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Biomimetic Transannular Oxa-Conjugate Addition Approach to the 2,6-Disubstituted Dihydropyran of Laulimalide Yields an Unprecedented Transannular Oxetane

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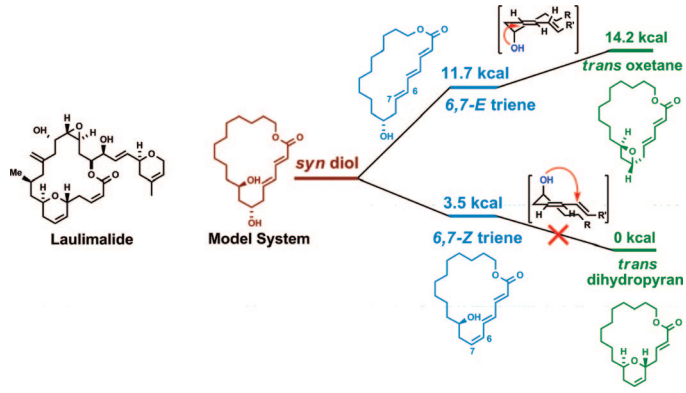

2,6-Disubstituted dihydropyrans are a common feature in many bioactive polyketides, including the anticancer marine polyketide laulimalide. While much of the uncharacterized biosynthetic pathway for laulimalide can be confidently postulated, the biosynthetic origins of the *trans* 2,6-disubstituted dihydropyran cannot. We hypothesize that a transannular oxa-conjugate addition in a macrocyclic laulimalide precursor could be the origin of the 2,6-dihydropyran. To test this hypothesis, we constructed a model containing the key functional groups for oxa-conjugate addition-mediated dihydropyran formation. Under acid-mediated conditions, the model under went regiospecific oxa-conjugate addition producing a stable *trans* oxetane as the only regioisomer. The desired, more stable dihydropyran was not detected. This unprecedented regiospecificity is unexpected due to the ring strain of the oxetane and the anticipated facile ring opening retro-oxa-conjugate addition. The oxetane is stable to acid and basic conditions, as are a number of literature acyclic oxetanes that could undergo similar retro-oxa-conjugate addition. While the source of the oxetane kinetic stability is yet to be characterized, it may enable general oxetane construction via oxa-conjugate addition. The more stable dihydropyran regioisomer could not be generated due to poor geometrical orbital alignment and hard−soft incompatibility between the hard oxygen nucleophile and the soft activated polyenoate electrophile. These factors disfavor the breaking of conjugation by oxa-conjugate addition. Based on these results we propose that dihydropyran formation does not occur on completed polyketide macrocycles as we had proposed but rather during polyketide biosynthesis on the growing polyketide chain.

Introduction

2,6-Disubstituted dihydropyrans are a common structural feature in many bioactive polyketide natural products, including laulimalide (Figure 1, **1**),[1,2] scytophycin C (**2**),[3−5] and swinholide A (**3**).[6,7] Their ubiquity has led to a number of excellent methods for their synthesis.[8−20] In this study, we examine the

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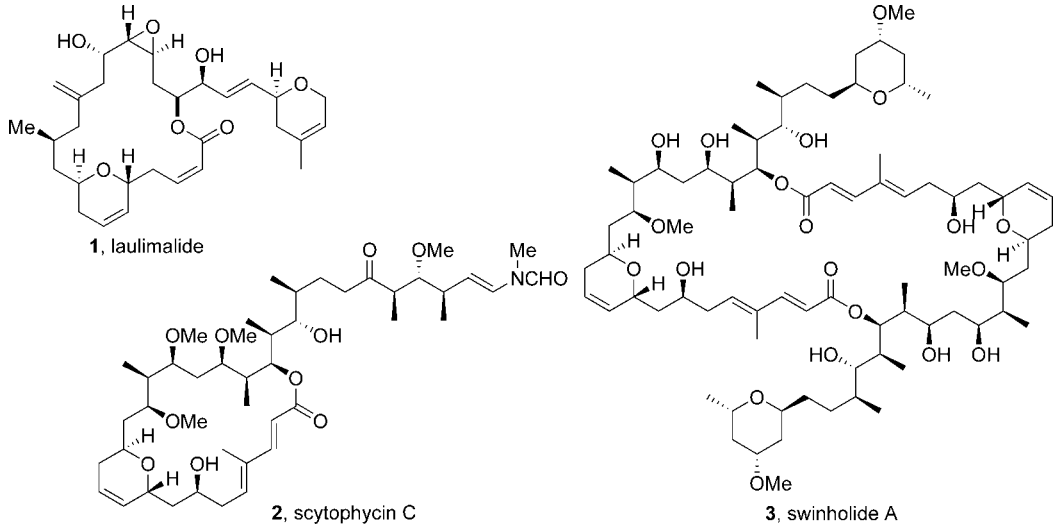

