5.6 mL). The resulting solution was then stirred at −78°C under argon. 1.7 M *t*-BuLi in hexane (0.16 mL, 0.28 mmol) was added dropwise followed by the immediate addition of an aliquot of trimethyl borate (46.9 μL, 0.42 mmol). The reaction mixture was then brought to 0°C and stirred. After 0.5 h, both 30% H_2O_2 (0.20 mL, 1.96 mmol) and 2N KOH (0.20 mL, 0.40 mmol) were added and the reaction allowed to stir for 15 h. The reaction was diluted in a large amount of ether and washed with saturated $Na_2S_2O_3$ (aq), water and brine. The ether layer was dried over $MgSO_4$, filtered and concentrated. The crude material was then column purified to yield phenol **35** (18.1 mg, 65.5 μmol, 47%).

Compound **35**. White foam; R_f=0.6 (50% EtOAc/hexane); IR (film) ν_{max} 3392, 2980, 1721, 1641, 1613, 1469, 1395, 1379, 1318, 1298, 1267, 1202, 1124, 1053, 996, 883; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.51 (d, J=10.0 Hz, 1H), 5.64 (d, J=10.0 Hz, 1H), 5.38 (s, broad, 1H), 1.71 (s, 6H), 1.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 146.3, 145.9, 140.1, 129.6, 115.2, 113.7, 109.6, 106.3, 105.5, 79.0, 28.2, 25.7; HRMS calcd for $C_{15}H_{16}O_5$ (M+H^+) 277.107, found 277.1078.

6.1.22. Silyl ether 36. To a solution of phenol **35** (125.1 mg, 0.45 mmol) in dichloromethane (5.00 mL) at 0°C under argon was added DIPEA (0.32 mL, 1.81 mmol) followed by dropwise addition of SEMCl (0.24 mL, 1.36 mmol). The reaction mixture was allowed to stir for 15 h before it was diluted with dichloromethane and washed with water and brine. The dichloromethane layer was dried over $MgSO_4$, filtered and concentrated. The crude material was column purified (5% Et_2O/hexane then, 25% Et_2O/hexane) to yield **36** (141.7 mg, 0.35 mmol, 77%).

Compound **36**. White foam; R_f=0.65 (30% EtOAc/hexane); IR (film) ν_{max} 2953, 1738, 1472, 1391, 1377, 1306, 1292, 1202, 1052, 885, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 6.51 (d, J=10.0 Hz, 1H), 5.64 (d, J=10.0 Hz, 1H), 5.19 (s, 2H), 3.76–3.82 (m, 2H), 1.71 (s, 6H), 1.49 (s, 6H), 0.92–0.99 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 150.9, 147.9, 141.4, 130.0, 117.7, 115.5, 110.8, 106.6, 105.1, 94.7, 78.3, 66.7, 28.4, 26.0, 18.2, −1.2; HRMS calcd for $C_{21}H_{30}O_6Si$ (M+Na^+) 429.1704, found 429.1706.

6.1.23. Dialdehyde 37. To a stirring solution of **36** (125.9 mg, 0.31 mmol) in *t*-BuOH/THF/H_2O (10:3:1, 3.00 mL) at 25°C was added NMO (58.0 mg, 0.50 mmol) and 2.5% OsO_4 in *t*-BuOH (11.6 μL, 0.93 μmol). After stirring for 15 h, the reaction mixture was diluted with dichloromethane and washed with 10% $NaHSO_3$, water and brine. The dichloromethane layer was then dried over $MgSO_4$, filtered and concentrated. The crude material was chromatographed in silica gel with Et_2O/hexane/CH_2Cl_2 (2:2:1) to yield the corresponding diol (122.8 mg, 0.28 mmol, 90%) as a white foam. R_f=0.2 (30% EtOAc/hexane); IR (film) ν_{max} 3462, 2951, 2899, 1715, 1613, 1474, 1377, 1291, 1205, 1104, 1004, 862, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 5.14 (s, 2H), 4.91 (d, J=4.8 Hz, 1H), 3.74–3.80 (m, 3H), 3.58 (s, broad, 1H), 3.12 (s, broad, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 0.88–0.94 (m, 2H), −0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 151.7, 151.3, 142.1, 116.9, 112.1, 106.9, 104.7, 94.7, 79.6, 70.8, 66.8, 61.9, 26.2, 25.8, 25.2, 22.2, 18.1, 14.4, −1.2; HRMS calcd for $C_{21}H_{32}O_8Si$ (M+Na^+) 463.1759, found 463.1758. To a stirring solution of the above diol (71.2 mg, 0.16 mmol) in dichloromethane (3.20 mL) at 0°C was added $Pb(OAc)_4$ (86.0 mg, 0.19 mmol). TLC showed the reaction to be complete after 20 min. The slight excess of $Pb(OAc)_4$ was quenched by the addition of ethylene glycol. The reaction mixture was then diluted in ethyl acetate and washed with $NaHCO_3$, water and brine. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material **37** (70.2 mg, 0.16 mmol, >99%) was used to the next without any further purification.

