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Explorations of Caffeic Acid Derivatives: Total Syntheses of Rufescenolide, Yunnaneic Acids C and D, and Studies toward Yunnaneic Acids A and B

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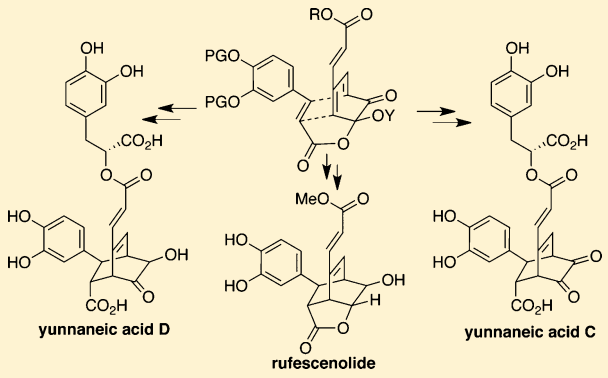
Supporting Information

ABSTRACT: Yunnaneic acids A–D, isolated from the roots of *Salvia yunnanensis*, are hexameric (A and B) and trimeric (C and D) assemblies of caffeic acid that feature an array of synthetically challenging and structurally interesting domains. In addition to being caffeic acid oligomers, yunnaneic acids A and B are formally dimeric and heterodimeric adducts of yunnaneic acids C and D. Herein we report the first total syntheses of yunnaneic acids C and D featuring the formation of their bicyclo[2.2.2]octene cores in a single step from simple precursors via an oxidative dearomatization/Diels–Alder cascade that may have biogenetic relevance. In addition, exploitation of the key intermediate resulting from this cascade reaction has enabled rapid access to the structurally related caffeic acid metabolite rufescenolide through an unexpected Lewis acid-mediated reduction. Finally, we report the results of extensive model studies toward forming the dimeric yunnaneic acids A and B. These explorations indicate that the innate reactivities of the monomeric fragments do not favor spontaneous formation of the desired dimeric linkages. Consequently, enzymatic involvement may be required for the biosynthesis of these more complex family members.



INTRODUCTION

Plants throughout the world convert caffeic acid (also known as dihydroxycinnamic acid) into an array of structurally distinct natural products. Among these, some of the most stereochemically dense and complex family members include the yunnaneic acids. These compounds, including **2**–**5** (Figure 1), were isolated from the roots of *Salvia yunnanensis*,[1] a plant found in southern China that has been used in traditional folk medicine.[2] Little to no information, however, is known about their specific bioactivity or mode of action. Formally, compounds **2** and **3** are trimers and **4** and **5** are hexamers of caffeic acid, though they also could be considered products arising by the merger of caffeic acid with the caffeic acid-derived natural product rosmarinic acid (**1**). Moreover, as can be noted upon careful inspection, the structure of yunnaneic acid B (**5**) contains two units of yunnaneic acid C, while yunnaneic acid A (**4**) contains one molecule each of yunnaneic acid C (**2**) and D (**3**).

Over the course of the past several years, our group has cultivated an interest in developing strategies for the rapid, efficient, and selective synthesis of members of oligomeric natural product families,[3] including not only polyphenols[4] but also other molecule classes such as alkaloids.[5] Indeed, it was during one of these studies toward the related natural product helicterin B (**6**) (Scheme 1) that the yunnaneic acids first caught our attention when, in efforts to make its core, we found that exposure of molecules such as hydroxyketone **7** to various acids and bases led to unsymmetrical dimer **8** in good yield.[4b] Its spirocycle, as verified by X-ray crystallography, closely resembles that found within both yunnaneic acids A and B. Given this result, as well as our successful and controlled preparation of several members of the helicterin class,[4b] we wanted to determine whether we could prepare this group of oligomers as well. Careful analysis of these oligomers revealed, however, that despite some structural similarities to the helicterins, a number of critical differences exist between these two families of molecules, such that the yunnaneic acids present a wholly unique, and potentially more difficult, set of synthetic challenges.

For instance, unlike helicterin B, which we prepared via a homodimerization of a single hydroxyketal, and spirocyclic dimer **8**, whose precursor was a single hydroxyketone, reaching yunnaneic acid A (**4**) requires the controlled union of two different monomeric fragments. Yunnaneic acid B (**5**) presents a similar challenge in that, although it formally comprises two molecules of yunnaneic C (**3**), mechanistically the dimerization requires selective hydration of one of the carbonyls of the diketone starting material followed by nucleophilic attack onto

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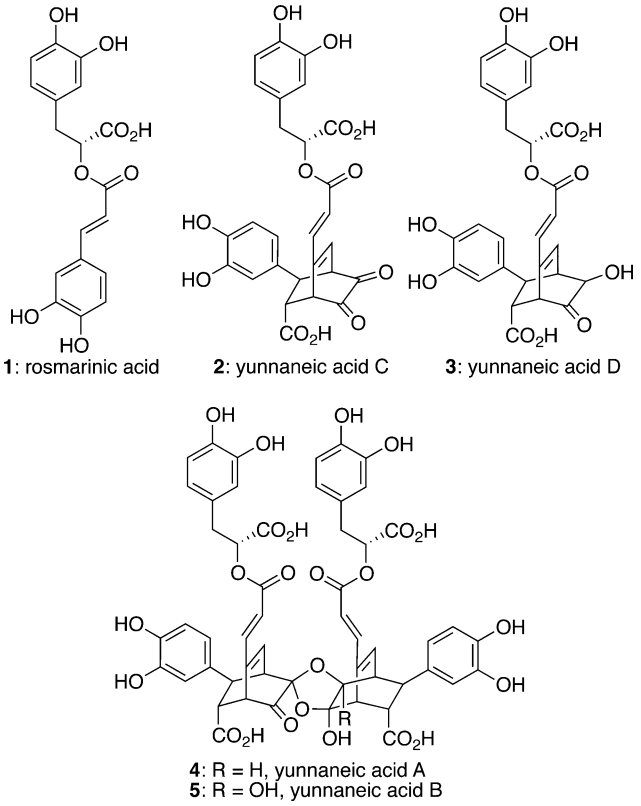
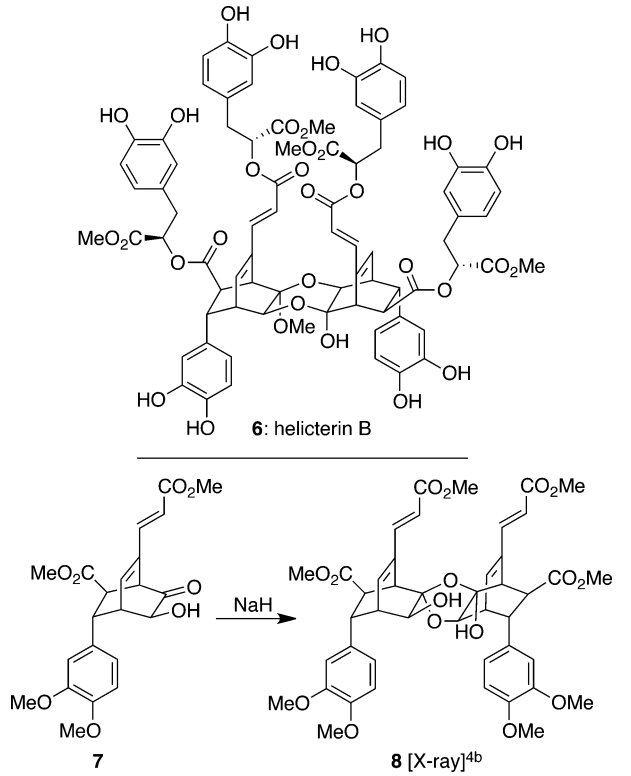


Figure 1. Structures of the caffeic acid derivatives yunnaneic acids.

a nonhydrated diketone. Thus, in either case, the union of two subtly different monomers is required, a challenging proposition given that multiple additional reactive pathways can be envisioned to afford unwanted side products. Additionally, while the two classes possess the same overall components in their bicyclo[2.2.2]octene cores, likely arising from a Diels–Alder reaction between two derivatives of caffeic acid (vide infra), the substituents decorating their bicycles differ in both regio- and stereochemistry. The cores typical of the helicterins are formally *endo* Diels–Alder products, which we constructed previously via a retro-Diels–Alder/Diels–Alder cascade process under thermodynamic control, while the yunnaneic acids formally reflect *exo* Diels–Alder adducts. Thus, a successful synthesis of these molecules would require an entirely unique synthetic approach. In particular, a way had to be found to overcome the stereo- and regiochemistry commonly observed in Diels–Alder reactions leading to bicyclo[2.2.2]octenes.

Herein we report our studies to access this unique group of caffeic acid oligomers, efforts leading to the first total syntheses of yunnaneic acids C and D as well as the structurally related metabolite rufescenolide. To solve these compounds' core regio- and stereochemical challenges, we employed a modified Wessely oxidation/intramolecular Diels–Alder cascade, which allowed us to forge the bicyclo[2.2.2]octene core in a single step.[6] This process may suggest a unique biogenetic hypothesis for their formation, one different from that proposed in the literature;[1] it also may constitute the most complex example of such a process to date. In addition, we discuss our explorations into the dimerization behavior of model versions of the monomeric natural products. These studies suggest that the innate reactivities of these monomers do not favor the spontaneous and selective formation of the naturally occurring

Scheme 1. Structure of Helicterin B (6), an Oligomeric Natural Product with Pseudo-C_2 Symmetry, and an Unforeseen Dimerization of a Model Precursor under Basic Conditions



dimers. As a result, formation of the requisite bonds in nature may require enzymes.

RESULTS AND DISCUSSION

1. Monomer Retrosynthesis, Strategic Considerations, and Preliminary Synthetic Studies. As noted above, the core bicyclic domain of the yunnaneic acid monomers C (**2**) and D (**3**) potentially arises in nature via a Diels–Alder reaction. The key question, however, is just how that *exo*-selective event occurs. The original isolation team posited elements of the idea shown in Scheme 2, wherein dearomatization of rosmarinic acid (**1**), either to **9** or to **11**, affords a diene that can then react with the double bond within caffeic acid to deliver yunnaneic acids C (**2**) and D (**3**). In the latter case, the alcohol-bearing chiral center within **11** could control the facial presentation of the two fragments to afford enantiopure material,[7] while in the former enzymes would likely be needed for chiral control since the lone stereogenic center within **1** is quite remote from the reactive center. However, why such a union would be *exo*-selective and proceed with the requisite regiocontrol is unclear without invoking a "Diels–Alderase" enzyme.[8] An alternative hypothesis, adapted from a similar pathway proposed by Tezuka for the biosynthesis of the helicterin natural products,[9] would involve the union of radicals as shown in the lower part of Scheme 2 to generate **14**, with enol attack then leading to yunnaneic acid C (**2**). However, one could object to such a pathway[10] on the grounds that an intermediate such as **14** could easily rearomatize; attack by oxygen instead of carbon after such a rearomatization event could lead to lithospermic acid (**16**), a related natural product[11] that has been the subject of much recent synthetic interest.[12]

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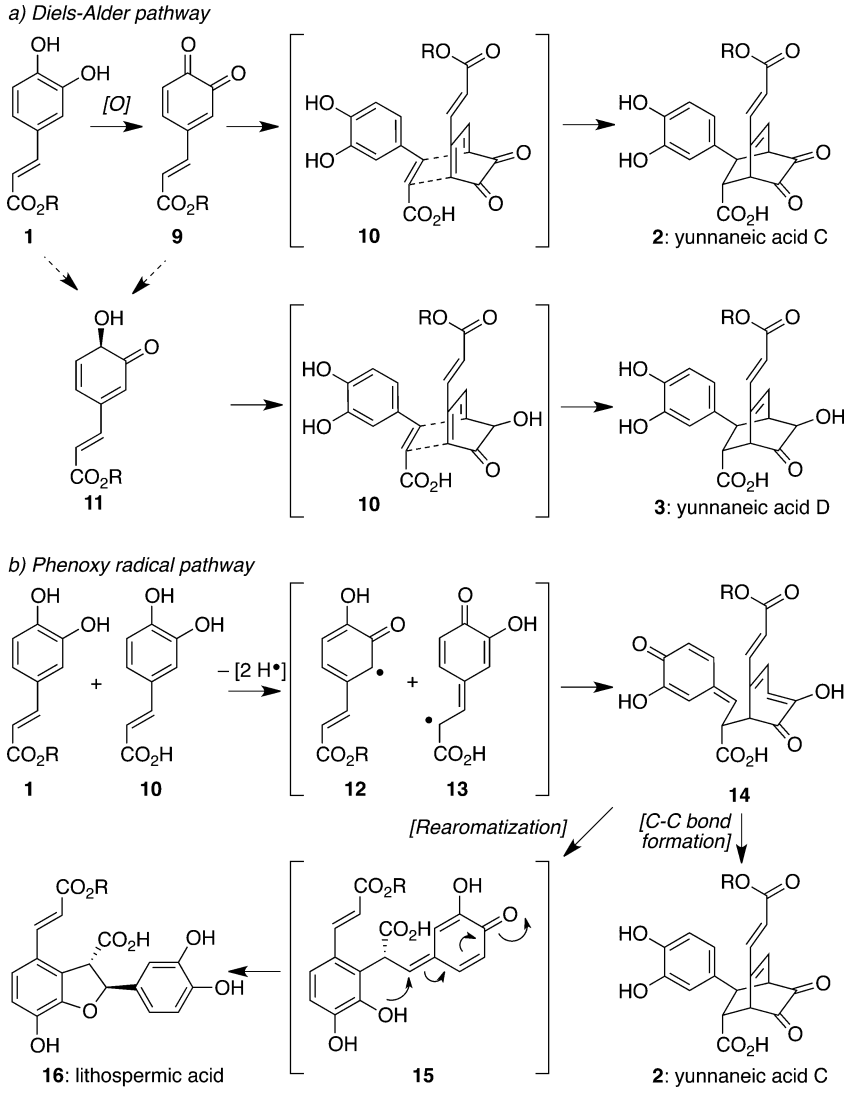
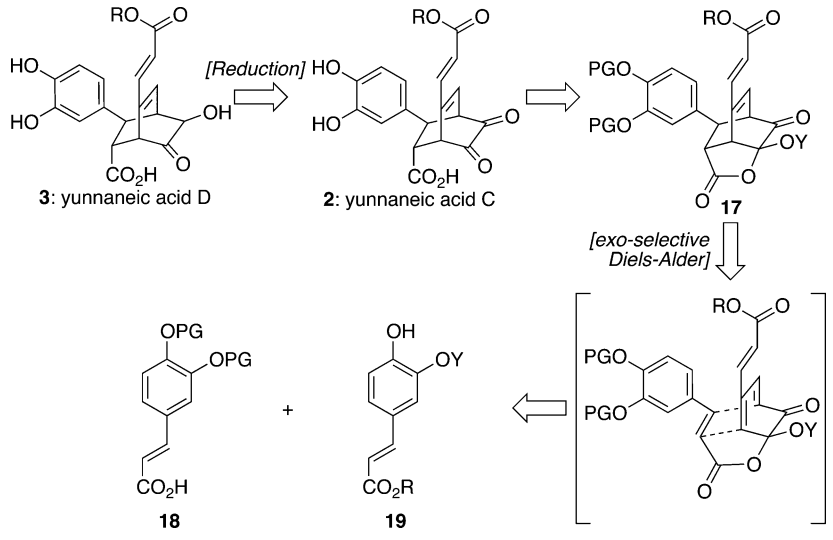
Scheme 2. Potential Biogenetic Hypotheses for the Synthesis of Yunnaneic Acids C (2) and D (3) as Well as a Possible Connection to the Related Natural Product Lithospermic Acid (16)



Scheme 3. Retrosynthetic Analysis of the Yunnaneic Acid Monomers via a Distinct Diels–Alder Approach



Our laboratory approach to the yunnaneic acids was predicated on the idea that a Diels–Alder reaction could well be the key to the core, but in order to effect an *exo*-selective event, an intramolecular variant[13] of that reaction would be

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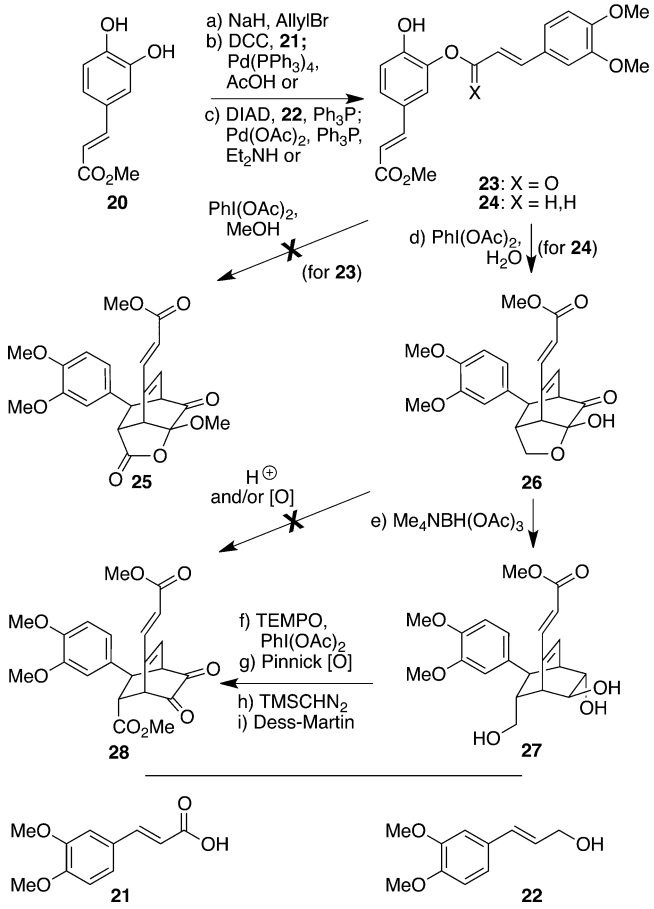
needed rather than the intermolecular version shown in Scheme 2. As shown in Scheme 3, we hoped to tether the dienophile portion to a masked *ortho*-benzoquinone (MOB), which could then undergo a [4 + 2]-cycloaddition with the appropriate regio- and stereochemistry. In addition to being a powerful and simplifying retrosynthetic disconnection, such a transformation in the forward sense would result in a tricyclic product (**17**) containing the latent 1,2-diketone of **2** (a reactive domain whose instability could pose chemoselectivity problems if carried through several steps unmasked) having one carbonyl protected as a ketal, potentially allowing for chemoselective reduction of the unprotected ketone to access the alcohol moiety found in **3**.