FIGURE 1. Marine polyketides including laulimalide **1**, scytophycin C **2**, and swinholide A **3** contain 2,6-disubstituted *trans*-dihydropyrans.

feasibility of a biomimetic oxa-conjugate addition route to transannular 2,6-disubstituted dihydropyrans. Our study focuses on testing transannular oxa-conjugate addition as a method for the construction of the macrocyclic core of the anticancer marine polyketide laulimalide and sheds light on the biosynthetic origins of the 2,6-disubstituted dihydropran in laulimalide.

Laulimalide **1**, also known as fijianolide, was first isolated in 1988 in trace amounts from the sponges *Hyattella* sp. and *Cacospongia mycofijiensis* in two different locations in the South Pacific Ocean.[1,2] Laulimalide was reported to have potent antimitotic activity and an IC_{50} in the low nanomolar range indicating great potential as an anticancer agent.[21] Its mechanism of action is very similar to the clinically approved anticancer agents Taxol and ixabepilone (an epothilone analogue). Laulimalide binds to and stabilizes microtubules,[22] causing cell division to stop.[21] Unlike Taxol and ixabepeline, which bind to the same site on the microtubule monomer tubulin, laulimalide has been shown to bind to a different site, retaining activity toward Taxol-resistant cancer cell lines.[23] This compound offers potential to satisfy an unmet clinical treatment of Taxol-resistant breast cancers. However, the low yields associated with harvesting laulimalide from natural sources have severely hampered development of this compound. Development of a biomimetic synthesis of laulimalide will help address the scarcity of the compound and provide the first insights into the uncharacterized biosynthetic pathway for laulimalide.

There are two main proposed biosynthetic pathways for the formation of dihydropyrans, nucleophilic addition of an intramolecular alcohol into an epoxide or into an activated olefin. Epoxide opening is hypothesized to occur in the polyether antibiotics[24,25] such as goniodomin A.[26,27] This mechanism leads to oxygenation α to the ether linkage. Most dihydropyran containing polyketide natural products do not possess this residual α-oxygenation, indicating that this mechanism occurs infrequently.

The alternative mechanism is addition into an activated olefin, oxa-conjugate addition, which we hypothesize occurs in laulimalide biosynthesis. Oxa-conjugate addition-mediated formation of transannular dihydropyrans can occur either during polyketide biosynthesis on the incomplete, linear polyketide intermediate[28] or after polyketide biosynthesis, on the macrolactone. If addition is occurring after macrolactone formation (Figure 2), there is potential for nonenzyme catalyzed oxa-conjugate addition to occur with high diastereoselectivity and reaction rates due to favorable conformational effects of the macrocycle.[29] We thus set out to test if transannular oxa-conjugate addition on polyketide macrocycles could be a viable, biomimetic synthetic route for installing this functionality into lauliamlide.

Herein we describe synthesis of a model of a laulimalide biosynthetic intermediate and investigate its conversion into the macrocyclic core of laulimalide. We demonstrated that under

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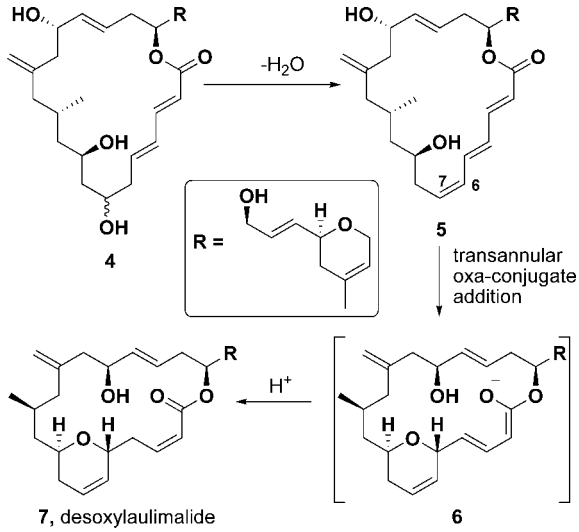