Compound **37**. R_f=0.18 (30% EtOAc/hexane); IR (film) ν_{max} 2950, 1734, 1700, 1611, 1465, 1295, 1205, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 9.77 (s, 1H), 7.92 (s, 1H), 5.15 (s, 2H), 3.64–3.70 (m, 2H), 1.78 (s, 6H), 1.40 (s, 6H), 0.91–0.96 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 187.2, 152.9, 152.2, 145.8, 120.5, 119.2, 109.4, 107.5, 92.9, 87.0, 67.5, 26.2, 22.2, 18.2, −1.0; HRMS calcd for $C_{21}H_{30}O_8Si$ (M+Na^+) 461.1602, found 461.1614.

6.1.24. Lactol 38. A solution of vacuum dried dialdehyde **37** (71.2 mg, 0.16 mmol) in dry dichloromethane (1.60 mL) at

0°C was stirred under argon. To this solution was added an aliquot of 0.2 M *m*-CPBA in CH_2Cl_2 (0.41 mL, 81.2 μmol) every 0.5 h for 6 h. The reaction mixture was then diluted in a large amount of ethyl acetate and washed with $Na_2S_2O_3$ (aq), saturated $NaHCO_3$ (aq) and brine. The ethyl acetate layer was then dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in methanol (1.60 mL) and stirred at 0°C. To this solution was added an aliquot of 1 M NaOH (40.6 μL, 40.6 μmol) every 10–15 min until the reaction was complete by TLC. The reaction mixture was then neutralized by the addition of saturated NH_4Cl (aq). The reaction mixture was subsequently partitioned between ethyl acetate and water. The ethyl acetate layer was then washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was column purified (10%–30% Et_2O/hexane) to yield **38** (20.8 mg, 48.7 μmol, 30%).

Compound **38**. R_f=0.24 (30% EtOAc/hexane); IR (film) ν_{max} 3389, 2951, 1736, 1617, 1485, 1378, 1320, 1206, 1060, 1022, 858, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 5.20–5.24 (m, 3H), 3.77–3.82 (m, 2H), 3.58 (s, broad, 1H), 1.76 (s, 3H), 1.75 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H), 0.94–0.99 (m, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 141.9, 141.6, 140.2, 129.1, 109.3, 107.1, 105.6, 94.8, 93.7, 76.1, 67.0, 26.1, 26.0, 23.3, 22.4, 18.4, −1.0; HRMS calcd for $C_{20}H_{30}O_8Si$ ($M+Na^+$) 449.1602, found 449.1621.

6.1.25. Phenol 39. Methytriphenylphosphonium bromide (47.2 mg, 0.13 mmol) was dried under high vacuum and then dissolved in dry THF (1.30 mL) and stirred under argon at 25°C. 1.0 M NaHMDS in THF (0.11 mL, 0.11 mmol) was added dropwise and the resulting solution allowed to stir for 15 min before setting on an ice bath at 0°C. The vacuum dried lactol **38** (18.8 mg, 44.1 μmol) was dissolved in dry THF (1.00 mL) and then added dropwise to the Wittig reagent at 0°C. After 15 min, the reaction mixture was allowed to warm to room temperature and stir another 45 min. The reaction mixture was diluted with a large amount of ether and washed with saturated NH_4Cl (aq), water and brine. The ether layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (10% Et_2O/hexane then, 15% Et_2O/hexane) to yield **39** (10.7 mg, 25.1 μmol, 57%).