Initial efforts along these lines focused on the use of hypervalent iodine to effect an oxidative dearomatization of a suitably functionalized phenol followed by a spontaneous intramolecular Diels–Alder reaction. Indeed, such transformations have been reported previously, albeit on less complex substrates with nucleophiles/dienophiles that could be used as the reaction solvent.[14] Unfortunately, our attempts to adapt such conditions to our system with pieces of general flavor **18** and **19** failed, with intractable mixtures of products being the only result, even when large excesses (up to 20 equiv) of the dienophilic carboxylic acid or more reactive hypervalent iodine sources [such as $PhI(OC(O)CF_3)_2$] were used. A major roadblock to the success of this approach may well have been the insolubility of the carboxylic acid in the solvents commonly used for these transformations.

To obviate this problem, we next pursued a strategy of tethering the dienophile to the phenol prior to dearomatization via an ester linkage in the form of **23** (Scheme 4). This material was prepared in two steps by an initial selective allylation of catechol **20** at the 4-position and coupling of the remaining phenol with acid **21**, followed directly by deallylation under Pd-catalyzed conditions. To our dismay, the only observable reaction product when **23** was subjected to $PhI(OAc)_2$ in MeOH was solvent-initiated cleavage of the side chain. Thus, we next pursued a more robust tether in the form of an ether (i.e., **24**). To our delight, when this variant was subjected to $PhI(OAc)_2$ in the presence of water (MeOH could also be used) in 1,4-dioxane at 80 °C, the phenol underwent a smooth dearomatization and Diels–Alder reaction in the same pot, furnishing three new bonds and delivering tricycle **26** in 67% yield. Although this step proceeded well, the preceding Mitsunobu and deallylation reactions afforded disappointing product yields; indeed, it is perhaps unsurprising that selective deallylation of a substrate containing two allylic ethers proved troublesome.[15] Nevertheless, we could obtain sufficient amounts of Diels–Alder product **26** to pursue its elaboration into model versions of yunnaneic acids C and D.

Our next experiments focused on opening the cyclic hemiketal within **26** and oxidizing the liberated primary alcohol in hopes of affording **28** directly. Unfortunately, no acid, oxidant, or combination thereof screened proved equal to the task, including those shown to be successful with similarly "locked" hemiketal groups.[16] Our analysis of this outcome was that perhaps it was too challenging to establish any effective equilibrium between the open and closed forms in this case because of the apparent high kinetic barrier to formation of the likely unstable diketone found in the open form. Consequently, we wondered whether we could work around this problem by reducing the neighboring ketone, a process that would make opening of the hemiketal more facile and provide a hydroxyketone intermediate that would not present the same potential instability issues as the corresponding diketone.

Scheme 4. Preliminary Synthetic Studies toward Yunnaneic Acid C[a]



[a]Reagents and conditions: (a) NaH (1.05 equiv), KI (0.1 equiv), allyl bromide (2.0 equiv), DMF, −50→25 °C, 16 h, 57%; (b) DCC (1.5 equiv), DMAP (0.1 equiv), **21** (1.5 equiv), CH_2Cl_2, 24 h; $Pd(PPh_3)_4$ (0.5 equiv), AcOH, 36 h, 67% (two steps); (c) DIAD (1.5 equiv), Ph_3P (1.5 equiv), **22** (1.2 equiv), THF, 0→25 °C, 24 h; $Pd(OAc)_2$ (0.2 equiv), Ph_3P (0.4 equiv), Et_2NH, THF, H_2O, 25 °C, 1 h, 26% (two steps); (d) $PhI(OAc)_2$ (1.1 equiv), H_2O, 1,4-dioxane, 75 °C, 5 min, 67%; (e) $Me_4NBH(OAc)_3$ (3.0 equiv), AcOH, MeCN, 25 °C, 16 h, 77%; (f) TEMPO (0.1 equiv), $PhI(OAc)_2$ (1.1 equiv), CH_2Cl_2, 25 °C, 3 h, 60%; (g) $NaClO_2$ (5.0 equiv), $NaH_2PO_4{\cdot}2H_2O$ (10.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH, H_2O, 25 °C, 2 h; (h) $TMSCHN_2$ (2.0 equiv), THF, MeOH, 0 °C, 30 min, 62% (two steps); (i) Dess–Martin periodinane (4.0 equiv), $NaHCO_3$ (7.5 equiv), CH_2Cl_2, 0→25 °C, 2 h, 35%. DIAD = diisopropyl azodicarboxylate; DCC = *N*,*N*-dicyclohexylcarbodiimide; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl free radical.

In the event, reduction of **26** with $Me_4NBH(OAc)_3$ afforded triol **27**. This material presumably resulted from initial reduction of the ketone from the *exo* face followed by rupture of the hemiketal and a second reduction event directed by the *endo*-disposed alcohol.[17] From here, the model version of yunnaneic acid C (i.e., **28**) was accessed via (1) selective oxidation of the primary alcohol,[18] (2) Pinnick oxidation of the resulting aldehyde, (3) esterification of the newly formed carboxylic acid with $TMSCHN_2$, and (4) oxidation of the *trans*-diol with Dess–Martin periodinane. Despite the ability to finally access this compound, however, the developed route

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clearly had a number of drawbacks, including excessive nonstrategic redox manipulation,[19] low yield in the final diol oxidation step (35%), and a lack of obvious inroads to the desired hydroxyketone regio- and stereochemistry pertinent to yunnaneic acid D.

2. Development of an Efficient and Scalable Route to the Monomeric Yunnaneic Acids: Model Studies and the Total Synthesis of Yunnaneic Acids C and D. In light of these inefficiencies, we reconsidered our initial goal of obtaining the desired Diels–Alder adduct directly from an appropriate carboxylic acid (dienophile) and phenol (latent diene) as retrosynthetically defined in Scheme 3 and initiated anew a search for an oxidizing agent that could effect such a transformation. A promising candidate was $Pb(OAc)_4$, a reagent known to dearomatize appropriately substituted phenols to MOB ketals in a process known as the Wessely oxidation.[20] Furthermore, it has been shown that replacement of the acetate ligands on the Pb(IV) center with an α,β-unsaturated carboxylate could result in a dearomatization event followed by a Diels–Alder reaction to generate a tricyclic product of the type that we sought.[6,21] To our delight, this protocol could be adapted to our system.

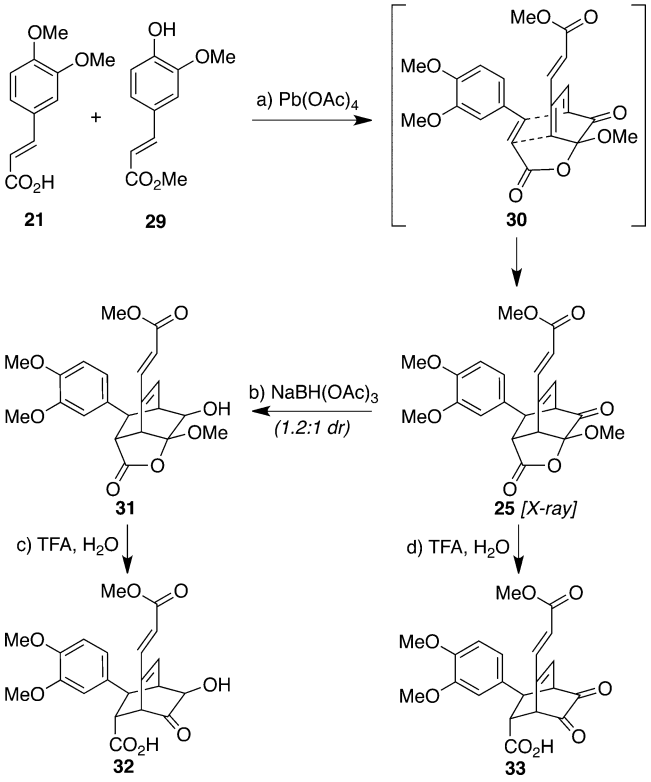
In the event, addition of phenol **29** (Scheme 5) to a solution of $Pb(OAc)_4$ and 7.0 equiv of carboxylic acid **21** in 1,4-dioxane at 25 °C resulted in the nearly instantaneous formation of the desired product **25**, which was isolated in 69% yield. Interestingly, whereas previous reports[6,21] of these reactions often involved performing the initial oxidation, solvent removal, and dissolution in a higher-boiling solvent followed by prolonged heating, this reaction occurred spontaneously and rapidly at ambient temperature—neither the dearomatized intermediate nor the starting material could be detected by TLC analysis immediately after addition of the phenol.

With the success of this protocol, we hoped that the newly formed tricycle would prove more amenable to the manipulations necessary to form the cores of yunnaneic acids C and D. Pleasingly, the γ-methoxylactone of **25** proved far more labile than the hemiketal of **26** (cf. Scheme 4), and the desired hydrolysis proceeded in good yield upon exposure to aqueous TFA to afford the model version of yunnaneic acid C (i.e., **33**) in 73% yield after 16 h of stirring. The desired hydroxyketone core of yunnaneic acid B could be formed following a nonselective reduction of the carbonyl group in **25** with $NaBH(OAc)_3$, which proceeded with 1.2:1 diastereoselectivity slightly favoring the desired isomer; the identity of these diastereomers was determined by the observation of an NOE between the α-hydrogen of the newly installed alcohol and the benzylic hydrogen as well as crystallographic analysis of structures obtained following subsequent steps (vide infra). Following careful separation of the two diastereomers, the *exo* alcohol **31** was subjected to the same acidic conditions as above to form the desired hydroxyketone matching that found in yunnaneic acid D, leading to **32**. As one measure of the overall efficiency of the developed sequences, several hundred milligrams of each model compound could be obtained from a single material batch, ample supplies for subsequent dimerization studies in pursuit of yunnaneic acids A and B (vide infra).

With model work complete, our next task was to translate the developed approach to fully functionalized materials. A key consideration was identifying an appropriate array of protecting groups that would allow us to readily access and efficiently isolate the highly polar final natural products but would be sufficiently robust to survive the intervening reaction conditions. As shown in Scheme 6, our key material was phenol **34**, a rosmarinic acid derivative synthesized readily in large quantity over the course of seven straightforward steps (see the Supporting Information). We selected benzyl ether and allyl ester protecting groups following several rounds of exploration, as both were used in a previously reported synthesis of rosmarinic acid.[22] Pleasingly, upon application of the dearomatization protocol, the desired Diels–Alder adduct **36** was obtained in a reasonable yield of 50%, albeit as a 1:1 mixture with its inseparable diastereomer (structure not drawn). This result, similar to that observed in our Diels–Alder reaction leading to the core of the helicterins,[4b] reveals that the lone chiral center within **34** is seemingly too remote to dictate the facial presentation of the reactive partners in an absolute sense; therefore, nature might need to deploy an enzyme to achieve an appropriate chiral environment to produce the single antipode observed. Nevertheless, despite the absence of selectivity observed in our reaction, the event constitutes, to the best of our knowledge, the most complex example of an oxidative dearomatization/Diels–Alder cascade affording a nondimeric adduct in which the diene and dienophile are not tethered prior to the reaction.[23]

In order to complete the syntheses of yunnaneic acids C and D, we needed a method to separate the mixture of two diastereomers afforded by the Diels–Alder reaction. To our dismay, no solvent system proved capable of doing so, even

Scheme 5. Successful Approach to Yunnaneic Acid C and D Core Structures 32 and 33[a]



[a]Reagents and conditions: (a) **21** (7.0 equiv), $Pb(OAc)_4$ (1.1 equiv), CH_2Cl_2, 25 °C, 1 h; then 1,4-dioxane, 25 °C, 30 min; then **29** (1.0 equiv), 25 °C, 5 min, 69%; (b) $NaBH(OAc)_3$ (5.0 equiv), THF, AcOH, 25 °C, 3 h, 71%; (c) TFA, H_2O, CH_2Cl_2, 25 °C, 3 h, 95%; (d) TFA, H_2O, CH_2Cl_2, 25 °C, 16 h, 73%. TFA = trifluoroacetic acid.

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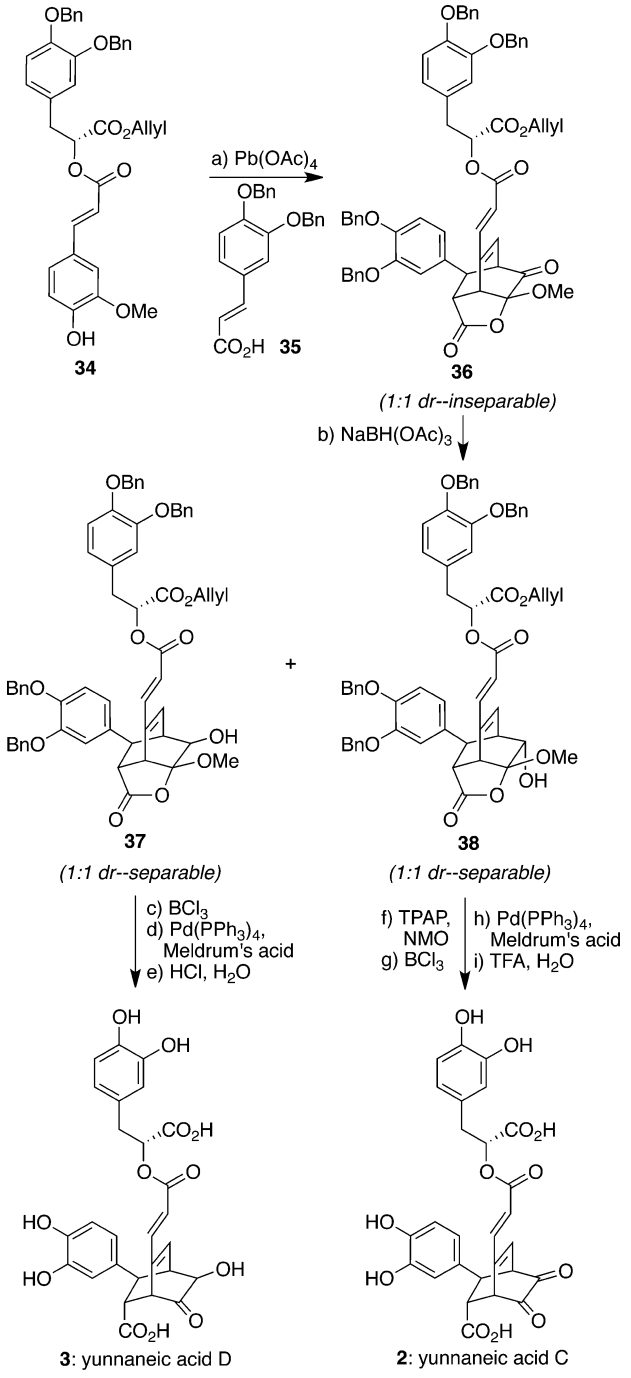
Scheme 6. Total Synthesis of Yunnaneic Acids C (2) and D (3)[a]



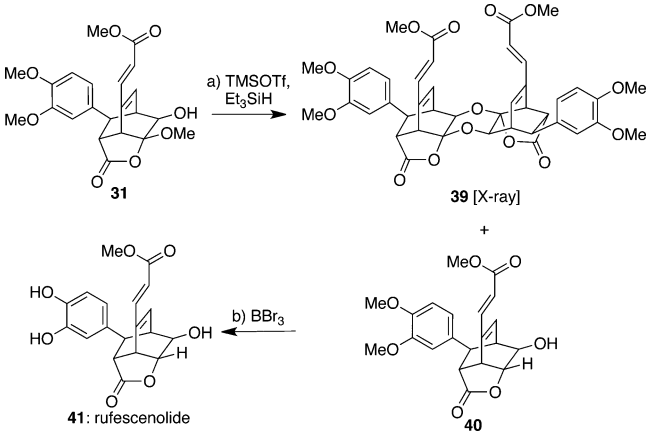
[a]Reagents and conditions: (a) **35** (7.0 equiv), $Pb(OAc)_4$ (1.1 equiv), CH_2Cl_2, 25 °C, 1 h; then 1,4-dioxane, 25 °C, 30 min; then **34** (1.0 equiv), 25 °C, 5 min, 50%; (b) $NaBH(OAc)_3$ (5.0 equiv), AcOH, THF, 25 °C, 82% (1.5:1 **37**:**38**); (c) BCl_3 (8.0 equiv), CH_2Cl_2, −78 °C, 5 min; (d) $Pd(PPh_3)_4$ (5 mol %), Meldrum's acid (1.5 equiv), THF, 25 °C, 15 min, 55% (two steps); (e) HCl, H_2O, CH_2Cl_2, 25 °C, 2 h, 95%; (f) TPAP (5 mol %), NMO (2.0 equiv), 4 Å molecular sieves, CH_2Cl_2, 0 °C, 1 h, 67%; (g) BCl_3 (8.0 equiv), CH_2Cl_2, −78 °C, 79%; (h) $Pd(PPh_3)_4$, 10 mol % Meldrum's acid (1.5 equiv), THF, 25 °C, 15 min; (i) TFA, H_2O, CH_2Cl_2, 25 °C, 16 h, 50% (two steps). DMAP = 4-dimethylaminopyridine, NMO = *N*-methylmorpholine-*N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate. For **34** and **35**, see the Supporting Information.

when preparative TLC or semipreparative HPLC was used. Fortunately, treatment of the Diels−Alder product with $NaBH(OAc)_3$, as in the model system (cf. Scheme 5), effected a clean reduction of the ketone, resulting in four diastereomers (two *exo* alcohols and two *endo* alcohols) that could be separated by careful preparative TLC. The two undesired *endo* alcohols could then be oxidized back to the ketone via a Ley−Griffith oxidation[24] and carried forward to yunnaneic acid C (**2**) and an epimer of its enantiomer by (1) debenzylation under Lewis acidic conditions, (2) palladium-catalyzed deallylation, and (3) acid-mediated rupture of the γ-methoxylactone. The *exo* alcohols could be subjected to a similar sequence to afford yunnaneic acid D (**3**). In each case, comparison of the spectra for each of the diastereomers made assignment of the correct material facile, with several significant differences observed for the incorrect diastereomer; for the natural products themselves, all of the spectral data were in accordance with those reported previously.[25] Thus, the first total syntheses of yunnaneic acids C and D were completed in 13 steps and 12 steps, respectively.