FIGURE 2. Proposed biomimetic mechanism for dihydropyran formation in laulimalide.

acid-catalyzed conditions the model substrate undergoes elimination, generating a postulated activated triene, followed by oxa-conjugate addition. This sequence occurs as proposed except oxa-conjugate addition occurs with highly unusual regioselectivity providing an unexpectedly stable oxetane-containing product in place of the proposed dihydropyran. Our studies indicate that oxetane formation occurs by oxa-conjugate addition and the postulated activated triene possesses the 6,7*E* configuration. The 6,7*Z* activated triene intermediate is unreactive and does not convert into oxetane or dihydropyran. We propose that orbital alignment and hard−soft incompatibility between the hard oxygen nucleophile and the soft activated olefin electrophile disfavor the breaking of conjugation by oxa-conjugate addition, preventing dihydropyran formation. Based on these results, we hypothesize that for laulimalide and, in general, dihydropyran formation occurs during polyketide biosynthesis, rather than on a completed macrocycle as we had originally proposed.

Results and Discussion

A potential mechanism for transannular dihydropyran formation in laulimalide and related dihydropyran containing compounds is oxa-conjugate addition. We hypothesized that a nonenzymatic, transannular oxa-conjugate addition reaction could be involved in the biosynthesis of laulimalide (Figure 2). Oxa-conjugate addition of a compound like triene **5** can occur with facial selectivity to generate the *trans* dihydropyran. Following γ-protonation of the extended enolate/enol generated from conjugate addition, the α,β-unsaturated lactone **7** can be generated. Because triene **5** contains the biosynthetically difficult to access 6,7*Z* olefin, we further postulated that this olefin could be accessed through stereocontrolled elimination of a C7-hydroxy group. The introduction of the *Z* olefin into the macrocycle would have the added benefit of decreasing the entropic barrier to oxa-conjugate addition, promoting formation of the transannular dihydropyran system. Successful synthetic conversion of compounds similar to diol **4** or triene **5** into the laulimalide macrocyclic core would provide evidence supporting this oxa-conjugate addition biogenesis.

Kinetic and theremodynamically controlled oxa-conjugate additions have proven to be effective transformations for pyran synthesis. In the total synthesis of apicularen A, a transannular dihydropyrone was assembled through a reversible acid-catalyzed addition into an α,β-unsaturated ketone.[30−33] Base-mediated tetrahydropyran[34−40] formation has been used extensively and has been instrumental in the kinetic controlled synthesis of a number of pyrans in important natural products including spongistatin 1,[41] polycaveronoside,[42] bryostatins,[36,43] tetronasin,[44] and spirastrellolide A.[45] The flexibility to access both kinetic and thermodynamically controlled reaction profiles suggested that it could be possible to tune the stereochemical outcome of transannular dihydropyran formation in the context of laulimalide formation.

While oxa-conjugate addition is an attractive method for pyran formation, there is limited precedent for dihydropyran formation via this mechanism.[46−48] Acid-catalyzed oxa-conjugate addition of an alcohol to a *Z*,*E*-dienoate was used to complete the synthesis of oscillatoxin D[46] and has been seen as a side reaction in acid-catalyzed elimination of a hydroxy dienone.[47] Of particular relevance to this study was the spontaneous transannular oxa-conjugate addition of the chlorohydryan derivative of radicicol, generating a *trans* dihydropyran.[48] These three examples suggested that spontaneous or acid-catalyzed transannular oxa-conjugate addition could be used to generate the key dihydropyran in laulimalide.

In the published total syntheses of laulimalide[49−58] the principal approach to dihydropyran formation is stereoselective

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C-glycoside formation;[59] however, ring-closing metathesis, dihydropyrone reduction,[60,61] and intramolecular S_N2' substitution[62] are also employed. In all cases, the dihdyropryan system was generated prior to macrolactonization. Our approach, relying on dihydropryan formation after macrocyclization, thus represents a major departure from the current state-of-the-art in laulimalide synthesis.