Compound **39**. R_f=0.32 (50% Et_2O/hexane); IR (film) ν_{max} 3382, 2952, 2897, 1734, 1611, 1468, 1317, 1205, 1065, 1005, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.47 (s, 1H), 6.17 (dd, *J*=17.6, 10.8 Hz, 1H), 5.25 (dd, *J*=17.6, 0.8 Hz, 1H), 5.19 (s, 2H), 5.09 (dd, *J*=10.8, 0.8 Hz, 1H), 3.76–3.81 (m, 2H), 1.74 (s, 6H), 1.48 (s, 6H), 0.95–0.99 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 149.2, 147.3, 142.9, 140.4, 131.2, 113.7, 111.4, 106.2, 104.4, 94.7, 83.6, 67.0, 26.7, 25.8, 18.1, −1.3; HRMS calcd for $C_{21}H_{32}O_7Si$ ($M+Na^+$) 447.1815, found 447.1829.

6.1.26. α-Bromoisobutyraldehyde 40. To a solution of isobutyraldehyde (39.7 g, 0.55 mol) and $AlCl_3$ (2.00 g, 15.0 mmol) in ether (600 mL) at 0°C was added bromine (88.0 g, 0.55 mol) dropwise. After 5 h of continued stirring at 0°C, deionized water was added to the reaction mixture. The ether layer was separated, dried over $MgSO_4$ and filtered. The ether was then distilled away from the crude product by simple distillation. Continued distillation yielded pure α-bromoisobutyraldehyde (**40**) as a colorless liquid (57.1 g, 0.38 mol, 69% yield).

Compound **40**. Bp 110–115°C/760 mmHg; IR (neat) ν_{max} 2977, 2715, 1735, 1107, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 1.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 63.9, 26.6. Compound **40** was stored neat over K_2CO_3 at −80°C as it was found to trimerize readily in the presence of a trace amount of acids. Spectroscopic data of the trimer: IR (film) ν_{max} 2974, 1462, 1337, 1109, 907; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (s, 3H), 1.77 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ102.8, 61.5, 28.1. The monomeric α-bromoisobutyraldehyde (**40**) can be regenerated from the trimeric species by distillation. Heating the trimer through its melting point (129–131°C) resulted in a liquid that will boil at 191–193°C and gave **40** as its distillate.

6.1.27. Alkene 10. Phenol **39** (116.0 mg, 0.27 mmol) was dissolved in dry THF (2.70 mL) and stirred under argon at 0°C. 1.0 M *t*-BuOK in THF (0.30 mL, 0.30 mmol) was added dropwise turning the reaction slightly yellow. The reaction mixture was allowed to warm to 25°C whereupon it turned a green–brown in color. The reaction mixture was then concentrated under reduced pressure and dried under high vacuum for 2 h. While under argon, solid 18-C-6 (72.2 mg, 0.27 mmol) was added to the reaction vessel followed by acetonitrile (2.00 mL). The reaction mixture was allowed to stir for 15 min at 25°C and was then promptly taken to 0°C. Freshly prepared 0.4 M α-bromoisobutyraldehyde (**40**) in acetonitrile (1.00 mL, 0.41 mmol) was added dropwise. The reaction was then brought to room temperature and subsequently heated at 60°C for 1 h. The reaction mixture was then diluted in a large amount of ether and washed with water and brine. The ether layer was then dried over $MgSO_4$, filtered and concentrated. The crude material was then column chromatographed (10% ether/hexane) to yield the corresponding aldehyde **10** (108.1 mg, 0.22 mmol, 80%). Subsequent studies have shown that solid *t*-BuOK can be used in acetonitrile thereby by-passing the intermediate concentration step. R_f=0.50 (50% Et_2O/hexane); IR (film) ν_{max} 2986, 2952, 1740, 1605, 1462, 1381, 1350, 1289, 1205, 1070, 1005, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.45 (s, 1H), 6.16 (dd, *J*=17.6, 10.8 Hz, 1H), 5.13 (dd, *J*=17.6, 0.8 Hz, 1H), 5.01 (dd, *J*=10.8, 0.8 Hz, 1H), 3.63–3.68 (m, 2H), 1.70 (s, 6H), 1.46 (s, 6H), 1.31 (s, 6H), 0.90–0.95 (m, 2H), −0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 160.6, 147.1, 146.8, 146.4, 143.0, 139.3, 113.1, 109.0, 108.6, 106.3, 92.9, 85.8, 84.2, 66.9, 27.0, 25.8, 22.0, 17.9, −1.3. ESI calcd for $C_{25}H_{38}O_8Si_1$ ($M+Na^+$) 517, found 517. Methytriphenylphosphonium bromide (74.8 mg, 0.21 mmol) was dried under vacuum suspended in THF (2.00 mL) and stirred under argon at 25°C. 1.0 M NaHMDS in THF (0.16 mL, 0.16 mmol) was added dropwise and the resulting yellow solution allowed to stir for 15 min before setting on an ice bath at 0°C. This solution was treated with a solution of the above vacuum dried aldehyde (51.8 mg, 0.10 mmol) in dry THF (1.00 mL). After 15 min, the reaction mixture was allowed to warm to room temperature and stir another 45 min. The reaction mixture was diluted with a large amount of ether and washed with saturated NH_4Cl (aq),