Two aspects of this synthetic endgame deserve further comment. First, a set of two orthogonal protecting groups for the four phenolic groups and the ester proved necessary because it was found that the side-chain carboxylic acid needed to remain protected while the benzyl ethers were cleaved; when the free acid was present under the debenzylation conditions, significant side-chain cleavage was observed. Second, yunnaneic acid D was found to isomerize readily, presumably to a different hydroxyketone stereo- and/or regioisomer, upon standing in the presence of residual acid that lingered following the final ketal-opening step. In fact, this isomerization occurred even during the course of attempted removal of trace acids such as TFA via coevaporation. Thus, the selection of an appropriate acid in this final step was crucial, with HCl proving to be ideal in that it was sufficiently strong to effect the unmasking of the desired ketone while easy enough to remove in the course of a standard, nonbasic aqueous workup.

3. Total Synthesis of Rufescenolide. While our work on the yunnaneic acids was proceeding, the isolation of the unique natural product rufescenolide (**41**) (Scheme 7) from the

Scheme 7. Total Synthesis of Rufescenolide (41) from Intermediate 31[a]



[a]Reagents and conditions: (a) TMSOTf (3.0 equiv), Et_3SiH (20 equiv), CH_2Cl_2, 25 °C, 2.5 h, 54% (**39**), 25% (**40**); (b) BBr_3 (6.0 equiv), CH_2Cl_2, 0 °C, 10 min, 55%.

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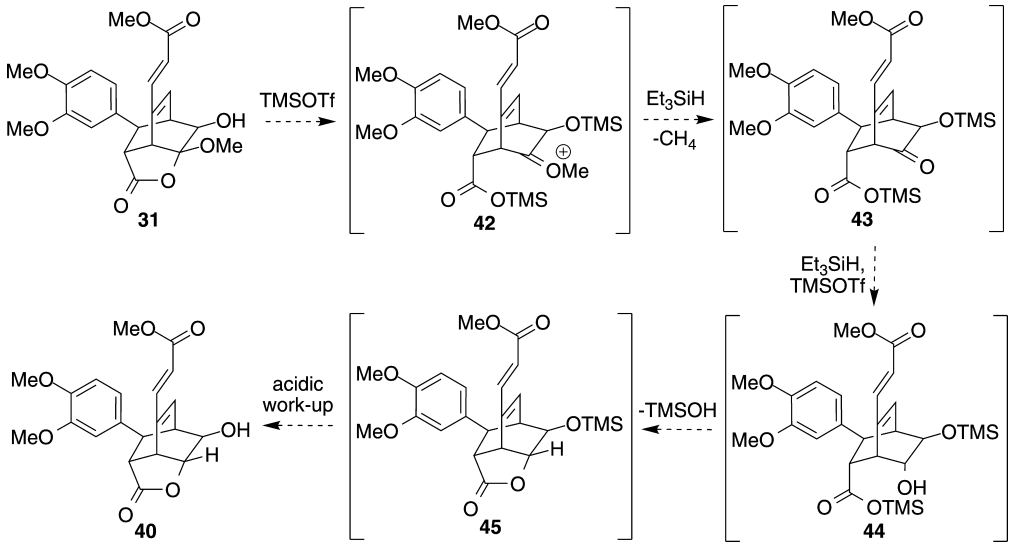
Scheme 8. Proposed Mechanism for the Transformation of 31 to 40



Brazilian shrub *Cordia rufescens* was reported.[26] Rufescenolide is a caffeic acid derivative with a structure remarkably similar to that of model Diels–Alder product **25** (cf. Scheme 5) and is, to our knowledge, the only bridged polycyclic caffeic acid natural product containing a lactone. This target piqued our interest not only because of rufescenolide's structural homology to the readily available **25** but also because of the resulting implications for the biosynthesis of the yunnaneic acids. Indeed, one could imagine that the bicyclo[2.2.2]octene motif could conceivably arise in nature via an intramolecular Diels–Alder reaction, which may explain the unusual regio- and stereochemistry of the aryl and carboxyl substituents on the bicycles of the yunnaneic acids.[27] Given this resemblance, we wondered whether we could utilize **25** and/or its reduced variant **31** to achieve a concise synthesis of rufescenolide (**41**).

To accomplish this goal, we required a method to replace the methoxy group of the γ-methoxylactone within the core with a hydrogen atom. One potential way to effect such a transformation would be to react the γ-methoxylactone with a suitable Lewis acid in the presence of a hydride source to intercept the intermediate oxacarbenium ion (structure not shown). However, the success of such an approach seemed unlikely because the lactone oxygen within the tricyclic system of **25** or **31** is unlikely to effectively stabilize the necessarily nonplanar carbocation generated by abstraction of the methoxy group by the Lewis acid. Thus, it was with only a modest hope for success that we attempted to apply such a protocol to the synthesis of rufescenolide. Despite these reservations, however, we found that upon reaction of **31** with TMSOTf and Et_3SiH,[28] the desired reduced product (i.e., **40**) could be obtained in 54% yield along with the C_2-symmetric dimer **39** (25% yield, structure verified by X-ray crystallography). The overall mechanism for this transformation is not currently definitive; for now, we would posit that ring opening to form an oxacarbenium ion resembling **42**, followed by the intermediates shown in Scheme 8, could be one pathway where similar steps from the dimer of **42** would account for the formation of **39**. In any event, rufescenolide was then obtained from **40** in 55% yield following deprotection of the phenolic methyl ethers through 10 min of exposure to BBr_3 in CH_2Cl_2 at 0 °C. Overall, this synthesis required just four steps from phenol **29**.[29]

In addition, this synthesis reinforces the potential value of the intramolecular Diels–Alder product as a key intermediate for the controlled assembly of a number of different related natural products. In addition to providing access to compounds **2**, **3**, and **41** as described in this work, an intermediate with the general structure of **46** could potentially lead to the synthesis of both yunnaneic acids E (**47**) and F (**48**) as well (see Scheme 9).[2] The versatility of such an intermediate, when juxtaposed with the proposed biosynthesis and the isolation of tricyclic rufescenolide (**41**), could suggest that from a biogenetic perspective, nature might deploy the enantiocontrolled synthesis of a core like **46** as a means to accomplish the stereocontrolled preparation of a number of target molecules.

4. Explorations into the Dimerization Behavior of Model Yunnaneic Acid Compounds. With a concise route to the monomeric natural products established, our attention now turned to their dimerization into yunnaneic acids A (**2**) and B (**3**). As discussed above, both of these events are formally heterodimerizations and were expected to be quite challenging relative to the homodimerizations we had previously accomplished within the helicterin program, not only because of the mixed dimerization requirement but also because of the open question of whether the free carboxylic acid substituent on the core is a critical component. Indeed, its ability to potentially attack the neighboring ketone or to hydrogen bond with various substituents could play a critical role in success, as could potentially protecting that group to remove such additional properties. Thus, we felt that we needed to explore both options overall.

In assessing some starting points for investigation, we were mindful not only of our own studies with the helicterins but also a number of additional literature precedents, work which globally indicates that each template often requires unique and specific conditions for dimerization to be achieved. For instance, one additional example of a self-dimerization of a hydroxyketone comes in the form of the union of two molecules of salicortin (**49**) to form idesolide (**50**) (Scheme 10). Iwabuchi[30a] and Kuwahara[30b] independently were able to effect this dimerization in 2010 under basic conditions; while assuring to our work in that such an event could take place, it also provides a cautionary tale in that extensive earlier studies by the Snider group[30c] highlighted alternate reaction pathways

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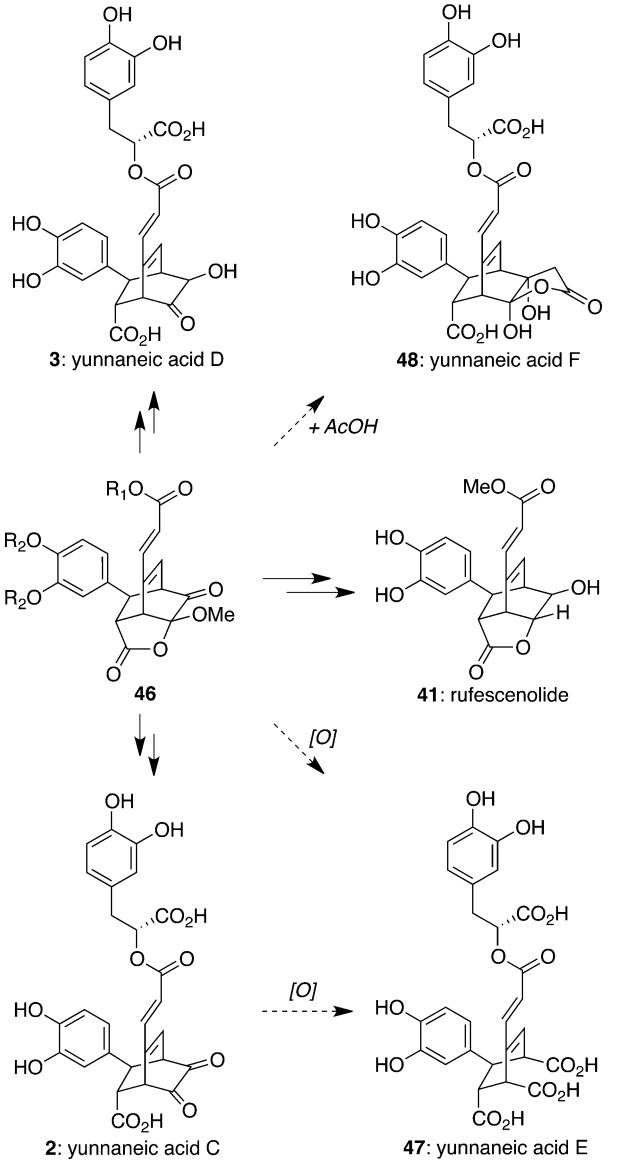
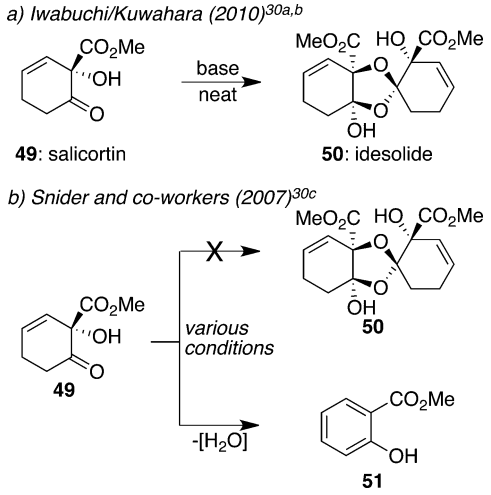
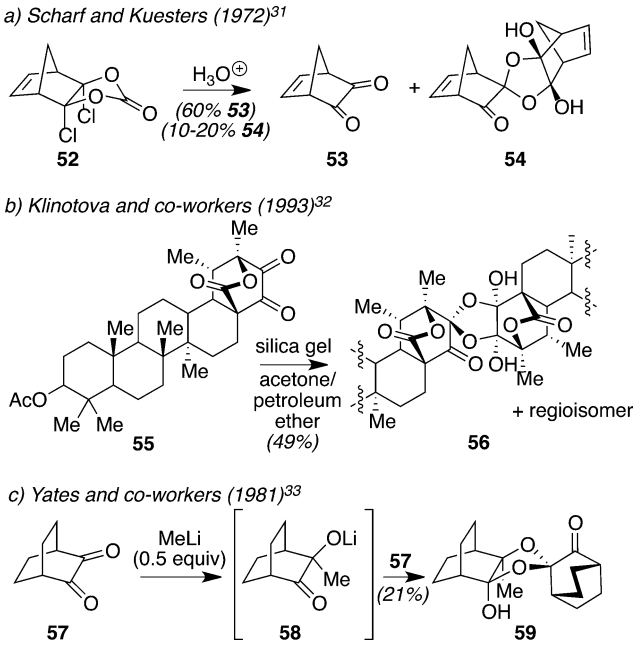
Scheme 9. Potential Ability To Utilize Intermediate 46 To Access All Members of the Yunnaneic Acid Family as Well as Related Structures



Scheme 10. Dimerization Studies into the Natural Product Idesolide (50) via a Hydroxyketone Precursor



Scheme 11. Selected Examples of Diketone Dimerizations



that did not lead to the dimer. One challenge in this case could be that there exists a high kinetic barrier for dimerization, especially compared with an alternative aromatization pathway leading to **51**. These studies also highlight the importance of concentration, as success was achieved only under solvent-free conditions.

In terms of more direct precedent, specifically diketone dimerizations as needed for yunnaneic acid B, there are three major examples that reflect such processes (Scheme 11). The first, observed by Scharf and Kuesters,[31] formed the reactive 1,2-diketone moiety in situ through acidic hydrolysis of the carbonate within **52**, leading to a minor amount (10−20% yield) of dimer **54** in the same pot. A similar dimerization was observed by Klinotova[32] when simple exposure of terpene derivative **55** to silica gel afforded **56** along with another dimeric regioisomer (structure not shown) in 49% yield. However, to highlight the specificity of such an event, it is clearly substrate-dependent in that many other 1,2-diketones, including our own for the model yunnaneic acid core, do not undergo such facile dimerization when exposed to silica gel. Finally, in what is an example of a yunnaneic acid A-type dimerization, Yates and Langford[33] showed that treatment of diketone **57** with 0.5 equiv of MeLi could afford **58**, which then reacted with the remaining **57** in solution to afford mixed dimer **59** in 21% yield. Thus, this precedent provided a conceptual underpinning for what we hoped to achieve for the heterodimerization needed in our case.