Dihydropyran formation in laulimalide using an elimination transannular oxa-conjugate addition[30,31] cascade reaction presented a number of concerns. In particular, the limited examples of dihydropyran formation by oxa-conjugate addition were a concern and suggested that it may be difficult for nucleophiles to access the electrophilic carbons within extended conjugated systems. In addition to concerns over the reactivity of the system, the degree of facial selectivity during oxa-conjugate addition, and the regio- and stereochemical outcome of enolate/enol protonation/tautomerization remained unknown. While concerns over facial selectivity were mollified by the successful transannular formation of the *trans* dihydropyran of radicicol,[48] the regio- and stereocontrolled formation of the 2,3*Z* olefin in laulimalide was expected to be a challenge.[63] Because of the large orbital contribution of the HOMO on the α-carbon of extended metal enolates, kinetic protonation accesses the undesired β,γ-unsaturated systems. The desired regiochemistry can be accessed via thermodynamic equilibration of the β,γ-unsaturated system to the α,β-unsaturated system. However in laulimalide syntheses, equilibration of the unsaturated macrolactone has produced a 1:1 mixture of the *E* and *Z* olefins.[49,59] The regio- and stereochemical outcome of this reaction sequence thus needed to be probed to determine if this chemistry could be applied to the synthesis of laulimalide.

We focused on the synthesis of a laulimalide model system to test transannular dihydropyran formation. A 20-member macrolactone laulimalide model, **8**, featuring a 1,3-diol and an *all-trans* dieneoate system was designed. Elimination could afford the desired *Z* isomer **7** or the undesired *E* olefin **14**, enabling us to examine the stereochemistry of elimination. Oxa-conjugate addition of **9** could lead to the four possible dihydropyrans **10**−**13**, each of which would provide insight into the stereochemical outcome of oxa-conjugate addition and enolate/enol protonation/tautomerization. Identification of reaction conditions that effectively catalyze conversion of **8** to **10**−**13** would provide the necessary experimental validation to carry out the synthesis of laulimalide via this approach and support this mechanism as a potential biogenesis of the laulimalide dihydropyran.

Ab Initio Calculations. To gain insight into the energetic landscape of the elimination oxa-conjugate addition pathway for dihydropyran formation from **8**, computational analysis was performed on key model compounds. The focus of the computation studies was to obtain relative energies of the intermediate isomers on the pathway, conformations of their corresponding lowest energy structures, and descriptions of the highest occupied and lowest unoccupied molecular orbitals. Ab initio density functional theory (DFT) calculations were performed using the three-parameter functional of Becke,[64] correlation functional of Lee, Yang, and Parr,[65] and the 6-31G basis set at the d,p level (B3LYP/6-31G, d,p level). Gaussian 03W, version 6 was used to compute zero-point energies of energy-minimized structures. No imaginary frequencies were found indicating a minimum energy potential for each compound presented. The ΔE for the isomers was calculated relative to the lowest energy 6,7*Z* dihydropyran diastereomer **10**. To compare the energies of isomeric **9**−**14** to **8**, which differ in composition by loss of water, the zero-point energy of the energy-minimized structure of H_2O was calculated and added to the calculated zero-point energies of **9**−**14**. This provides a reasonable method for comparing the relative energies of the nonisomers as **8** is isodesmic to H_2O with **10**−**13**, **15**, and **16** and isogyric to H_2O with **9** and **14**.

Computational analysis predicts stereochemically controlled elimination of diol **8**. Formation of the 6,7*Z* olefin in triene **7** is crucial, as the 6,7*E* isomer **14** cannot undergo oxa-conjugate addition due to the *trans* olefin geometry. Calculations predict that triene **9** is 8.2 kcal/mol more stable than triene **14** (Figure 3). Thus, thermodynamically controlled elimination or elimination with a late transition state is predicted to provide the required isomer **9** as the major product.