water and brine. The ether layer was dried over $MgSO_4$, filtered and concentrated and the crude material was purified by column chromatography (5% Et_2O/hexane) to yield **10** (36.1 mg, 73.3 μmol, 70%).

Compound **10**. R_f=0.65 (50% Et_2O/hexane); IR (film) ν_{max} 3087, 2982, 2952, 1741, 1456, 1346, 1287, 1123, 1066, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.19 (dd, J=17.6, 10.8 Hz, 1H), 6.18 (dd, J=17.4, 10.8 Hz, 1H), 5.14 (s, 2H), 5.07 (d, J=17.6 Hz, 1H), 5.06 (d, J=17.6 Hz, 1H), 4.98 (dd, J=10.8, 0.8 Hz, 1H), 4.97 (dd, J=10.8, 0.8 Hz, 1H), 3.73–3.77 (m, 2H), 1.71 (s, 6H), 1.47 (s, 6H), 1.45 (s, 6H), 0.94–0.98 (m, 2H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ160.9, 149.0, 148.3, 147.1, 143.3, 143.0, 140.2, 112.9, 112.8, 110.7, 108.5, 106.2, 94.1, 85.3, 84.4, 77.2, 66.6, 27.0, 26.9, 25.8, 18.1, −1.2; HRMS calcd for $C_{26}H_{40}O_7Si_1$ ($M+Na^+$) 515.2435, found 515.2413.

6.1.28. Ketone 42. Alkene **10** (35.7 mg, 72.5 μmol) was dissolved in toluene (0.75 mL) and stirred under argon at 110°C. After 45 min, the reaction mixture was concentrated under reduced pressure. The crude material was purified by preparative TLC (50% Et_2O/hexane) to yield **42** (30.3 mg, 61.6 μmol, 85%).

Compound **42**. R_f=0.65 (50% Et_2O/hexane); IR (film) ν_{max} 2953, 1741, 1283, 1071, 836; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 5.02 (d, J=8.0 Hz, 1H), 4.94 (d, J=7.6 Hz, 1H), 4.41–4.36 (m, 1H), 3.81–3.68 (m, 2H), 2.71 (dd, J=13.9, 10.3 Hz, 1H), 2.67–2.62 (m, 1H), 2.55 (d, J=9.9 Hz, 1H), 2.43 (d, J=13.2 Hz, 1H), 1.79 (dd, J=13.2, 9.9 Hz, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H), 1.24 (s, 3H), 0.95 (d, J=8.1 Hz, 1H), 0.93 (d, J=8.1 Hz, 1H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ200.7, 158.7, 140.3, 135.6, 125.5, 117.5, 104.9, 92.5, 84.2, 83.9, 83.4, 83.1, 66.1, 49.0, 32.6, 30.2, 29.0, 28.7, 28.4, 27.9, 25.7, 18.3, −1.2; HRMS calcd for $C_{26}H_{40}O_7Si$ ($M+Na^+$) 515.2435, found 515.2439.

6.1.29. Carboxylic acid 43. Acetonide **42** (24.6 mg, 49.9 μmol) was dissolved in methanol (0.50 mL) and stirred at 0°C. 10% NMe_4OH (aq) (0.60 mL, 55.7 mmol) was then added dropwise turning the reaction mixture slightly yellow. The reaction mixture was allowed to warm to 25°C and stir for an additional 30 minutes. After the reaction was shown to be complete by TLC, acetic acid was added to neutralize the reaction mixture. The reaction mixture was then partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by preparative TLC (75% Et_2O/hexane) to yield **43** (12.7 mg, 27.9 mmol, 56%).