Some of our initial efforts began with protected forms of our key compounds (e.g., **60** and **25** in Scheme 12) in terms of both the *exo*-disposed acids and the ketone domains, largely to get a sense of their reactivities. For instance, we were pleased to find early on that compound **60** could dimerize to the same type of core as in the helicterins under conditions we developed previously (i.e., $BF_3{\cdot}OEt_2$) because this result indicated that these compounds should have dimerization behavior similar to that observed in the helicterin program. Thus, we moved onto heterodimerization attempts, hoping that the formation of an

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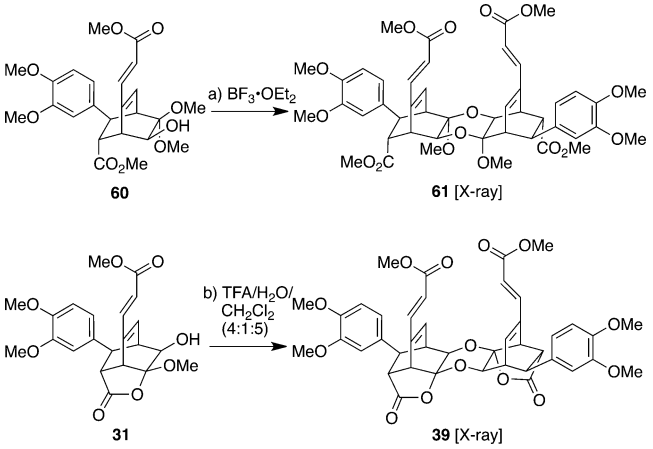
Scheme 12. Iniital Dimerization Experiments Using Protected Carboxylic Acids[a]



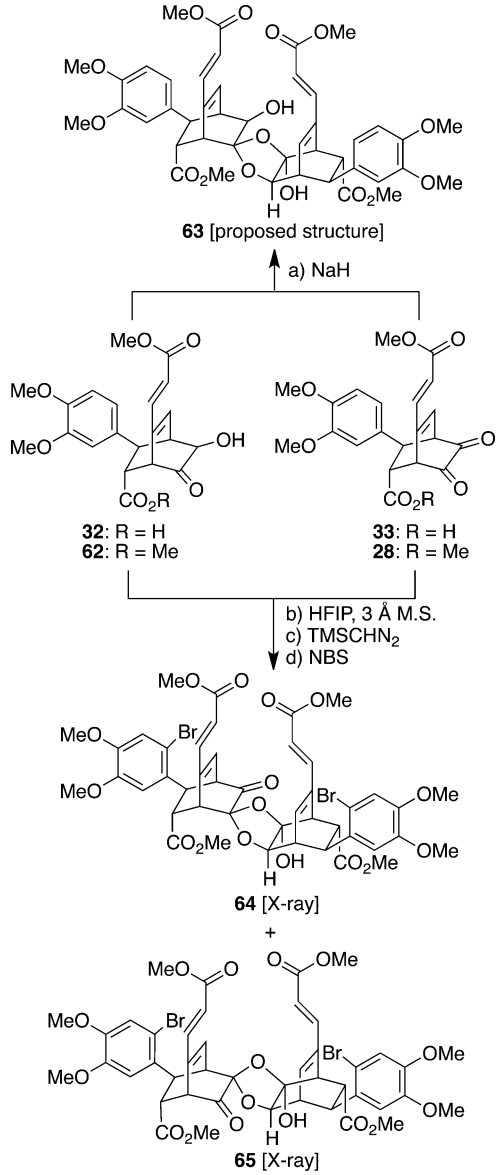
[a]Reagents and conditions: (a) $BF_3{\cdot}OEt_2$ (4.0 equiv), CH_2Cl_2, 0 °C, 30 min, 36%; (b) TFA, H_2O, CH_2Cl_2 (4:1:5), 25 °C, 3 h, <5%.

oxacarbenium ion derived from **60** (or a suitably protected derivative) could be followed by attack of the alcohol of an appropriate hydroxyketone to form a yunnaneic acid A-type heterodimer. However, despite the initial success in effecting homodimerization of **60**, the only other definitive outcome of our work with this molecule and related compounds was the unexpected formation of homodimer **39**, the same material observed in our rufescenolide synthesis, which was formed as a very minor product upon treatment of **31** with aqueous TFA.[34]

Turning next to alternate approaches for reaching yunnaneic acid A, we treated model monomer pairs **32** and **33** or **62** and **28** (Scheme 13) with an array of acids and bases. In all cases, these events led to either complex mixtures, recovered starting materials, or the selective and unproductive dimerization of the hydroxyketone component to form what we propose to be structure **63**.[35] In the example shown where NaH was used as the base, the diketone appeard to decompose under the strongly basic conditions, and we noted that the same dimeric product (i.e., **63**) was obtained when hydroxyketone **62** alone was treated with NaH. Indeed, these dimerization reactions failed in all variants of polar aprotic solvents, while nonpolar solvents proved to be incapable of dissolving the starting materials.

Thus, in an effort to obviate these problems, we turned next to protic but non-nucleophilic solvents. We found that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was unique in providing the proper conditions to effect pseudodimerization of **32** and **33**, affording a rather unstable dimer alongside a second dimer formed in smaller amounts that likewise proved unstable. Although such instability hampered our ability to characterize these dimers directly, immediate esterification of the crude dimerization products with $TMSCHN_2$ increased their stability and enabled far easier isolation of the dimers of interest. Although they could not be crystallized into materials suitable for X-ray diffraction, their brominated counterparts (formed by exposure to 4 equiv of NBS at 25 °C for 14 h) proved amenable to crystallization. X-ray analysis of those materials revealed that our dimeric compounds, following derivatization, were **64** and **65**. Unfortunately, neither structure matched that reported for yunnaneic acid A. Although we had indeed achieved the selective union of the two distinct monomers with no apparent homodimerization, it was found

Scheme 13. Mixed Dimerization Experiments[a]



[a]Reagents and conditions: (a) NaH (10 equiv), THF, 0→25 °C, 30 min, 15%, 52% b.r.s.m.; (b) HFIP, 3 Å molecular sieves, CH_2Cl_2, 25 °C, 14 h; (c) $TMSCHN_2$ (4.0 equiv), Et_2O, MeOH, −78 °C, 30 min, 26% (two steps), 4:1 **64:65**; (d) NBS (4.0 equiv), MeCN, 25 °C, 80%. HFIP = hexafluoro-2-propanol, NBS = *N*-bromosuccinimide.

that in the case of the major product **64**, the wrong carbonyl of the diketone had been engaged by the hydroxyketone. In the case of the minor product **65**, the desired carbonyl had undergone attack, but the wrong pair of enantiomers had reacted, resulting in a compound that was diastereomeric to the natural product.

Application of similar conditions to diketones such as **66** (Scheme 14) alone, in hopes of affording the yunnaneic acid B core, also afforded a mixture of dimers, albeit in lower yield. As was the case with the heterodimers discussed above, these compounds proved rather unstable. Nevertheless, one of these dimers, **67**, was characterized by X-ray crystallography when an appropriately brominated diketone was subjected to the same dimerization conditions.[36] Once again, we had obtained a dimer whose structure did not match that of the natural product. In

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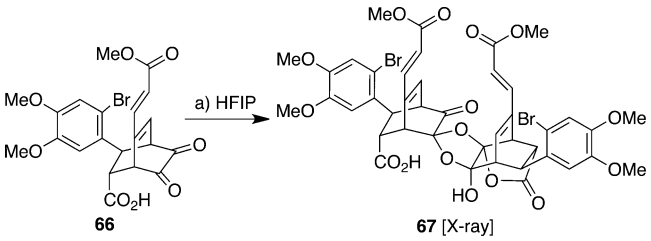
Scheme 14. Diketone Dimerization Experiments[a]



66 67 [X-ray]

[a]Reagents and conditions: (a) HFIP, 50 °C, 16 h, 5%.

this case, rather than attack of a water molecule on the diketone as required, the pendant carboxyl group had attacked the ketone, followed by attack of the resulting hemiketal oxygen on a second diketone molecule. Furthermore, ketalization had occurred on the undesired carbonyl of the diketone (*syn* to the carboxyl group). Unfortunately, X-ray-quality crystals of the other two isolated dimers from these experiments have proven elusive. Interestingly, the carboxylic acid of the diketone appears to be critical to the success of these HFIP-mediated dimerizations; the analogous methyl ester does not react.

Globally, our dimerization studies show that the appropriate monomers can be made to engage with each other to afford cores reminiscent of the yunnaneic acids under very specific reaction conditions, but in no case did we observe the correct connectivities corresponding to the natural products. What this body of results may suggest is that nature uses enzymes to help guide the union of the two pieces; in other words, it seems unlikely that these dimers are artifacts of the isolation team's efforts, given that spontaneous and/or facile dimerizations were not observed with any of our materials. If true, this statement has interesting implications for the biosynthesis of these oligomers, since it implies that extra energy may be required to form the requisite bonds when there are clearly additional reaction pathways that are open to these types of reactive pieces.

CONCLUSION

We have developed the first total syntheses of yunnaneic acids C and D through an oxidative dearomatization/Diels–Alder cascade on a complex substrate that completely controls the relative stereo- and regiochemistry of the carbon substituents on the bicyclic core. Furthermore, this strategy would appear to be applicable to the synthesis of other caffeic acid metabolites (as exemplified by our total synthesis of rufescenolide) and highlights the value of a single, versatile intermediate in affording a number of different natural product structures in a controlled manner.[4] Moreover, the processes developed for the monomer syntheses are readily scalable, allowing for extensive studies of their dimerization. Such experiments have shown that although it is possible to selectively couple the monomeric diketone and hydroxyketone, the structures formed in nature do not seem commensurate with the innate reactivities of the monomers. This outcome may point to some kind of enzymatic assistance for nature's dimerization process. In any event, on the basis of what has been achieved in the present work, studies of the biochemical properties of our natural products, and, potentially of more importance, unnatural analogues and synthetic intermediates, can now begin in earnest and will be reported in due course.

EXPERIMENTAL SECTION

General Procedures. Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Dry methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), and tetrahydrofuran (THF) were obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns; triethylamine (Et_3N) was distilled from KOH; acetone, methanol (MeOH), and dimethylformamide (DMF) were purchased in anhydrous form and used as received. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on silica gel plates (60F-254) using UV light and an aqueous solution of cerium ammonium sulfate and ammonium molybdate and heat as visualizing agents. Preparative TLC was carried out on 0.50 mm silica gel plates (60F-254). Silica gel (60 Å, academic grade, particle size 40–63 μm) was used for flash column chromatography. NMR spectra were recorded on 300 MHz, 400 MHz, and 500 MHz spectrometers and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on an FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB) with Xe as the carrier gas and *m*-nitrobenzyl alcohol as the matrix on a double-focusing sector-type mass spectrometer. Optical rotations were recorded on a digital polarimeter.

(*E*)-Methyl 3-(4-(Allyloxy)-3-hydroxyphenyl)acrylate (S1). (*E*)-Methyl 3-(3,4-dihydroxyphenyl)acrylate (**20**) (0.890 g, 4.59 mmol, 1.0 equiv) was dissolved in DMF (24 mL), and solid KI (0.083 g, 0.50 mmol, 0.1 equiv) was added at 25 °C. The resultant solution was then cooled to −50 °C, and NaH (60% dispersion in mineral oil, 0.193 g, 5.20 mmol, 1.05 equiv) was added. After the resultant yellow solution was stirred for 5 min at −50 °C, allyl bromide (0.75 mL, 9.9 mmol, 2.0 equiv) was added, and the reaction mixture was allowed to gradually warm to 25 °C and then stirred for an additional 16 h. Upon completion, the reaction mixture was poured into 1 M HCl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were then washed with water (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude product was purified by flash column chromatography (silica gel, hexanes:EtOAc, 9:1→1:1) to give phenol **S1** (0.605 g, 57% yield, 4.5:1 mixture of regioisomers favoring the 3-hydroxy isomer) as a white solid alongside the diallylated compound (0.228 g, 18% yield) and recovered starting material (0.120 g, 13% yield). [Note: drawn structures of all of these additional compounds are provided in the Supporting Information.] **S1**: R_f = 0.31 (hexanes:EtOAc, 4:1); IR (film) ν_{max} 3387, 2960, 2865, 1694, 1629, 1609, 1580, 1504, 1426, 1316, 1267, 1163, 1123, 1023, 979, 934, 860, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 16.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.12–6.04 (m, 1H), 5.69 (s, 1H), 5.44 (dd, J = 17.5, 1.5 Hz, 1H), 5.37 (dd, J = 10.5, 1.0 Hz, 1H), 4.67 (app dt, J = 4.0, 1.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 147.5, 146.1, 144.7, 132.3, 128.2, 121.6, 118.7, 115.9, 113.3, 111.9, 69.8, 51.6; HRMS (FAB) calcd for $C_{13}H_{14}O_4^+$ $[M]^+$ 234.0892, found 234.0904.

(*E*)-Methyl 3-(3-(((*E*)-3-(3,4-Dimethoxyphenyl)allyl)oxy)-4-hydroxyphenyl)acrylate (24).[37] To a solution of allyl ether **S1** (0.380 g, 1.60 mmol, 1.0 equiv), (*E*)-3-(3,4-dimethoxyphenyl)prop-2-en-1-ol (**21**) (0.373 g, 1.90 mmol, 1.2 equiv), and Ph_3P (0.628 g, 2.40 mmol, 1.5 equiv) in THF (16 mL) at 0 °C was added DIAD (0.47 mL, 2.40 mmol, 1.5 equiv). The resultant orange solution was then allowed to warm slowly to 25 °C and stirred for 24 h. Upon completion, the reaction mixture was concentrated directly, and the resultant oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3→1:1) to give the desired Mitsunobu product as a colorless oil. Pressing forward, this new intermediate was dissolved in THF (7.5

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mL), and Ph_3P (0.135 g, 0.51 mmol, 0.4 equiv) and H_2O (1.4 mL) were added sequentially at 25 °C. Et_2NH (3.75 mL, 36 mmol, 22.5 equiv) was then added, and the solution became yellow-green in color. Next, $Pd(OAc)_2$ (0.057 g, 0.26 mmol, 0.2 equiv) was added at 25 °C, and during the next few minutes of stirring, the solution became very dark green in color. The reaction mixture was then stirred for an additional 1 h at 25 °C. Upon completion, the reaction contents were concentrated directly, and the resultant residue was then diluted with EtOAc (40 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to give a dark-green oil. This crude material was then purified by flash column chromatography (silica gel, hexanes:Et_2O, 1:1→2:3) to give phenol **24** (0.150 g, 26% yield over two steps) as an off-white solid. **24**: R_f = 0.32 (hexanes:EtOAc, 3:2); IR (film) ν_{max} 3359, 2951, 2932, 1698, 1601, 1511, 1438, 1262, 1158, 1108, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 15.6 Hz, 1H), 7.10−7.07 (m, 2H), 6.98−6.93 (m, 3H), 6.84 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 15.6 Hz, 1H), 6.32−6.24 (m, 2H), 6.02 (br s, 1H), 4.77 (d, J = 6.0 Hz, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 150.4, 150.1, 149.2, 146.8, 145.8, 135.3, 129.9, 127.9, 124.0, 122.0, 121.0, 116.1, 115.9, 112.1, 112.0, 109.9, 70.9, 56.9, 56.8, 52.5; HRMS data could not be obtained because of the lability of the allylic ether.

(*E*)-Methyl 3-(8-(3,4-Dimethoxyphenyl)-7a-hydroxy-7-oxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)acrylate (26). A solution of $PhI(OAc)_2$ (0.052 g, 0.16 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise under an ambient atmosphere to a suspension of phenol **24** (0.054 g, 0.15 mmol, 1.0 equiv) in 1,4-dioxane/H_2O (2:1, 1.5 mL) at 75 °C. The resultant dark-red solution was stirred at 75 °C for 5 min and then cooled to 25 °C. The reaction mixture was then diluted with EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous layer was then extracted with EtOAc (2 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give a brown oil. Purification of this crude residue by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) afforded the desired Diels−Alder product **26** (0.039 g, 67% yield) as a pale-yellow oil. **26**: R_f = 0.20 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3421, 2953, 1741, 1631, 1516, 1438, 1314, 1256, 1178, 1144, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 15.6 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.4, 2.0 Hz, 1H), 6.29−6.21 (m, 2H), 4.38 (dd, J = 8.0, 3.2 Hz, 1H), 4.11 (s, 1H), 3.93 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (dd, J = 4.0, 2.0 Hz, 1H), 3.51 (dd, J = 7.2, 2.4 Hz, 1H), 3.43 (br s, 1H), 2.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 167.0, 148.9, 148.3, 141.2, 139.1, 133.6, 131.9, 119.7, 118.9, 111.4, 111.2, 96.4, 73.8, 55.9 (2C), 53.8, 51.9, 47.2, 45.9, 44.8; HRMS (FAB) calcd for $C_{21}H_{22}O_7^+$ $[M]^+$ 386.1366, found 386.1370.

(*E*)-Methyl 3-(8-(3,4-Dimethoxyphenyl)-7a-methoxy-2,7-dioxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)-acrylate (25). Solid $Pb(OAc)_4$ (95%, 1.20 g, 2.61 mmol, 1.1 equiv) was suspended in toluene (5 mL), and the suspension was concentrated directly to remove any residual AcOH. The resultant light-brown solid was then dissolved in CH_2Cl_2 (33 mL), and 3,4-dimethoxycinnamic acid (**22**) (3.45 g, 16.6 mmol, 7.0 equiv) was added at 25 °C, yielding an orange suspension. After the reaction mixture was stirred at 25 °C for 30 min, the suspension was concentrated directly. Upon complete removal of the solvent, the flask was back-filled with argon by attaching a balloon to the air inlet of the rotary evaporator. The resultant orange solid was then suspended in toluene (15 mL) and concentrated directly to remove any residual AcOH resulting from ligand exchange. This azeotroping procedure was then repeated. The subsequent orange solid was then resuspended in CH_2Cl_2 (33 mL), and the above procedure (i.e., stirring for 30 min, concentration, and azeotroping) was repeated. After the final azeotrope was performed, the orange solid was dissolved in anhydrous 1,4-dioxane (33 mL), and the resulting deep-red solution was stirred at 25 °C for 30 min. A solution of (*E*)-methyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (**29**) (0.493 g, 2.37 mmol, 1.0 equiv) in 1,4-dioxane (3 mL) was then added via syringe, resulting in rapid disappearance of the red color of the solution. After the mixture was stirred at 25 °C for an additional 2 min, ethylene glycol (0.160 mL, 2.61 mmol, 1.1 equiv) was added, resulting in the formation of a thick colorless slurry that was stirred vigorously at 25 °C for 20 min. Upon completion, the reaction contents were concentrated directly, and the resulting off-white solid was suspended in EtOAc and filtered. The solid residue was then rinsed with EtOAc (3 × 15 mL) and filtered. The combined filtrates were then washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. This crude residue was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3→2:3) to give the desired Diels−Alder adduct **25** (0.675 g, 69% yield) as a pale-yellow foam along with the undesired compound (*E*)-methyl 3-(3-acetoxy-3-methoxy-4-oxocyclohexa-1,5-dien-1-yl)acrylate (**S2**) (0.074 g, 12% yield) as a yellow oil. [Note: the excess carboxylic acid could be recovered from the aqueous layer by acidifying it to pH 2 and extracting twice with EtOAc.]