Calculations also predict triene **9** to be reactive to conjugate addition. Analysis of the LUMO for **9** shows that extended conjugation of the triene lowers the LUMO energy relative to **8**, promoting nucleophilic addition. Examination of the lowest energy conformation of triene **9** shows the nucleophilic alcohol remains in close proximity to the electrophilic carbon C5 and is poised for a 6-*exo-trig* addition to generate the *cis* dihydropyran. These data suggest that oxa-conjugate addition is kinetically accessible.

Examination of the relative energies of the dihydropyrans **10**−**13** show that thermodynamically controlled addition is also expected to provide access to the dihydropyran systems. The lowest energy product isomers **10** and **11** are substantially lower energy than reactive intermediate **9**. Thus, thermodynamically controlled oxa-conjugate addition is expected to access the *trans* dihydropyran **10** predominantly, though with modest selectivity over the *cis* dihydropyran **11**.

From the undesired 6,7*E* trienaote system **14**, oxa-conjugate addition can access the highly strained oxetanes **15** and **16**. Formation of high-energy oxetanes over much lower energy ethers has been observed experimentally.[66] For, example electrophile-induced etherification of *syn* and *anti* (*Z*)-2-ene-1,5-diols generated *trans* oxetanes over the predicted furans. Presumably, these 4-exo cyclizations are under kinetic control and are favored by steric effects. Computational analysis of **15** and **16** shows these compounds to be substantially higher energy than the isomeric dihydropyran systems.

Model System Synthesis. Based on the encouraging results of the computation study, synthesis of **8** was undertaken to experimentally investigate the elimination oxa-conjugate addition mediated formation of transannular dihydropyrans. Construction of the model system began by oxidizing the commercially available alcohol 11-bromo-1-undecanol **17** with pyridinium

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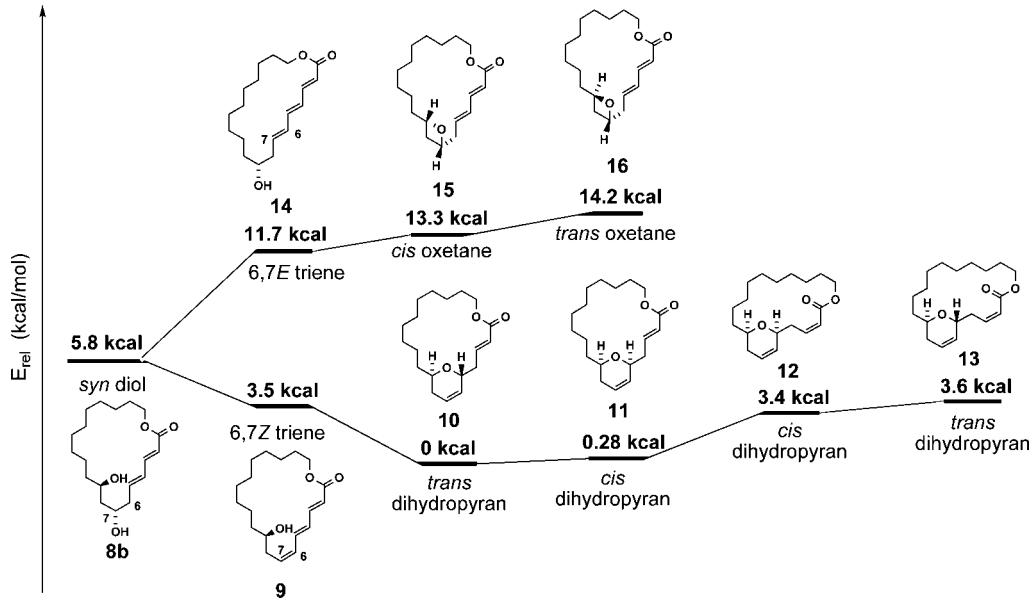


FIGURE 3. Ab initio calculations using density functional theory (DFT) B3LYP predicts stereoselective elimination and four energetically favored dihydropyran diastereomers through transannular oxa-conjugate addition.