Compound **43**. R_f=0.2 (75% Et_2O/hexane); IR (film) ν_{max} 3359, 1745, 1692, 1250, 837; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.13 (br s, 1H), 5.03 (d, J=8.0 Hz, 1H), 4.92 (d, J=8.0 Hz, 1H), 4.60–4.56 (m, 1H), 3.84–3.70 (m, 2H), 2.71 (dd, J=14.0, 10.0, 1H), 2.64–2.59 (m, 1H), 2.39 (d, J=13.2 Hz, 1H), 2.28 (d, J=10.0 Hz, 1H), 1.73 (dd, J=13.2, 10.0 Hz, 1H), 1.59 (s, 6H), 1.55 (s, 3H), 1.24 (s, 3H), 0.96 (t, J=8.4 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 167.5, 142.9, 135.2, 128.3, 118.3, 92.5, 84.3, 84.1, 83.7, 82.4, 66.1, 50.0, 32.7, 30.1, 29.1, 28.7, 25.9, 18.3, 17.9, −1.2; HRMS calcd for $C_{23}H_{36}O_7Si$ ($M-H^+$) 451.2157, found 451.2161.

6.1.30. Carboxylic acid 7. Compound **43** (5.6 mg, 12.4 μmol) was dissolved in methanol (0.25 mL) and stirred at 25°C. To this solution was added 2N HCl (aq) (0.13 mL) dropwise. After 1 h, the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by preparative TLC (0.5% AcOH/Et_2O) to afford **7** (4.2 mg, 11.5 μmol, 93%).

Compound **7**. R_f=0.25 (0.01% AcOH/Et_2O); IR (film) ν_{max} 3359, 1745, 1692; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.18 (br s, 1H), 4.59–4.56 (m, 1H), 2.76 (dd, J=14.0, 10.5 Hz, 1H), 2.66–2.62 (m, 1H), 2.28 (d, J=9.5 Hz, 1H), 2.06 (d, J=13.0 Hz, 1H), 1.84 (dd, J=13.0, 9.5 Hz, 1H), 1.60 (s, 6H), 1.56 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 167.8, 145.5, 136.3, 130.6, 118.7, 85.0, 84.7, 83.6, 83.0, 50.8, 35.5, 30.4, 29.8, 29.3, 26.5, 18.4; HRMS calcd for $C_{17}H_{22}O_6$ ($M-H^+$) 321.1337, found 321.1351.

6.1.31. Acetate 45. Claisen/Diels–Alder adduct **42** (15.7 mg, 31.9 μmol) was dissolved in methanol (0.35 mL) and stirred at 25°C. To this solution was added 2N HCl (aq) (0.25 mL) dropwise. After 1 h, the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by preparative TLC (80% Et_2O/hexane) to afford **44** (11.0 mg, 30.3 μmol, 95%). This material was then transferred to a sealed tube, dissolved in $CHCl_3$ (0.50 mL) and stirred at 0°C. To this solution was added pyridine (24.5 μL, 0.30 mmol), acetyl chloride (21.5 μL, 0.30 mmol), acetic anhydride (28.6 μL, 0.30 mmol) and DMAP (0.4 mg, 3.0 μmol). The reaction mixture was then allowed to heat at 80°C. After 20 h, the reaction appeared to be complete and was then partitioned between $CHCl_3$ and water. The chloroform layer was then dried over $MgSO_4$, filtered and concentrated. The crude material was purified by preparative TLC (75% Et_2O/hexane) to yield **45** (11.3 mg, 27.9 μmol, 92%). X-Ray quality crystals were grown by first dissolving the pure product in a minimal amount of ether and then allowing the solvent to slowly evaporate over the course of 2 days.

Compound **45**. R_f=0.4 (75% Et_2O/hexane); IR (film) ν_{max} 2987, 1744, 1228, 1048, 880; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 4.49–4.45 (m, 1H), 2.75 (dd, J=13.6, 10.4 Hz, 1H), 2.67–2.62 (m, 1H), 2.59 (d, J=13.2 Hz, 1H), 2.56 (d, J=10.0 Hz, 1H), 2.23 (s, 3H), 1.83 (dd, J=12.8, 10.0 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 168.7, 158.6, 139.4, 135.7, 124.0, 117.2, 104.9, 84.3, 83.4, 83.2, 82.8, 48.3, 31.4, 30.2, 29.0, 28.7, 28.03, 27.95, 25.7, 21.1, 18.2; HRMS calcd for $C_{22}H_{28}O_7$ (M+Na+) 427.1727, found 427.1727.