25: R_f = 0.44 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 2951, 2839, 1792, 1747, 1710, 1633, 1515, 1314, 1193, 1024, 916 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J =15.5 Hz, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.49 (s, 1H), 6.37 (m, 2H), 6.23 (d, J = 16 Hz, 1H), 4.13 (d, J = 5 Hz, 1H), 3.82−3.73 (m, 10H), 3.71−3.61 (m, 4H), 3.27 (d, J = 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 172.9, 166.6, 149.0, 148.7, 140.4, 137.1, 133.5, 131.0, 119.6, 119.3, 111.2 (2C), 99.5, 56.3, 55.9 (2C), 53.9, 52.0, 47.4, 44.9, 43.9; HRMS (FAB) calcd for $C_{22}H_{22}O_8^+$ $[M]^+$ 414.1315, found 414.1302.

S2: R_f = 0.65 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 2953, 1707, 1691, 1436, 1248, 1168, 1104, 1087, 1014, 977, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 16.5 Hz, 1H), 7.17 (d, J = 10 Hz, 1H), 6.41 (s, 1H), 6.28 (d, J = 10 Hz, 1H), 6.24 (d, J = 16 Hz, 1H), 3.81 (s, 3H), 3.50 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 169.6, 166.4, 141.3, 137.1, 136.2, 132.7, 126.9, 120.6, 92.7, 51.9, 51.6, 20.4; HRMS data could not be obtained because the product was not sufficiently stable, but an $[M + H]^+$ peak at m/z 267.11 was observed via LRMS (FAB).

(*E*)-Methyl 3-(8-(3,4-Dimethoxyphenyl)-7-hydroxy-7a-methoxy-2-oxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)acrylate (31) and (*E*)-Methyl 3-(8-(3,4-Dimethoxyphenyl)-7-hydroxy-7a-methoxy-2-oxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)acrylate (S3). Diels−Alder adduct **25** (0.630 g, 1.52 mmol, 1.0 equiv) was dissolved in THF/AcOH (1:1, 14 mL). $NaBH(OAc)_3$ (1.61 g, 7.61 mmol, 5.0 equiv) was added at 25 °C, and the resultant yellow solution was stirred at 25 °C for 3 h. Upon completion, an aqueous solution of Rochelle's salt (0.5 M, 38 mL) was added, and the mixture was stirred for an additional 20 min at 25 °C, after which time it was carefully poured into saturated aqueous $NaHCO_3$ (50 mL; CAUTION: vigorous bubbling was observed) and extracted with EtOAc (50 mL). The organic layer was then washed with saturated aqueous $NaHCO_3$ (50 mL), and the combined aqueous layers were re-extracted with EtOAc (2 × 50 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give a colorless oil. Purification of this crude residue by flash column chromatography (silica gel, CH_2Cl_2:Et_2O, 19:1→9:1) gave *exo* alcohol **31** (0.228 g, 36% yield) as a white solid and *endo* alcohol **S3** (0.221 g, 35% yield) as a cloudy, colorless oil.

31: R_f = 0.34 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3505, 2949, 1777, 1713, 1634, 1518, 1351, 1256, 1197, 1025, 929 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 6.5 Hz, 1H), 6.47 (d, J = 2.5 Hz, 1H), 6.38 (dd, J = 8.5, 2.0 Hz, 1H), 6.08 (d, J = 16 Hz, 1H), 4.11 (app t, J = 3.5 Hz, 1H), 3.89 (d, J = 4.5 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.58 (s, 3H), 3.45 (app dt, J = 7.0, 3.0 Hz, 1H), 3.36 (br s, 1H), 2.90 (dd, J = 4.5, 2.0 Hz, 1H), 2.51 (d, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 167.0, 148.8, 148.2, 141.5, 139.8, 133.3, 132.9, 119.5, 117.0, 111.2, 111.1, 109.8, 74.2, 55.9, 52.9, 51.9, 47.8, 47.3, 44.2, 40.4; HRMS (FAB) calcd for $C_{22}H_{24}O_8^+$ $[M]^+$ 416.1471, found 416.1465.

S3: R_f = 0.34 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3477, 3059, 2993, 2951, 2844, 1780, 1716, 1633, 1605, 1518, 1255, 1203, 1175, 1026, 948, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 10.0 Hz, 1H), 6.51−6.49 (m, 2H), 6.36 (dd, J =

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8.0, 2.0 Hz, 1H), 6.09 (d, J = 16 Hz, 1H), 3.86 (dd, J = 5.0, 2.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68 (app t, J = 2.5 Hz, 1H), 3.62 (d, J = 2.0 Hz, 1H), 3.47 (s, 3H), 3.15 (app dt, J = 7.0, 3.0 Hz, 1H), 2.98 (dd, J = 5.0, 2.0 Hz, 1H), 2.92 (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 167.1, 148.8, 148.1, 141.4, 139.2, 134.3, 133.6, 119.6, 117.8, 111.5, 111.0, 107.7, 72.3, 55.9, 52.1, 51.9, 48.1, 47.5, 42.7, 39.8; HRMS (FAB) calcd for $C_{22}H_{24}O_8^+$ $[M]^+$ 416.1471, found 416.1454.

(1*R*,2*R*,3*S*,4*R*)-3-(3,4-Dimethoxyphenyl)-8-hydroxy-6-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (32). Reduction product **31** (0.200 g, 0.49 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (2.5 mL), and then H_2O (1.25 mL) and TFA (1.25 mL) were added sequentially at 25 °C. After the resultant colorless, cloudy mixture was vigorously stirred at 25 °C for 3 h, the reaction contents were concentrated directly to give a white solid, from which residual TFA was removed by further coevaporations with toluene (2 × 5 mL) to afford the desired hydroxy ketone **32** (0.196 g, 99%), which was carried forward without further purification. **32**: R_f = 0.19 (CH_2Cl_2:MeOH, 9:1); IR (film) ν_{max} 3395, 2948, 2913, 2841, 1713, 1630, 1590, 1517, 1314, 1255, 1144, 1025 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.44 (d, J = 16.0 Hz, 1H), 6.89–6.79 (m, 3H), 6.74 (dd, J = 8.5, 2.0 Hz, 1H), 6.22 (d, J = 15.5 Hz, 1H), 4.09 (d, J = 2.5 Hz, 1H), 3.83–3.78 (m, 10H), 3.67 (d, J = 4.0 Hz, 1H), 3.26 (app dt, J = 4.0, 2.0 Hz, 1H), 2.82 (dd, J = 5.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.3, 171.6, 167.5, 149.0, 148.0, 141.1, 140.3, 136.8, 136.2, 119.3, 117.1, 111.7 (2C), 71.4, 55.1, 55.0, 51.1, 50.9, 50.8, 46.5, 31.3; HRMS (FAB) calcd for $C_{21}H_{22}O_8Na^+$ $[M + Na]^+$ 425.1212, found 425.1213.

(1*R*,2*R*,3*S*,4*R*)-3-(3,4-Dimethoxyphenyl)-6-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-7,8-dioxobicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (33). Diels–Alder adduct **25** (0.240 g, 0.58 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.5 mL), and then H_2O (1.25 mL) and TFA (1.25 mL) were added sequentially at 25 °C. After the resultant mixture was vigorously stirred at 25 °C for 16 h, the reaction contents were concentrated directly to give a yellow oil, from which residual TFA was removed by further coevaporations with toluene (2 × 5 mL). Purification of the resultant crude yellow oil by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 97:3→19:1) gave diketone **33** (0.170 g, 73% yield) as a yellow foam. **33**: R_f = 0.61 (CH_2Cl_2:MeOH, 9:1); IR (film) ν_{max} 3385, 3056, 3002, 2954, 2831, 1793, 1740, 1717, 1634, 1518, 1258, 1197, 1145, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 16.0 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 6.44 (br s, 1H), 6.35–6.31 (m, 2H), 6.17 (d, J = 15.5 Hz, 1H), 4.01 (dd, J = 4.0, 1.5 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.74–3.68 (m, 2H), 3.19 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 149.1, 148.8, 139.8, 138.4, 133.4, 120.1, 119.5, 111.3, 56.0, 55.4, 52.1, 48.6, 44.7, 40.1; HRMS (FAB) calcd for $C_{21}H_{20}O_8^+$ $[M]^+$ 400.1158, found 400.1190.

(*R*)-1-(Allyloxy)-3-(3,4-bis(benzyloxy)phenyl)-1-oxopropan-2-yl (*E*)-3-(4-Hydroxy-3-methoxyphenyl)acrylate (34). Rosmarinic acid (**1**) (5.00 g, 13.9 mmol, 1.0 equiv) was dissolved in THF/MeOH (10:1, 110 mL) at 25 °C, and the resultant solution was cooled to −78 °C. $TMSCHN_2$ (2.0 M in Et_2O, 6.6 mL total, 0.95 equiv) was then added at −78 °C in 0.55 mL portions every 5 min until the complete volume had been added. The low-temperature bath was then removed, and the reaction mixture was allowed to warm to 25 °C, during which time the solution turned a brown color. The solution was then stirred for an additional 1 h at 25 °C. Upon completion, the reaction was quenched by the addition of glacial AcOH (~3 drops; no bubbling was observed, indicating complete consumption of the $TMSCHN_2$), and the mixture was concentrated directly. The resultant crude brown oil was filtered through a pad of silica gel, eluting with CH_2Cl_2/MeOH (9:1), and the filtrate was concentrated directly. The resulting brown foam was then dissolved in DMF (70 mL), and solid K_2CO_3 (11.5 g, 83.4 mmol, 6.0 equiv) and benzyl bromide (9.9 mL, 83.4 mmol, 6.0 equiv) were added sequentially at 25 °C. The reaction suspension was then heated to 55 °C and stirred vigorously at that temperature for 16 h. Upon completion, the reaction contents were cooled to 25 °C, poured into 1 M HCl (140 mL), and extracted with Et_2O (3 × 140 mL). The combined organic layers were then washed with 1 M HCl (3 × 140 mL) and brine (140 mL), dried ($MgSO_4$), filtered, and concentrated to give a yellow oil (**S4**), which was carried forward without further purification. Next, **S4** was dissolved in CH_2Cl_2/MeOH (1:1, 160 mL) at 25 °C, and solid NaOMe (0.750 g, 13.9 mmol, 1.0 equiv) was added. The resulting dark-yellow solution was stirred at 25 °C for 4.5 h. Upon completion, the reaction mixture was poured into saturated aqueous NH_4Cl (600 mL) and extracted with EtOAc (3 × 600 mL). The combined organic layers were then washed with brine (600 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude white solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3→3:2) to give methyl (*E*)-3-(3,4-bis(benzyloxy)phenyl)acrylate (**S5**) (4.93 g, 95% yield over three steps) as a white solid along with methyl (*R*)-3-(3,4-bis(benzyloxy)phenyl)-2-hydroxypropanoate (**S6**) (4.41 g, 81% yield over three steps) as a white crystalline solid. **S6**: R_f = 0.60 (hexanes:EtOAc, 1:1); $[\alpha]_D^{22}$ = +7.8 (c = 0.5, $CHCl_3$); IR (film) ν_{max} 3480, 3066, 3032, 2926, 1733, 1606, 1589, 1512, 1459, 1427, 1265, 1218, 1137, 1091, 1020, 736, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 10H), 6.89 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 2.0 H, 1H), 6.74 (dd, J = 8.4, 2.0 Hz, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 4.42 (ddd, J = 6.4, 4.4, 2.0 Hz, 1H), 3.74 (s, 3H), 3.05 (dd, J = 14.0, 4.4 Hz, 1H), 2.89 (dd, J = 14, 6.4 Hz, 1H), 2.63 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 148.8, 148.1, 137.5, 137.4, 129.7, 128.5, 127.8 (2C), 127.4 (2C), 122.5, 116.7, 115.1, 71.3, 52.4, 40.1; HRMS (FAB) calcd for $C_{24}H_{24}O_5^+$ $[M]^+$ 392.1624, found 392.1624.

Chiral alcohol **S6** (3.99 g, 10.2 mmol, 1.0 equiv) was dissolved in THF/MeOH/H_2O (3:1:1, 50 mL) at 25 °C. The resultant mixture was cooled to 0 °C, and solid LiOH (0.600 g, 14.3 mmol, 1.4 equiv) was added. The ice bath was then removed, and the mixture was heated to 45 °C and stirred under an ambient atmosphere for 6 h. Upon completion, the reaction mixture was cooled to 25 °C, poured into 1 M HCl (160 mL), and extracted with EtOAc (3 × 150 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude white solid was dissolved in DMF (40 mL), and K_2CO_3 (2.20 g, 15.9 mmol, 1.5 equiv) and allyl bromide (1.40 mL, 15.87 mmol, 1.5 equiv) were added sequentially at 25 °C. The reaction mixture was then stirred at 25 °C for 2 h before being poured into 1 M HCl (160 mL) and extracted with Et_2O (3 × 80 mL). The combined organic layers were washed with H_2O (5 × 80 mL), dried ($MgSO_4$), filtered, and concentrated to give allyl (*R*)-3-(3,4-bis(benzyloxy)phenyl)-2-hydroxypropanoate (**S7**) (4.08 g, 96% yield) as a white solid of sufficient purity to press forward without further purification. **S7**: R_f = 0.44 (hexanes:EtOAc, 1:1); $[\alpha]_D^{22}$ = +16.9 (c = 0.5, $CHCl_3$); IR (film) ν_{max} 3421, 3034, 2945, 1726, 1592, 1519, 1454, 1429, 1386, 1270, 1251, 1241, 1229, 1168, 1140, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 10H), 6.90 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 8.0, 1.6 Hz, 1H), 5.96–5.86 (m, 1H), 5.35 (dd, J = 17.2, 1.2 Hz, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 4.68–4.59 (m, 2H), 4.44 (dd, J = 10.4, 5.6 Hz, 1H), 3.07 (dd, J = 14.0, 4.4 Hz, 1H), 2.95 (dd, J = 14.0, 6.8 Hz, 1H), 2.69 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 148.8, 148.1, 137.5, 137.4, 131.5, 129.6, 128.5 (2C), 127.8 (2C), 127.4, 127.3, 122.6, 119.2, 118.7, 115.2, 71.4, 71.3, 66.2, 40.0; HRMS (FAB) calcd for $C_{26}H_{26}O_5^+$ $[M]^+$ 418.1780, found 418.1793.

To a solution of crude alcohol **S7** (4.08 g, 9.76 mmol, 1.0 equiv) and (*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)acrylic acid (**S8**) (9.00 g, 29.3 mmol, 3.0 equiv, prepared according to the method of Snyder and Kontes[4b]) in CH_2Cl_2 (55 mL) at 25 °C were sequentially added DMAP (1.91 g, 15.6 mmol, 1.6 equiv) and EDCI (3.74 g, 19.5 mmol, 2.0 equiv). The resulting yellow solution was then stirred at 25 °C for 3 h. Upon completion, the reaction mixture was diluted with EtOAc (165 mL) and washed with 1 M HCl (165 mL) and brine (165 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to give the desired intermediate as a viscous yellow oil. Pressing forward without any additional purification, this crude yellow oil was dissolved in THF (60 mL) and cooled to 0 °C, and AcOH (0.6 mL) and TBAF (1.0 M in THF, 29.3 mL, 29.3 mmol, 3.0 equiv) were added sequentially. The resulting solution was then stirred for 1 h at 0 °C. Upon completion, the reaction mixture was poured into 1 M HCl (180 mL) and extracted with EtOAc (180 mL).

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The organic layer was then washed with brine (180 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to give phenol **34** (4.97 g, 82% yield over four steps) as a clear, pale-yellow oil. **34**: R_f = 0.48 (hexanes:EtOAc, 1:1); $[\alpha]_D^{22}$ = +17.4 (c = 0.5, $CHCl_3$); IR (film) ν_{max} 3419, 3034, 1750, 1713, 1632, 1603, 1591, 1455, 1429, 1380, 1314, 1268, 1154, 1029, 984, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 15.6 Hz, 1H), 7.47−7.30 (m, 10H), 7.09 (dd, J = 8.4, 2.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 6.95−6.90 (m, 3H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 6.33 (d, J = 15.6 Hz, 1H), 5.93 (s, 1H), 5.92−5.85 (m, 1H), 5.39−5.27 (m, 2H), 5.26 (dd, J = 9.2, 1.2 Hz, 1H), 5.16 (s, 2H), 5.15 (s, 2H), 4.65−4.63 (m, 2H), 3.91 (s, 3H), 3.19−3.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 166.4, 149.0, 148.3, 148.2, 146.8, 146.2, 137.4, 137.2, 131.5, 129.3, 128.5, 127.8, 127.8, 127.4, 127.3, 126.8, 123.4, 122.5, 118.8, 116.6, 115.2, 114.8, 114.4, 109.4, 72.9, 71.5, 71.4, 65.9, 56.0, 37.1; HRMS (FAB) calcd for $C_{36}H_{34}O_8^+$ $[M]^+$ 594.2254, found 594.2250.