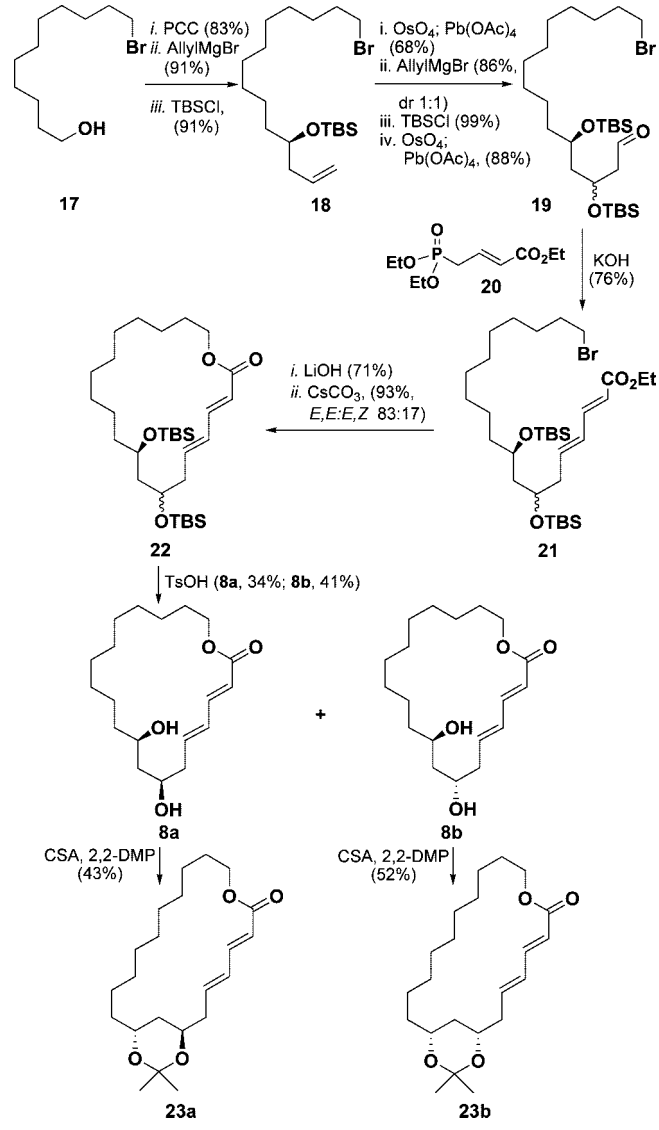
chlorochromate (PCC) to the aldehyde in 83% yield. Addition of allylmagnesium bromide afforded the corresponding alcohol in 91% yield, which was protected with a tertbutyldimethylsilyl (TBS) group to give the silyl ether, **18**, in 91% yield. The olefin was then dihydroxylated using potassium ferricyanide, and potassium osmate(VI) dihydrate followed by oxidative cleavage with lead tetraacetate, providing the corresponding aldehyde in 68% yield from **18**. The aldehyde was converted in 86% yield to a 1:1 diastereomeric mixture of homoallylic alcohols by addition allylmagnesium bromide. Protection as a TBS ether followed by oxidative cleavage of the olefin afforded aldehyde **19** in 88%.

In order to generate the dienoate system, a Horner−Wadsworth−Emmons-type olefination strategy developed by Roush[67] was employed. Treatment of aldehyde **19** with phosphonate **20** gave the dienoate ester **21** with 4:1 diastereoselectivity for the *E*,*E* olefin versus the *E*,*Z* in an overall yield of 80%. Ester **21** was transformed to the free acid using lithium hydroxide in quantitative yield. Macrolactonization generated **22** in 93% yield using cesium carbonate in DMF[68] and was followed by deprotection of the TBS groups. As expected, deprotection provided a separable mixture of both diastereomers the *anti*-**8a** and *syn*-**8b** diols present in a 1:1 diastereomeric ratio. Separation of the diastereomers was achieved without difficulty; however, the *E*,*E*-*anti* diol was inseparable from the undesirable *E*,*Z* diols, as was also observed by Roush.[67]

The stereochemistry of the cyclization precursors **8a** and **8b** was unambiguously determined by ^{13}C NMR analysis of the corresponding 1,3-*syn* and *anti* acetonides.[69] The diols were protected using 2,2-dimethoxypropane in acetone with camphorsulfonic acid to afford 52% yield of the *anti* acetonide **23a** and 43% yield of the *syn* acetonide **23b** (Scheme 1).