6.1.32. Ester 48. To a solution containing **43** (10.0 mg, 22.1 μmol) and quinone **6** (7.3 mg, 26.5 μmol) in acetonitrile (0.50 mL) was added DIPEA (15.2 μL, 44.2 μmol) turning the reaction mixture into a deep purple solution.

Solid HATU (10.1 mg, 26.5 μmol) was then added portionwise making the reaction mixture a red–brown after just 5 min. After 5 min, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase preparative TLC (neat acetonitrile) to afford **48** (9.7 mg, 13.7 μmol, 62%). The use of reverse-phase silica gel was required since product **48** was found to readily decompose on normal phase silica gel.

Compound **48**. R_f=0.80 (75% Et_2O/hexane); IR (film) ν_{max} 3450, 2924, 1720, 1681, 1094; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 6.46 (d, J=10.4 Hz, 1H), 5.64 (d, J=9.6 Hz, 1H), 5.48 (br s, 1H), 5.02 (d, J=7.7 Hz, 1H), 5.01–4.97 (m, 1H), 4.89 (d, J=8.1 Hz, 1H), 4.86–4.82 (m, 1H), 3.81–3.68 (m, 2H), 3.14–3.12 (m, 2H), 2.65 (dd, J=12.1, 7.3 Hz, 1H), 2.71–2.59 (m, 1H), 2.44 (d, J=13.2 Hz, 1H), 2.34 (d, J=9.9 Hz, 1H), 1.79 (dd, J=13.2, 9.9 Hz, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.603 (s, 3H), 1.595 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H), 1.25 (s, 3H), 0.94 (t, J=8.4 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 182.4, 174.2, 162.3, 149.3, 146.4, 145.1, 135.3, 135.0, 130.2, 128.0, 118.2, 118.1, 116.9, 115.8, 114.7, 92.4, 84.2, 84.0, 83.0, 82.4, 81.0, 66.1, 50.0, 32.9, 30.1, 29.2, 28.5, 28.4, 26.0, 25.9, 23.5, 18.3, 18.1, 17.9, −1.2; HRMS calcd for $C_{39}H_{52}O_{10}Si$ ($M+Na^+$) 731.3222, found 731.3209.

6.1.33. *seco*-Lateriflorone (49). Coupling product **48** (4.5 mg, 6.3 μmol) was dissolved in methanol (0.25 mL) and stirred at 25°C. To this solution was added 2N HCl (aq) (0.13 mL) dropwise. After 1 h, the reaction mixture was partitioned between ethyl acetate and water. The ethyl acetate layer was dried over $MgSO_4$, filtered and concentrated. The crude material was purified by reverse-phase preparative TLC (10% EtOAc/hexane) to afford *seco*-lateriflorone **49** (3.4 mg, 5.90 μmol, 93%). The use of reverse-phase silica gel was required because the coupled products were found to readily decompose on normal phase silica gel.

Compound **49**. R_f=0.55 (75% Et_2O/hexane); IR (film) ν_{max} 3457, 2924, 1719, 1657, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.45 (d, J=9.6 Hz, 1H), 5.63 (d, J=9.6 Hz, 1H), 5.55 (br s, 1H), 5.00–4.96 (m, 1H), 4.86–4.82 (m, 1H), 3.83 (br s, 1H), 3.17–3.08 (m, 2H), 2.68 (dd, J=11.7, 7.7 Hz, 1H), 2.74–2.62 (m, 1H), 2.33 (d, J=9.5 Hz, 1H), 2.08 (d, J=12.8 Hz, 1H), 1.92 (dd, J=13.2, 9.9 Hz, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.50 (s, 6H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 182.4, 174.2, 165.4, 149.3, 148.7, 146.6, 135.5, 135.1, 130.7, 130.2, 118.0, 116.6, 115.8, 115.6, 114.7, 83.9, 83.8, 82.8, 81.1, 78.3, 50.1, 35.2, 30.0, 29.8, 29.2, 28.5, 28.3, 26.0, 25.8, 23.4, 18.1, 17.9; HRMS calcd for $C_{33}H_{38}O_9$ ($M+Na^+$) 601.2408, found 601.2417.

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