Diels−Alder Adduct 36. $Pb(OAc)_4$ (3.77 g, 8.10 mmol, 1.1 equiv) was suspended in toluene (5 mL) and concentrated directly to remove any trace/adventitious AcOH that might have been present. The resulting light-brown solid was then dissolved in CH_2Cl_2 (100 mL), and (*E*)-3-(3,4-bis(benzyloxy)phenyl)acrylic acid (**35**) (18.5 g, 51.4 mmol, 7.0 equiv) was added at 25 °C. The resultant orange suspension was then stirred vigorously at 25 °C for 30 min. Upon completion, the suspension was concentrated directly. The flask was then back-filled with argon by attaching a balloon to the air inlet of the rotary evaporator. The orange solid was then suspended in toluene (50 mL) and concentrated to remove any residual AcOH resulting from ligand exchange. This azeotroping procedure was then repeated. The orange solid was then resuspended in CH_2Cl_2, and the above procedure (i.e., stirring for 30 min, concentration, azeotroping) was repeated. Next, the orange solid was suspended in anhydrous 1,4-dioxane (100 mL), and the resulting orange suspension was stirred at 25 °C for 30 min. A solution of (*R*)-1-(allyloxy)-3-(3,4-bis(benzyloxy)phenyl)-1-oxopropan-2-yl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate (**34**) (4.37 g, 7.30 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) was then added via syringe, resulting in the disappearance of the orange color of the original suspension and a significant thickening of the mixture. The reaction flask was swirled manually to ensure efficient mixing, and ethylene glycol (0.5 mL, 8.87 mmol, 1.2 equiv) was then added at 25 °C. After the mixture was vigorously stirred at 25 °C for 20 min, the reaction contents were concentrated directly. The resulting white solid was then suspended in EtOAc (50 mL) and filtered. The solid residue was then thoroughly rinsed with EtOAc (3 × 15 mL) and filtered. The combined filtrates were then washed with brine (500 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow solid was then suspended in Et_2O (50 mL), filtered, and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1→3:2) to give the desired Diels−Alder product **36** (3.45 g, 50% yield, ∼1:1 mixture of inseparable diastereomers) as a clear, colorless oil. Separation of the two diastereomers of the product proved to be possible after their ketones were reduced to the corresponding alcohols. The separate diastereomers were then oxidized to regenerate the ketones (vide infra), and the final individual spectra separately matched the combined spectral information for the original mixture of diastereomers generated from the Diels−Alder reaction of **34**.

36a: R_f = 0.75 (hexanes:EtOAc, 1:1); $[\alpha]_D^{22}$ = +24.7 (c = 0.5, $CHCl_3$); IR (film) ν_{max} 3486, 3066, 3031, 2926, 2149, 1796, 1750, 1721, 1632, 1592, 1513, 1464, 1429, 1380, 1262, 1163, 1016, 920, 853, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.40 (m, 6H), 7.40−7.30 (m, 15H), 6.89−6.86 (m, 2H), 6.83−6.77 (m, 2H), 6.45 (d, J = 2.4 Hz, 1H), 6.25 (br d, J = 6.0 Hz, 1H), 6.19 (d, J = 16.0 Hz, 1H), 5.85 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.34−5.22 (m, 3H), 5.17−5.06 (m, 8H), 4.65−4.54 (m, 2H), 3.93 (dd, J = 5.2, 2.0 Hz, 1H), 3.68 (s, 3H), 3.68 (m, 1H), 3.61 (dd, J = 6.8, 2.8 Hz, 1H), 3.19−3.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 172.6, 171.1, 169.2, 165.5, 148.9, 148.7, 148.6, 148.3, 141.5, 137.2, 137.1, 136.9 (2C), 136.8, 134.1, 131.4 (2C), 128.8, 128.6 (2C), 128.5, 127.9 (2C), 127.8, 127.4, 127.3, 127.2, 122.5, 120.6, 118.9, 118.5, 116.5, 115.0, 114.6, 99.1, 73.5, 71.6, 71.3 (2C), 71.1, 66.0, 60.4, 56.2, 54.4, 47.4, 44.9, 44.3, 36.9; HRMS (FAB) calcd for $C_{59}H_{52}O_{12}^+$ $[M]^+$ 952.3459, found 952.3472.

36b: R_f = 0.75 (hexanes:EtOAc, 1:1); $[\alpha]_D^{22}$ = −4.0 (c = 1.0, $CHCl_3$); IR (film) ν_{max} 3486, 3066, 3031, 2926, 2149, 1796, 1750, 1721, 1632, 1592, 1513, 1464, 1429, 1380, 1262, 1163, 1016, 920, 853, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.42 (m, 6H), 7.39−7.28 (m, 15H), 6.90−6.87 (m, 2H), 6.84−6.77 (m, 2H), 6.45 (d, J = 1.6 Hz), 6.38 (dd, J = 8.0, 1.6 Hz, 1H), 6.26−6.21 (m, 1H), 6.16 (d, J = 16.0 Hz, 1H), 5.85 (ddt, J =17.2, 10.4, 5.6 Hz), 5.32−5.23 (m, 3H), 5.15−5.09 (m, 8H), 4.67−4.57 (m, 2H), 3.94 (dd, J = 5.2, 2.4 Hz, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 3.61 (dd, J = 6.8, 2.8 Hz, 1H), 3.21−3.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.3, 172.6, 169.2, 165.4, 148.9, 148.7, 148.6, 148.3, 141.5, 141.3, 137.2, 137.1, 136.9, 136.8, 134.1, 131.4 (2C), 128.9, 128.6, 128.5, 128.0, 127.9, 127.8, 127.4, 127.3, 127.2, 122.4, 120.6, 118.8, 118.5, 118.4, 116.5, 115.0 (2C), 114.6, 99.2, 73.6, 73.5, 71.6, 71.5, 71.3, 71.2, 71.1, 66.0 (2C), 60.4, 56.2, 56.1, 54.3, 47.4, 44.9, 44.1, 36.9; HRMS (FAB) calcd for $C_{59}H_{52}O_{12}^+$ $[M]^+$ 952.3459, found 952.3472.

***exo*-Alcohol 37 and *endo*-Alcohol 38.** Diels−Alder product **36** (2.1 g, 2.20 mmol) was dissolved in THF/AcOH (1:1, 20 mL). $NaBH(OAc)_3$ (2.3 g, 11.0 mmol, 5.0 equiv) was added at 25 °C, and the resulting pale-yellow solution was stirred at 25 °C for 4 h. An aqueous solution of Rochelle's salt (0.5 M, 50 mL) was then added, and the resultant mixture was stirred for 20 min, after which time it was carefully poured into saturated aqueous $NaHCO_3$ (100 mL; CAUTION: vigorous bubbling was observed) and extracted with EtOAc (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), and the combined aqueous layers were re-extracted with EtOAc (2 × 100 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The resultant crude colorless residue was purified by flash column chromatography (silica gel, CH_2Cl_2:Et_2O, 19:1→9:1) to give two pairs of diastereomers (i.e., two *exo* alcohols and two *endo* alcohols), each as a clear colorless oil (1.72 g total, 82% yield, ∼1.5:1 *exo*:*endo*). Each pair of diastereomers was separated by preparative TLC in 30 mg batches (CH_2Cl_2:Et_2O, 97:3, 4−5 developments per plate).

37a: R_f = 0.52 (CH_2Cl_2:Et_2O, 9:1); $[\alpha]_D^{22}$ = +94.3 (c = 0.95, $CHCl_3$); IR (film) ν_{max} 3503, 3063, 3032, 2946, 2863, 1779, 1752, 1717, 1633, 1604, 1513, 1454, 1382, 1264, 1206, 1162, 1023, 931, 737, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43−7.28 (m, 21H), 6.88−6.85 (m, 2H), 6.80−6.76 (m, 2H), 6.45 (d, J = 2.5 Hz, 1H), 6.42−6.39 (m, 2H), 6.06 (d, J = 16.0 Hz, 1H), 5.83 (ddt, J = 17.5, 10.5, 5.5 Hz, 1H), 5.32−5.21 (m, 3H), 5.14−5.06 (m, 8H), 4.61 (ddt, J = 12.0, 5.5, 1.0 Hz, 1H), 4.56 (ddt, J = 13.0, 5.5, 1.5 Hz, 1H), 4.07 (app t, J = 3.5 Hz, 1H), 3.78 (d, J = 4.5 Hz, 1H), 3.52 (s, 3H), 3.38 (app quintet, J = 3.0 Hz, 1H), 3.29 (br s, 1H), 3.15 (dd, J = 14.5, 5.0 Hz, 1H), 3.10 (dd, J = 14.5, 3.0 Hz, 1H), 2.74 (dd, J = 4.5, 1.5 Hz, 1H), 2.34 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 169.3, 165.7, 149.0, 148.5, 148.4, 148.3, 142.7, 140.4, 137.3, 137.2, 137.1, 137.0, 133.8, 132.8, 131.4, 128.9, 128.6, 128.5 (3C), 127.9 (3C), 127.8, 127.4, 127.3 (2C), 127.2, 122.5, 120.6, 118.9, 116.7, 116.2, 115.2 (2C), 114.8, 109.7, 74.1, 73.3, 71.6, 71.4 (2C), 71.3, 66.0, 52.9, 47.8, 47.1, 44.2, 40.4, 37.0; HRMS (FAB) calcd for $C_{59}H_{54}O_{12}^+$ $[M]^+$ 954.3615, found 954.3619.

37b: R_f = 0.52 (CH_2Cl_2:Et_2O, 9:1); $[\alpha]_D^{22}$ = −92.0 (c = 0.75, $CHCl_3$); IR (film) ν_{max} 3523, 3032, 2949, 1779, 1717, 1632, 1512, 1261, 1205, 1161, 1140, 1080, 1020, 930, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.30 (m, 21H), 6.92−6.90 (m, 2H), 6.84−6.80 (m, 2H), 6.48 (d, J = 2.5 Hz, 1H), 6.45−6.41 (m, 2H), 6.07 (d, J = 16.0 Hz, 1H), 5.87 (ddt, J = 17.5, 10.5, 6.0 Hz, 1H), 5.36−5.24 (m, 3H), 5.17−5.09 (m, 8H), 4.65−4.59 (m, 2H), 4.10 (app t, J = 3.5 Hz, 1H), 3.82 (d, J = 4.5 Hz, 1H), 3.59 (s, 3H), 3.41 (app quintet, J = 3.0 Hz, 1H), 3.32 (br s, 1H), 3.19 (dd, J = 14.5, 4.5 Hz, 1H), 3.12 (dd, J = 14.0, 8.5 Hz, 1H), 2.76 (d, J = 4.5, 1.5 Hz, 1H), 2.40 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 169.3, 165.7, 149.0, 148.5, 148.3 (2C), 142.6, 140.5, 137.3, 137.2, 137.1, 137.0, 133.8, 132.8, 131.4, 129.0, 128.5 (5C), 127.9, 127.8, 127.4, 127.3 (2C), 127.2 (2C), 122.5, 120.6, 118.9, 116.6, 116.2, 115.2 (2C), 114.8, 109.7, 74.1, 73.4, 71.6, 71.4 (2C), 71.3, 66.0, 53.0, 47.9, 47.0, 44.2, 40.3, 37.0.

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38a: R_f = 0.41 (CH_2Cl_2:Et_2O, 9:1); $[\alpha]_D^{22}$ = +79.6 (*c* = 0.75, $CHCl_3$); IR (film) ν_{max} 3474, 3062, 3024, 2936, 1780, 1754, 1718, 1633, 1513, 1454, 1262, 1204, 1163, 1139, 1021, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.30 (m, 21H), 6.91−6.88 (m, 2H), 6.82−6.79 (m, 2H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.44−6.40 (m, 2H), 6.09 (d, *J* = 15.5 Hz, 1H), 5.86 (ddt, *J* = 17.5, 10.5, 6.0 Hz, 1H), 5.35−5.23 (m, 3H), 5.14−5.07 (m, 8H), 4.63 (dd, *J* = 13.0, 5.5 Hz, 1H), 4.59 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.78 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.65 (dd, *J* = 5.0, 2.5 Hz, 1H), 3.55 (br s, 1H), 3.45 (s, 3H), 3.17−3.09 (m, 3H), 2.85 (dd, *J* = 4.5, 1.5 Hz, 1H), 2.48 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 169.3, 165.8, 149.0, 148.5, 148.3, 148.2, 142.5, 139.8, 137.3, 137.2, 137.1, 137.0, 134.1, 131.4, 129.0, 128.5 (3C), 127.9 (2C), 127.8, 127.4 (2C), 127.3 (2C), 127.2, 122.5, 120.8, 118.9, 117.0, 116.6, 115.3, 115.2, 114.8, 107.5, 73.3, 72.1, 71.6, 71.4, 71.3 (2C), 66.0, 53.4, 52.2, 48.1, 47.3, 42.8, 39.9, 37.0; HRMS (FAB) calcd for $C_{59}H_{54}O_{12}^+$ $[M]^+$ 954.3615, found 954.3622.

38b: R_f = 0.41 (CH_2Cl_2:Et_2O, 9:1); $[\alpha]_D^{22}$ = −64.7 (*c* = 0.80, $CHCl_3$); IR (film) ν_{max} 3474, 3062, 3024, 2936, 1780, 1754, 1718, 1633, 1513, 1454, 1262, 1204, 1163, 1139, 1021, 736, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46−7.29 (m, 21H), 6.92−6.89 (m, 2H), 6.83−6.79 (m, 2H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.44−6.38 (m, 2H), 6.07 (d, *J* = 16.0 Hz, 1H), 5.88 (ddt, *J* = 12.5, 8.0, 5.5 Hz, 1H), 5.34−5.24 (m, 3H), 5.14−5.10 (m, 8H), 4.67−4.59 (m, 2H), 3.78 (dd, *J* = 4.5, 1.5 Hz, 1H), 3.63 (br s, 1H), 3.56 (br s, 1H), 3.48 (s, 3H), 3.21−3.07 (m, 3H), 2.84 (dd, *J* = 4.5, 1.5 Hz, 1H), 2.51 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 169.3, 165.7, 149.0, 148.5, 148.3, 148.1, 142.4, 139.8, 137.3, 137.1 137.0, 134.1, 131.4, 129.0, 128.5 (5C), 127.9 (3C), 127.8, 127.4, 127.3 (3C), 127.2, 122.5, 120.7, 118.9, 117.1, 116.6, 115.4, 115.2, 114.8, 107.5, 73.4, 72.1, 71.6, 71.4, 71.3, 66.0, 52.2, 48.1, 47.2, 42.7, 39.8, 37.0.

Compound 36b (as a Single Diastereomer).[38] To a stirred suspension of pulverized and activated 4 Å molecular sieves (0.035 g, 0.5 g/mmol of alcohol) and NMO (0.017 g, 0.15 mmol, 2.0 equiv) in CH_2Cl_2 (1.0 mL) at 25 °C was added *endo*-alcohol **38b** (0.070 g, 0.073 mmol, 1.0 equiv) as a solution in CH_2Cl_2 (0.5 mL). The resulting slurry was stirred at 25 °C for 10 min and then cooled to 0 °C, and TPAP (1 mg, 0.003 mmol, 0.05 equiv) was added in a single portion. The resulting black slurry was stirred at 0 °C for 1 h. Upon completion, the reaction mixture was filtered through a plug of silica gel (eluted with hexanes:EtOAc, 7:3) and concentrated to give **36b** (0.045 g, 67% yield) as a pale-yellow oil.

Carboxylic Acid S9.[39] *exo*-Alcohol **37b** (0.107 g, 0.112 mmol, 1.0 equiv) was dissolved in benzene (1.0 mL). The solution was concentrated to remove any trace/adventitious H_2O, and the concentrate was dissolved in CH_2Cl_2 (2.0 mL) at 25 °C. The resultant solution was cooled to −78 °C, and BCl_3 (0.9 mL, 1.0 M in CH_2Cl_2, 8.0 equiv) was added in a single portion. The resulting yellow solution was then stirred at −78 °C for 5 min, after which time pH 7 phosphate buffer (0.18 M, 1.0 mL) was added, and the flask was immediately immersed in a warm water bath to melt the ice that formed upon addition of the buffer solution. This mixture was then diluted with EtOAc (10 mL) and washed with brine (10 mL). The aqueous layer was then re-extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant crude pale-brown oil was then dissolved in THF (2.0 mL), and the mixture was degassed by bubbling argon through the solution for 10 min. To this mixture were sequentially added Meldrum's acid (24 mg, 0.168 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (6 mg, 0.006 mmol, 0.05 equiv) at 25 °C. The resultant yellow solution was then stirred at 25 °C for 15 min and concentrated directly. Purification of the resultant crude residue by preparative TLC (CH_2Cl_2:MeOH, 4:1 doped with 1% AcOH) gave deprotected compound **S9** (0.062 g, 55% yield over two steps) as a white solid. **S9**: R_f = 0.07 (CH_2Cl_2:MeOH, 4:1 doped with 1% AcOH); $[\alpha]_D^{22}$ = −40.9 (*c* = 1.0, MeOH); IR (film) ν_{max} 3233, 2962, 2925, 2361, 1773, 1702, 1528, 1599, 1401, 1268, 1206, 1024, 930, 668 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, *J* = 15.6 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.61−6.57 (m, 2H), 6.53 (d, *J* = 6.4 Hz), 6.47 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 6.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 4.85 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.18 (d, *J* = 4.0 Hz, 1H), 3.96 (d, *J* = 2.8 Hz, 1H), 3.46 (s, 3H), 3.22 (br s, 1H), 3.15 (dd, *J* = 6.0, 3.2 Hz, 1H), 3.03 (d, *J* = 12.4 Hz, 1H), 2.72 (dd, *J* = 14.4, 10.4 Hz, 1H), 2.65 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.4, 173.4, 166.6, 145.7, 145.5, 144.8, 144.1, 141.8, 140.4, 133.4, 133.2, 130.5, 129.4, 128.7, 120.0, 118.8, 118.0, 117.0, 116.2, 116.1, 115.9, 112.1, 77.0, 73.8, 53.3, 48.8, 47.7, 43.8; HRMS (FAB) calcd for $C_{28}H_{27}O_{12}^+$ $[M + H]^+$ 555.1503, found 555.1512.