To test our hypothesis of elimination and subsequent transannular oxa-conjugate addition we utilized reaction conditions

SCHEME 1. Synthesis of Model Systems 8a and 8b



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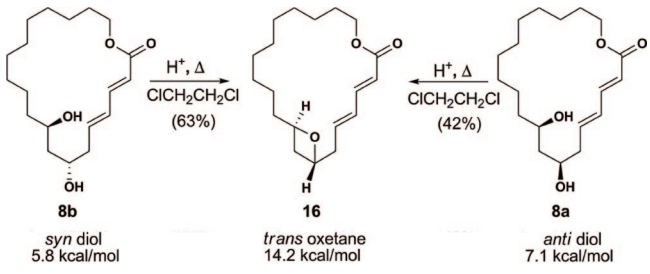
SCHEME 2. Single Diastereomer Formed by 1,8-Elimination, Oxa-Conjugate Addition Cascade Mechanism for Both *Syn* and *Anti* Diastereomers[a]



Key NOE Interactions

16

[a] Confirmed by COSY, HSQC, HMBC, NOESY. Key NOE interactions are displayed in the lowest energy conformation of **16**.

established from the total synthesis of apicularen A; Amberlyst 15 in dichlorethane at 80 °C.[30,31] The cyclization precursors, *anti* and *syn* diols **8a** and **8b**, both underwent acid-catalyzed elimination and transannular oxa-conjugate addition stereoselectively at elevated temperatures after 48 h to generate one product, the highly strained *trans* oxetane **16** in 42% and 63% yield, respectively.

Extensive 1D and 2D NMR characterization of the *trans* oxetane **16** was carried out. Characteristic ^{1}H NMR olefinic peaks (δ_H = 7.25 (m, 1H, C3), 6.24 (m, 2H, C4, C5), 5.78 (d, 1H, J = 15.4 Hz, C2) unambiguously identified the dienoate system. In addition, the significant downfield shifts of the methine protons at C7 and C9 (δ = 4.02, C9−H, δ = 4.22, C7−H) were indicative of oxetanes. The corresponding protons in dihydropyran systems, for example, occur at much higher field (δ = 2.7−3.6). The ^{13}C NMR provided signals consistent with the heteroatom-bonded carbons of an oxetane (δ = 79.6, 78.1),[66] and HSQC data showed that these carbons had one bond coupling to the downfield methine protons assigned to C7 and C9. HSQC and COSY data further confirmed the dienoate system and enabled the unambiguous assignment of the olefinic protons. HMBC correlations verified the critical connectivity of the oxetane structure. Observed NOE interactions were consistent with the structural assignment and allowed determination of the relative stereochemistry of the oxetane as *trans* from the presence of interactions with adjacent protons and the absence of an NOE between C7 and C9. Key interactions from the NOESY are detailed in Scheme 2.

Two acid-catalyzed mechanisms for the formation of oxetane **16** from the *syn* diol **8b** can be envisioned; S_N2 displacement or elimination followed by oxa-conjugate addition. The S_N2 pathway is stereospecific with inversion of configuration so the *anti* diastereomer **8a** should access the *cis* oxetane **15**. Having shown that the *syn* and *anti* diasteromers are configurationally stable under the reaction conditions and do not interconvert, the formation of *trans* oxetane **16** from the *anti* diol **8a** does not support a nucleophilic displacement mechanism of either the C7 or C9 alcohol. An alternative mechanism is an elimination oxa-conjugate addition cascade. If elimination of the C7 hydroxy group from **8a** or **8b** leads to the same activated triene intermediate, both diastereomers will provide the same oxetane product. Thus production of the *trans* oxetane **16** from **8a** and **8b** is consistent with an elimination oxa-conjugate addition mechanism where the elimination step provides a common activated triene intermediate.