Yunnaneic Acid D (3). Carboxylic acid **S9** (0.035 g, 0.063 mmol, 1.0 equiv) was suspended in CH_2Cl_2/H_2O (2:1, 1.5 mL), and HCl (4.0 M in dioxane, 0.5 mL) was added at 25 °C. The mixture was stirred at 25 °C for 2 h and then poured into brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. Subsequent coevaporation with toluene (2 × 2 mL) removed any residual 1,4-dioxane, affording yunnaneic acid D (**3**) (0.030 g, 88% yield) as a white powder. [Note: this compound appeared to isomerize readily in the presence of trace acid, and thus, removal of trace EtOAc from the crude product by prolonged drying could not be performed without compromising the purity of the sample.] **3**: IR (film) ν_{max} 3328, 2529, 2919, 2849, 1710, 1626, 1521, 1446, 1255, 1175, 1115, 1076, 978, 812 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.39 (d, *J* = 16.0 Hz, 1H), 6.90−6.84 (m, 2H), 6.76−6.72 (m, 3H), 6.64 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.57−6.53 (m, 1H), 6.22 (d, *J* = 16.0 Hz, 1H), 5.21 (dd, *J* = 8.5, 3.5 Hz, 1H), 4.01 (d, *J* = 1.5 Hz, 1H), 3.87 (br s, 1H), 3.55 (br s, 1H), 3.28 (d, *J* = 6.0 Hz, 1H), 3.12 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.99 (dd, *J* = 14.5, 8.5 Hz, 1H), 2.88 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 207.8, 175.5, 171.0, 166.5, 145.8, 145.6, 143.3, 141.9, 136.8, 136.3, 129.1, 121.7, 119.9, 117.9, 117.3, 116.1 (2C), 115.5, 74.1, 72.4, 51.1, 50.1, 48.8, 47.0, 37.4; HRMS (FAB) calcd for $C_{27}H_{24}O_{12}Na^+$ $[M + Na]^+$ 563.1166; HRMS data could not be obtained because of facile side-chain cleavage, but a molecular ion peak at *m*/*z* 563.11 was observed via LRMS (FAB). All of the spectroscopic data for this compound matched those reported by Tanaka and co-workers[1] (see Table S1 in the Supporting Information), noting that some isomerization of the characterization sample was observed during the time when the ^{13}C NMR spectrum was taken.

(*R*)-1-(Allyloxy)-3-(3,4-dihydroxyphenyl)-1-oxopropan-2-yl (*E*)-3-(8-(3,4-Dihydroxyphenyl)-7a-methoxy-2,7-dioxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)acrylate (S10). The debenzylation procedure described above for the synthesis of **S9** was applied to ketone **36b** (0.045 g, 0.031 mmol, 1.0 equiv) to give a crude brown oil. This crude product was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:3→3:7) to give tetraphenol **S10** (0.022 g, 79% yield) as a yellow oil. **S10**: R_f = 0.59 (CH_2Cl_2:MeOH, 9:1); $[\alpha]_D^{22}$ = −44.5 (*c* = 0.55, MeOH); IR (film) ν_{max} 3382, 2945, 2916, 1853, 1739, 1711, 1625, 1599, 1523, 1444, 1365, 1282, 1191 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.48 (d, *J* = 16.0 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.77−6.72 (m, 2H), 6.69−6.62 (m, 3H), 6.50−6.42 (m, 2H), 5.91 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.36−5.19 (m, 3H), 4.66 (dd, *J* = 5.2, 2.0 Hz, 1H), 4.65 (dd, *J* =5.2, 2.0 Hz, 1H), 4.62 (dd, *J* = 5.2, 0.8 Hz, 1H), 3.82 (br s, 1H), 3.73 (dd, *J* = 6.8, 2.8 Hz, 1H), 3.64 (s, 3H), 3.33 (dd, *J* = 5.2, 0.8 Hz, 1H), 3.12 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.03 (dd, *J* = 14.4, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 195.4, 173.0, 169.0, 165.5, 145.0, 144.6, 144.1, 141.8, 137.5, 135.1, 132.1, 131.0, 128.3, 127.6, 120.7, 119.2, 118.4, 117.5, 116.4, 115.2, 115.1, 115.0, 99.7, 73.6, 65.2, 56.5, 52.7, 47.4, 44.7, 42.9, 36.5; HRMS (FAB) calcd for $C_{31}H_{29}O_{12}^+$ $[M + H]^+$ 593.1659, found 593.1686.

Yunnaneic Acid C (2). To a degassed solution of tetraphenol **S10** (22 mg, 0.037 mmol, 1.0 equiv) in THF (1.0 mL) at 25 °C were sequentially added Meldrum's acid (8 mg, 0.056 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (4 mg, 0.004 mmol, 0.1 equiv). The resultant yellow solution was stirred at 25 °C for 15 min and then concentrated directly. The so-obtained residue was purified by preparative TLC (CH_2Cl_2:MeOH, 4:1 doped with 1% AcOH) to give a translucent colorless wax. This newly synthesized material was suspended in CH_2Cl_2/H_2O (2:1, 0.75 mL), and TFA (0.5 mL) was added at 25 °C. Over time, the initially colorless mixture became increasingly yellow, with the mixture being stirred at 25 °C for a total of 16 h. Upon completion, the reaction contents were poured into brine (5 mL) and

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extracted with EtOAc (3 × 5 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated to give yunnaneic acid C (**2**) (10 mg, 50% over two steps) as a yellow solid. **2**: IR (film) ν_{max} 3282, 2919, 1705, 1687, 1633, 1521, 1442, 1260, 1191, 1148 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.47 (d, J = 16.0 Hz, 1H), 6.84−6.83 (m, 2H), 6.76−6.60 (m, 5H), 6.43 (d, J = 15.5 Hz, 1H), 5.23 (dd, J = 9.0, 4.0 Hz, 1H), 4.34 (br s, 1H), 3.79 (app t, J = 3.0 Hz, 1H), 3.74 (dd, J = 6.5, 2.5 Hz, 1H), 3.32−3.25 (m, 1H), 3.14 (dd, J = 14.5, 4.0 Hz, 1H), 3.01 (dd, J = 14.5, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.6, 171.3, 166.4, 146.0, 145.8, 145.4, 144.9, 139.4, 136.2, 129.0, 121.5, 120.1, 120.0, 117.4, 116.2, 116.1, 115.9, 74.3, 66.1, 56.9, 54.9, 45.7, 37.4; HRMS data could not be obtained because of instability of the diketone. All of the spectroscopic data for this compound matched those reported by Tanaka and co-workers[1] (see Table S2 in the Supporting Information).

Quinoxaline Derivative (S11).[1] The following was performed on a diastereomeric mixture. Yunnaneic acid C (**2**) and its diastereomer (~1:1, 0.027 g total, 0.049 mmol, 1.0 equiv) were dissolved in EtOH/AcOH (4:1, 1.6 mL). The light-brown solution was degassed via the freeze−pump−thaw method (liquid N_2; repeated twice). 1,2-Phenylenediamine (0.011 g, 0.10 mmol, 2.0 equiv) was then added. The resulting brown solution was stirred at 60 °C for 19 h. Upon completion, the mixture was cooled to 25 °C and concentrated directly. The resulting red-orange oil was taken up in EtOAc/1 M HCl (1:1, 10 mL). The layers were separated, and the organic layer was washed with 1 M HCl (2 × 5 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to give the crude quinoxaline as a brown solid (1:1 d.r.). This material was separated by reversed-phase semipreparative HPLC (C18, 5 μ, 250 mm × 9.6 mm, H_2O/MeCN, 95%→65% for 40 min, 65% for 20 min, UV detector at 280 nm, t_R (undesired) = 44.9 min, t_R (desired) = 46.8 min) to afford pure quinoxaline **S11** (0.0025 g, 19% yield). **S11**: $[\alpha]_D^{22}$ = +103.4 (c = 0.05, MeOH); IR (film) ν_{max} 2922, 2851, 1707, 1625, 1521, 1445, 1260, 1020, 799 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.04−7.99 (m, 2H), 7.79−7.75 (m, 2H), 7.53 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 5.2 H, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.83−6.75 (m, 3H), 6.70−6.65 (m, 2H), 6.52 (d, J = 16.0 Hz, 1H), 5.24 (dd, J = 8.4, 4.0 Hz, 1H), 4.93 (app t, J = 2.0 Hz, 1H), 4.35 (dd, J = 6.4, 2.0 Hz, 1H), 3.63 (dd, J = 6.0, 1.2 Hz, 1H), 3.19 (dd, J = 6.0, 2.4 Hz, 1H), 3.14 (dd, J = 14.3, 4.0 Hz, 1H), 3.05 (dd, J = 14.4, 8.4 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.5, 170.8, 166.4, 157.8, 155.2, 145.9, 145.6, 145.1, 144.7 (2C), 141.7 (2C), 141.6, 141.3, 134.8, 130.0, 129.7 (3C), 128.9, 121.6, 120.0, 118.2, 117.3, 116.2, 115.9, 115.4, 74.0, 52.0, 51.5, 48.4, 46.7, 37.4; HRMS (FAB) calcd for $C_{33}H_{27}N_2O_{10}$ $[M + H]^+$ 611.1666, found 611.1648. All of the spectroscopic data for this compound matched those reported by Tanaka and co-workers[1] (see Table S3 in the Supporting Information).

(*E*)-Methyl 3-(8-(3,4-Dimethoxyphenyl)-7-hydroxy-2-oxo-2,3,3a,6,7,7a-hexahydro-3,6-methanobenzofuran-4-yl)acrylate (40).[28] Hydroxyketal **31** (0.075 g, 0.18 mmol, 1.0 equiv) was added to CH_2Cl_2 (9.0 mL), and the mixture was stirred at 25 °C until complete dissolution was achieved (typically 20 min). To this solution was then added Et_3SiH (0.57 mL, 3.60 mmol, 20.0 equiv). After 5 min of stirring at 25 °C, TMSOTf (0.10 mL, 0.54 mmol, 3.0 equiv) was added, and the resulting yellow mixture was stirred at 25 °C for 2.5 h. Three drops of pyridine were then added, after which the mixture became colorless and gas evolution was observed. The mixture was poured into 1.0 M HCl (35 mL) and extracted with EtOAc (2 × 35 mL). The combined organic layers were then washed with brine (35 mL), dried ($MgSO_4$), filtered, and concentrated to give a waxy, white solid. Purification of this crude residue by flash column chromatography (silica gel, CH_2Cl_2:Et_2O, 2:3) gave protected rufescenolide **40** (0.037 g, 54% yield) alongside the separable (2*E*,2′*E*)-dimethyl 3,3′-((6a*R*,7a*R*,13a*R*,14a*R*)-15,16-bis(3,4-dimethoxyphenyl)-2,9-dioxo-2,3,3a,6,6a,9,10,10a,13,13a-decahydro-3,6:10,13-dimethanodifuro[3,2-*d*:3′,2′-*k*]dibenzo[*b*,*e*][1,4]dioxine-4,11-diyl)diacrylate (**39**) (0.017 g, 25% yield).

40: R_f = 0.28 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3474, 2952, 2914, 1774, 1717, 1625, 1515, 1430, 1252, 1160, 1027, 983 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 16.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 6.4 Hz, 1H), 6.51 (d, J = 2.0 Hz, 1H), 6.43 (dd, J = 8.4, 2.0 Hz, 1H), 6.18 (d, J = 16.0 Hz, 1H), 4.34 (d, J = 4.8 Hz, 1H), 4.15 (d, J = 3.6 Hz, 1H), 3.97 (app t, J = 4.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.44−3.40 (m, 1H), 3.29 (br s, 1H), 2.75 (d, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 167.1, 148.8, 148.2, 141.3, 138.5, 134.7, 133.3, 119.6, 117.5, 111.2, 111.0, 82.2, 73.7, 55.9 (2C), 51.9, 46.7, 44.4, 44.2, 39.3; HRMS (FAB) calcd for $C_{21}H_{22}O_7^+$ $[M]^+$ 386.1366, found 386.1370.

39: R_f = 0.44 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 2956, 2838, 1784, 1715, 1635, 1516, 1437, 1314, 1254, 1188, 1026, 912, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 16.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.41 (dd, J = 8.4, 2.0 Hz, 1H), 6.37 (d, J = 6.4 Hz, 1H), 6.01 (d, J = 15.6 Hz, 1H), 4.29 (d, J = 3.6 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 6H), 3.62 (d, J = 4.4 Hz, 1H), 3.49 (app quintet, J = 3.2 Hz, 1H), 3.39 (br s, 1H), 2.91 (dd, J = 4.4, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 166.8, 148.9, 148.4, 140.8, 136.4, 133.1, 132.5, 119.7, 117.7, 111.2, 111.0, 106.6, 74.2, 55.9 (3C), 51.9, 47.1, 44.3, 43.6; HRMS (FAB) calcd for $C_{42}H_{40}O_{14}^+$ $[M]^+$ 768.2418, found 768.2448.

Rufescenolide (41). To a solution of **40** (0.012 g, 0.031 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 0.19 mL, 0.19 mmol, 6.0 equiv) in a single portion. The resultant dark-yellow solution was then stirred at 0 °C for 10 min. Upon completion, saturated aqueous $NaHCO_3$ (1.0 mL) was added, and the mixture was poured into water (5 mL) and then extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the resultant colorless oil by preparative thin-layer chromatography (hexanes:EtOAc, 3:7) afforded rufescenolide (**41**) (0.006 g, 55% yield) as an amorphous white solid. **41**: R_f = 0.56 (EtOAc); IR (film) ν_{max} 3354, 1766, 1696, 1630, 1518, 1438, 1271, 1172, 1116, 1074, 986 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.45 (d, J = 16.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 6.5 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 6.34 (dd, J = 8.4, 2.4 Hz, 1H), 6.27 (d, J = 16.0 Hz, 1H), 4.24 (d, J = 5.2 Hz, 1H), 4.11 (app t, J = 4.5 Hz, 1H), 4.01 (d, J = 3.6 Hz, 1H), 3.77 (s, 3H), 3.35 (m, 1H), 3.15 (br s), 2.66 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 179.4, 167.9, 144.7, 143.9, 142.1, 140.0, 133.9, 133.2, 118.8, 116.1, 114.7, 114.6, 82.7, 73.5, 50.8, 46.3, 44.2 (2C), 38.8; ^{13}C NMR (175 MHz, $CDCl_3$ containing ca. 5% CD_3OD) δ 178.3, 167.6, 144.0, 143.3, 141.8, 139.2, 134.0, 133.1, 119.5, 116.9, 114.7, 114.4, 82.4, 73.5, 51.9, 46.4, 44.4, 44.2, 39.1; HRMS (FAB) calcd for $C_{19}H_{19}O_7^+$ $[M + H]^+$ 359.1131, found 359.1125. All of the spectroscopic data for this material matched those reported by David and co-workers[26] (see Table S4 in the Supporting Information).

***C*$_2$-Symmetric Dimer 61.**[4b] To a solution of dimethyl ketal **60** (0.075 g, 0.16 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C was added BF_3·OEt_2 (0.09 mL, 0.65 mmol, 4.0 equiv) in a single portion. The resulting pale-orange solution was stirred at 0 °C for 30 min. Upon completion, saturated aqueous $NaHCO_3$ (0.5 mL) was added, and the mixture was warmed to 25 °C. The mixture was then poured into H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude pale-brown oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1→3:7) to give **61** (0.025 g, 36% yield) as a colorless waxy solid that could be crystallized from CH_2Cl_2/*n*-hexane (colorless prisms). **61**: R_f = 0.47 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 2961, 1720, 1631, 1516, 1436, 1265, 1236, 1169, 1132, 1028, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 16.0 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 6.67−6.64 (m, 4H), 6.26 (d, J = 6.4 Hz, 2H), 6.03 (d, J = 15.6 Hz, 2H), 3.85 (s, 6H), 3.84 (s, 6H), 3.83 (s, 6H), 3.74 (s, 6H), 3.69 (d, J = 3.2 Hz, 2H), 3.62 (br d, J = 6.0 Hz, 2H), 3.43 (app q, J = 4.4, 2.0 Hz, 2H), 3.37 (s, 6H), 3.05 (dd, J = 6.8, 1.2 Hz, 2H), 2.58 (dd, J = 6.8, 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.7, 148.8, 147.9, 142.2, 140.0, 136.7, 136.3, 119.3, 116.7, 111.1, 111.0, 100.2, 70.2, 55.9 (2C), 52.3, 51.7, 49.3, 48.9, 44.7, 39.9, 39.2; HRMS (FAB) calcd for $C_{46}H_{52}O_{16}^+$ $[M]^+$ 860.3255, found 860.3265.

(1*R*,2*R*,3*S*,4*R*)-Methyl 3-(3,4-Dimethoxyphenyl)-8-hydroxy-6-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-7-oxobicyclo[2.2.2]oct-5-ene-2-carboxylate (62). To a solution of carboxylic acid **32** (0.116

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g, 0.29 mmol, 1.0 equiv) in THF/MeOH (9:1, 3.0 mL) at −78 °C was added $TMSCHN_2$ (2.0 M in Et_2O, 0.18 mL, 0.36 mmol, 1.2 equiv). The resultant yellow solution was then stirred at −78 °C for 15 min, after which AcOH was added dropwise until all bubbling ceased. The resulting pale-yellow solution was then diluted with EtOAc (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was then extracted with EtOAc (2 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant crude white foam product was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:3) to give ester **62** (0.033 g, 28% yield) as a colorless oil. **62**: R_f = 0.39 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3458, 3069, 2999, 2954, 2841, 1740, 1631, 1518, 1464, 1437, 1314, 1256, 1196, 1174, 1087, 1026, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 16.0 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 6.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 8.5, 2.0 Hz, 1H), 6.11 (d, J = 15.5 Hz, 1H), 4.09 (d, J = 2.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (d, J = 1.5 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.58 (dd, J = 5.5, 2.0 Hz, 1H), 3.37 (app dt, J = 6.0, 2.0 Hz, 1H), 2.94 (dd, J = 5.5, 2.5 Hz, 1H), 2.91 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 174.2, 166.9, 149.0, 148.3, 140.7, 139.5, 135.6, 135.0, 119.1, 118.4, 111.2, 111.1, 71.5, 55.9 (2C), 52.9, 51.9, 49.8, 48.9, 46.4, 46.1; HRMS (FAB) calcd for $C_{22}H_{24}O_8^+$ $[M]^+$ 416.1471, found 416.1484.

Hydroxyketone Homodimer 63 (Proposed Structure).[4b] To a solution of hydroxyketone **62** (0.041 g, 0.099 mmol, 1.0 equiv) in THF (1.0 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.039 g, 0.99 mmol, 10.0 equiv). The resultant yellow slurry was then warmed to 25 °C and stirred for 1 h. Upon completion, the reaction was quenched by the addition of saturated aqueous NH_4Cl (1.0 mL), and the mixture was poured into water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. The resultant crude colorless oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:7) to give recovered starting material (15 mg, 37% yield) and dimeric product **63** (6 mg, 15% yield, 52% yield b.r.s.m.). **63**: R_f = 0.20 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3420, 2990, 2951, 2914, 2841, 1720, 1631, 1517, 1435, 1313, 1257, 1197, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 15.0 Hz, 1H), 7.36 (d, J = 15.5 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.73−6.69 (m, 3H), 6.66 (dd, J = 8.5, 2.0 Hz, 1H), 6.61 (dd, J = 8.5, 2.0 Hz, 1H), 6.57 (d, J = 6.0 Hz, 1H), 6.41 (d, J = 6.0 Hz, 1H), 6.19 (d, J = 16.0 Hz, 1H), 5.93 (d, J = 16.0 Hz, 1H), 4.74 (br s, 1H), 4.14 (d, J = 4.0 Hz, 1H), 3.85 (s, 9H), 3.81 (s, 6H), 3.76 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.58 (d, J = 6.5 Hz, 1H), 3.41 (d, J = 7.5 Hz, 1H), 3.27 (br s, 1H), 3.11−3.08 (m, 2H), 2.56−2.53 (m, 2H), 2.32 (dd, J = 7.5, 2.0 Hz, 1H); ^{13}C NMR δ 174.0, 172.5, 167.2, 148.9, 148.8, 148.1, 147.8, 140.9, 140.6 (2C), 140.1, 137.5, 136.5, 136.2, 135.9, 118.9, 118.1, 117.8, 111.5, 111.3, 111.2 (2C), 111.1, 106.2, 85.4, 55.9 (3C), 55.8, 52.5, 52.0, 51.8, 51.7, 49.5, 49.1, 46.4, 44.6, 43.3, 43.0, 41.7, 41.0; HRMS (FAB) calcd for $C_{44}H_{48}O_{16}^+$ $[M]^+$ 832.2942, found 832.2960.

Heterodimers S12 and S13. Diketone **33** (0.081 g, 0.20 mmol, 1.0 equiv) and hydroxyketone **32** (0.081 mg, 0.20 mmol, 1.0 equiv) were dissolved in CH_2Cl_2/HFIP (1:1, 0.4 mL), and pulverized 3 Å molecular sieves (80 mg) were added at 25 °C. The resulting yellow mixture was then stirred at 25 °C for 14 h. Upon completion, the sieves were removed by filtration, and the filtrate was concentrated. The resultant yellow foam was dissolved in Et_2O/MeOH (10:1, 2.2 mL), and the solution was cooled to −78 °C, after which $TMSCHN_2$ (2.0 M in Et_2O, 0.4 mL, 0.8 mmol, 4.0 equiv) was added. After the resultant yellow mixture was stirred at −78 °C for 30 min, AcOH was added dropwise until bubbling ceased. The mixture was then warmed to 25 °C, diluted with EtOAc (10 mL), and washed with water (10 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated. The resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1→2:3) to give a mixture of two dimers as a colorless oil (0.042 g, 26% combined yield over two steps, **S12**:**S13** = 4:1). These two dimeric products were then separated by preparative TLC (CH_2Cl_2:Et_2O, 9:1).

S12: R_f = 0.35 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3473, 2952, 2928, 2844, 1722, 1632, 1592, 1517, 1436, 1256, 1027, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 16.0 Hz, 1H), 6.78−6.73 (m, 3H), 6.69−6.61 (m, 4H), 6.46 (d, J = 6.0 Hz, 1H), 6.16 (d, J = 15.5 Hz, 1H), 6.07 (d, J = 16.0 Hz, 1H), 4.43 (d, J = 3.5 Hz, 1H), 3.87−3.82 (m, 15H), 3.78 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H), 3.69 (s, 3H), 3.61 (d, J = 7.0 Hz, 1H), 3.28 (app t, J = 5.0 Hz, 1H), 2.90 (dd, J = 6.5, 2.5 Hz, 1H), 2.74 (dd, J = 6.0, 1.5 Hz, 1H), 2.45 (dd, J = 7.5, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 172.6 (2C), 167.6, 166.6, 149.1, 148.9, 148.5, 148.0, 141.1, 140.8, 139.2, 138.8, 136.2 (2C), 134.9, 119.4, 119.2, 119.0, 117.5, 111.4, 111.3 (4C), 107.7, 101.7, 86.3, 56.0 (2C), 55.9 (2C), 52.7, 52.1, 52.0, 51.8, 50.6, 50.0, 49.4, 48.1, 44.0, 43.3, 42.2, 40.5; HRMS (FAB) calcd for $C_{44}H_{47}O_{16}^+$ $[M + H]^+$ 831.2864, found 831.2842.

S13: R_f = 0.35 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3461, 3062, 3009, 2951, 2834, 1724, 1632, 1518, 1436, 1313, 1258, 1198, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 15.5 Hz, 1H), 7.37 (d, J = 15.5 Hz, 1H), 6.80−6.75 (m, 4H), 6.71−6.68 (m, 2H), 6.46 (d, J = 6.5 Hz, 1H), 6.41 (d, J = 6.0 Hz, 1H), 6.25 (d, J = 16.0 Hz, 1H), 6.03 (d, J = 16.0 Hz, 1H), 4.36 (d, J = 3.0 Hz, 1H), 4.00 (d, J = 8.0 Hz, 1H), 3.91 (br s, 1H), 3.88−3.85 (m, 15H), 3.80 (s, 3H), 3.72 (s, 6H), 3.63 (d, J = 7.0 Hz, 1H), 3.49−3.47 (m, 2H), 3.13 (app t, J = 5.0 Hz, 1H), 2.65 (dd, J = 7.5, 2.0 Hz, 1H), 2.54 (dd, J = 7.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 172.5, 171.4, 167.2, 166.7, 149.1, 149.0, 148.5, 148.1, 143.2, 141.1, 140.8, 139.4, 136.1, 135.7, 134.6, 130.8, 120.0, 119.0, 118.9, 118.1, 111.5, 111.4 (2C), 111.1, 108.0, 101.1, 86.8, 55.9 (4C), 54.6, 52.2, 52.1, 51.8, 51.7, 49.1, 49.0, 44.5, 43.3 (2C), 40.8, 40.4; HRMS calcd for $C_{44}H_{47}O_{16}^+$ $[M + H]^+$ 831.2864, found 831.2861.

General Procedure for Heterodimer Bromination. To a solution of the dimer (1.0 equiv) in MeCN was added NBS (4.0 equiv) at 25 °C. The clear, colorless solution was stirred at 25 °C for 14 h. Upon completion, saturated aqueous Na_2SO_3 was added, and the resulting mixture was stirred vigorously for 15 min. Upon completion, the mixture was diluted with EtOAc and washed three times with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by preparative TLC (silica gel, hexanes:EtOAc, 2:3) to afford the dibrominated dimer.

64: white solid, crystallized from $CHCl_3$/*i*-PrOH (colorless prisms, 0.012 g, 53%); R_f = 0.35 (hexanes:EtOAc, 2:3); IR (film) ν_{max} 3463, 3002, 2951, 2844, 1720, 1632, 1506, 1506, 1486, 1376, 1312, 1257, 1195, 1164, 1063, 1029, 913, 842, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 15.6 Hz, 1H), 7.37 (d, J = 16.0 Hz, 1H), 7.07 (d, J = 4.0 Hz, 2H), 6.40 (d, J = 6.0 Hz, 2H), 6.34−6.28 (m, 3H), 6.06 (d, J = 16.0 Hz, 1H), 4.87 (s, 1H), 4.64 (d, J = 7.6 Hz, 1H), 4.48 (d, J = 3.2 Hz, 1H), 4.27 (d, J = 6.8 Hz, 1H), 3.99 (br s, 1H), 3.89 (s, 3H), 3.87 (s, 6H), 3.81 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.53 (br s, 1H), 3.37 (dd, J = 6.4, 1.2 Hz, 1H), 3.05−3.01 (m, 1H), 2.77 (dd, J = 7.6, 2.0 Hz, 1H), 2.66 (dd, J = 5.2, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 173.0, 172.0, 168.2, 167.7, 150.1, 149.7 (2C), 149.5, 144.4, 142.4, 140.1, 136.5, 134.5, 132.9, 131.6, 121.4, 119.5, 117.2, 117.0, 116.4, 116.2, 111.7, 111.4, 108.9, 101.9, 87.6, 57.3, 57.2 (4C), 55.0, 53.5, 53.3, 52.9, 52.8, 48.7, 48.5, 45.0, 44.4, 40.6, 40.0; HRMS calcd for $C_{44}H_{44}Br_2O_{16}Na^+$ $[M + Na]^+$ 1009.0894; HRMS data could not be obtained because of possible dimer instability, but a molecular ion peak at m/z 1009.01 was observed via LRMS (MALDI).

65: white solid, crystallized from $CHCl_3$/*i*-PrOH (colorless prisms, 0.007 g, 53%); R_f = 0.35 (hexanes:EtOAc, 2:3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 16.0 Hz, 1H), 7.36 (d, J = 16.0 Hz, 1H), 7.06 (d, J = 7.2 Hz, 2H), 6.54 (d, J = 6.4 Hz, 1H), 6.41−6.38 (m, 3H), 6.24 (d, J = 15.6 Hz, 1H), 6.15 (d, J = 15.6 Hz, 1H), 4.91 (s, 1H), 4.54 (d, J = 3.6 Hz, 1H), 4.49 (dd, J = 6.8, 2.0 Hz, 1H), 4.28 (d, J = 7.2 Hz, 1H), 3.95 (br s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (s, 6H), 3.77 (br s, 1H), 3.77 (s, 9H), 3.72 (s, 3H), 3.22−3.19 (m, 1H), 3.00−2.98 (m, 1H), 2.67 (dd, J = 6.8, 2.0 Hz, 1H), 2.63 (dd, J = 6.8, 2.0 Hz, 1H).

Diketone Homodimer S14. Diketone **33** (0.113 g, 0.28 mmol, 1.0 equiv) was dissolved in HFIP (0.09 mL), and the solution was stirred at 50 °C for 16 h. Upon completion, the yellow-colored solution was cooled to 25 °C, concentrated, and purified by preparative TLC (CH_2Cl_2:MeOH, 93:7) to give **S14** (10 mg, 5%

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yield) as a pale-yellow foam. **S14**: R_f = 0.18 (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3385, 3059, 2999, 2953, 2933, 2844, 1804, 1718, 1635, 1518, 1464, 1438, 1313, 1257, 1242, 1145, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 16.0 Hz, 1H), 7.42 (d, J = 16.0 Hz, 1H), 6.78−6.75 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.68 (dd, J = 8.0, 1.6 Hz, 1H), 6.53 (d, J = 6.4 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.44 (d, J = 6.4 Hz, 1H), 6.35 (dd, J = 8.4, 2.0 Hz, 1H), 6.17 (d, J = 16.0 Hz, 1H), 6.09 (d, J = 16.0 Hz, 1H), 5.66 (s, 1H), 4.06 (d, J = 8.0 Hz, 1H), 3.88−3.79 (m, 19H), 3.76 (br s, 1H), 3.60 (dd, J = 6.4, 1.2 Hz, 1H), 3.52 (br s, 1H), 3.47 (dd, J = 6.8, 3.2 Hz, 1H), 3.13 (br d, J = 4.0 Hz, 1H), 2.75 (dd, J = 8.0, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 172.0, 167.4, 166.7, 149.1, 148.8, 148.6, 148.1, 142.3, 140.9, 139.4, 137.6, 133.9, 133.4, 132.1, 130.9, 120.1, 119.6, 118.8, 118.5, 111.5, 111.3, 111.1, 111.0, 109.9, 105.4, 102.3, 56.0, 55.9 (2C), 54.3, 53.4, 52.1, 52.0, 48.8, 48.6, 47.0, 46.6, 44.0, 42.7, 40.0, 29.7; HRMS (FAB) calcd for $C_{42}H_{40}O_{16}^+$ $[M]^+$ 800.2316, found 800.2295.

Brominated Diketone 66. Following the general bromination procedure, Diels−Alder product **26** (0.140 g, 0.34 mmol, 1.0 equiv) was reacted with NBS (0.073 g, 0.41 mmol, 1.2 equiv) to give the brominated product as a pale-yellow solid (0.080 g, 48%). This material was then carried forward and subjected to the procedure for the acid-mediated hydrolysis of ketal lactone **25**. In the event, brominated Diels−Alder product **S15** (0.071 g, 0.14 mmol) gave the brominated diketone **66** (0.060 g, 90%) as a yellow solid. **66**: R_f = 0.18 (CH_2Cl_2:MeOH, 9:1); IR (film) ν_{max} 3409, 2955, 2843, 1790, 1743, 1711, 1633, 1517, 1440, 1316, 1249, 1197, 1145, 1025, 981, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 15.6 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 6.46−6.41 (m, 2H), 6.29 (d, J = 15.6 Hz, 1H), 4.11 (br d, J = 2.0 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.84 (br s, 4H), 3.32 (br d, J = 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 166.8, 149.1, 148.8, 139.9, 138.2, 133.1, 131.3, 120.2, 119.6, 111.3 (2C), 56.0 (2C), 55.0, 52.1, 48.3, 44.7; HRMS data could not be obtained because of instability of the diketone.

Brominated Diketone Homodimer 67. Diketone **66** (0.105 g, 0.22 mmol, 1.0 equiv) was dissolved in HFIP (0.055 mL). The resulting yellow mixture was stirred at 50 °C under ambient atmosphere for 16 h. Upon completion, the mixture was concentrated directly, and the yellow residue was purified by preparative TLC (CH_2Cl_2:MeOH, 92:8) to give brominated dimer **67** (0.005 g, 5%) as a white solid. The product was crystallized from $CHCl_3$/*i*-PrOH (colorless plates). **67**: R_f = 0.47 (CH_2Cl_2:MeOH, 9:1); IR (film) ν_{max} 3407, 2934, 1801, 1717, 1634, 1508, 1490, 1330, 1249, 1200, 1166, 1030, 847 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 16.0, 1H), 7.42 (d, J = 16.0 Hz, 1H), 7.07 (s, 1H), 7.02 (s, 1H), 6.43 (s, 1H), 6.38 (br s, 2H), 6.21 (d, J = 16.0 Hz, 1H), 6.12 (d, J = 16.0 Hz, 1H), 4.62 (d, J = 8.0 Hz, 1H), 4.18 (s, 1H), 3.98 (d, J = 4.5 Hz, 1H), 3.87 (s, 6H), 3.83 (s, 6H), 3.76 (s, 3H), 3.60 (s, 3H), 3.68−3.66 (m, 1H), 3.49 (d, J = 6.5 Hz, 1H), 3.12 (d, J = 4.5 Hz, 1H), 2.96 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 202.5, 171.7, 171.0, 166.6, 166.3 149.6, 149.4, 149.2 (2C), 148.8, 148.5, 143.3, 140.6, 140.0, 139.8, 136.6, 135.0, 133.4, 132.0, 130.7 (2C), 120.0, 119.5, 119.2, 116.2, 115.9, 115.8, 114.4, 113.6, 112.9, 111.5, 110.3, 105.0, 102.3, 55.6 (2C), 55.5, 55.3, 55.2, 54.0, 53.7, 51.1, 50.9, 47.1, 46.7, 46.5, 45.8, 44.4, 44.1, 41.4, 40.0; HRMS data could not be obtained because of instability of the dimer.

■ ASSOCIATED CONTENT

Supporting Information

Copies of spectral data, comparison tables of spectroscopic data for synthesized natural products, atomic coordinates for materials analyzed by X-ray crystallography, X-ray crystal structures, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

Ac = acetyl; Bn = benzyl; DIAD = diisopropylazodicarboxylate; DMAP = 4-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide; EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; NBS = *N*-bromosuccinimide; NMO = *N*-methylmorpholine-*N*-oxide; Ph_3P = triphenylphosphine; TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; TFA = trifluoroacetic acid; TMS = trimethylsilyl; TPAP = tetra-*n*-propylammonium perruthenate.

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(10) Although nature uses phenoxy radicals in many bond constructions and enzymes can effect the controlled merger of fragments in cases where many different reaction pathways exist, in this context the challenge in forming a final C−C bond prior to rearomatization renders it less appealing. For an informative discussion of polyphenolic natural products through such routes, see: Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouysegu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 586.

(11) Although clearly related, we must note that lithospermic acid has not been isolated from the same plant species as yunnaneic acids, so while the connection is provocative, it awaits verification from further studies.

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