Oxa-conjugate addition is an unlikely mechanism for formation of oxetanes. As oxa-conjugate additions are generally reversible, high-energy compounds such as oxetanes should not be generated in appreciable quantities. The high degree of ring strain generally facilitates rearrangements to acyclic products or oxolane-type products.[70,71] However, two examples of 2-substituted oxetanes containing β-electron-withdrawing groups exist.[72,73] While neither of these compounds are generated via oxa-conjugate addition, both compounds could undergo elimination to provide the corresponding ring opened α,β-unsaturated carbonyl compounds but do not. In fact, one of these oxetanes is carried through three steps of chemistry including, TBAF treatment, Swern oxidation, and Wittig olefination, attesting to its kinetic stability.[72]

Oxetane **16** is also surprisingly stable to acidic and basic conditions and does not undergo elimination to generate a triene intermediate. For example, treatment under prolonged strong acid conditions (Amberlyst 15, 80 °C, 48 h) does not lead to decomposition or oxetane opening. Under extended, mild acidic conditions ($CDCl_3$, 2 months) and mild basic conditions (Et_3N, 48 h) **16** can be recovered quantitatively. The stability of **16** and similar oxetanes suggests that the elimination reaction is not kinetically favorable. This is in direct contrast to the electronic arguments in favor of 1,4- or E1cB elimination, where the π orbital of the oxetane enol/enolate is energetically and geometrically aligned to interact with the ether σ^* orbital. Further study is needed to understand the fundamental principles responsible for the surprising stability of these oxetanes. If additional examples of 2-substituted oxetanes with β-electron-withdrawing groups demonstrate stability, oxa-conjugate addition may be a viable route for their general synthesis.

A substantial number of reaction conditions were screened to convert **8a** or **8b** into dihydropyrans **10**−**13**, however no viable reaction conditions were identified. Brønsted acidic conditions universally generated oxetane **16** from **8a** and **8b**. For example, *p*-toluenesulfonic acid and amberlyst in a variety of aprotic and protic solvents (e.g., dichloroethane, toluene, trifluoroethanol, acetonitrile, tetrahydrofuran, dichloromethane, and dimethylformamide) provided **16**. Lewis acidic reaction conditions proved unsuccessful at generating either the oxetane or dihydropyran products. For example, treatment of **8a** or **8b** with boron trifluoride etherate or zinc chloride gave no reaction, and the starting material could be recovered in good yield. Base-mediated E1cB elimination followed by oxa-conjugate addition seemed a viable route to generating the desired dihydropyrans.

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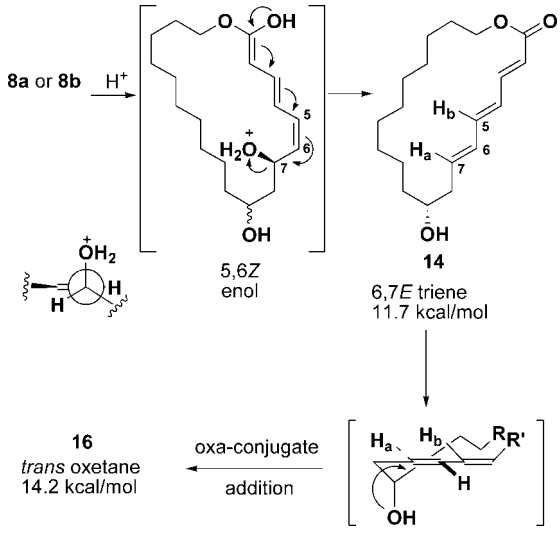


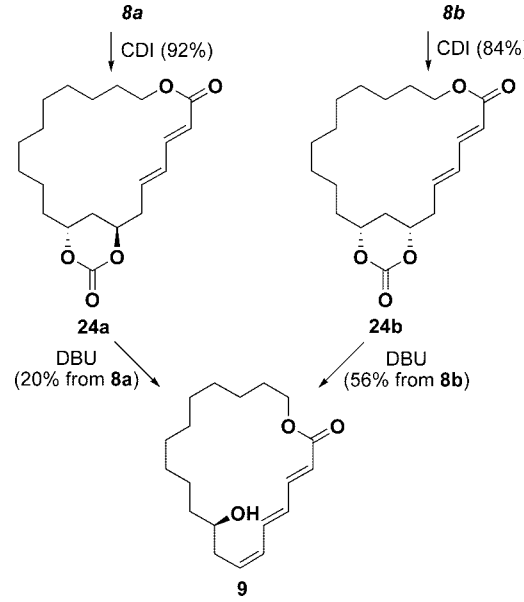
FIGURE 4. Proposed mechanism for elimination oxa-conjugate addition via the *s-cis* enol and 6,7*E* triene to generate the *trans* oxetane.

However, neither **8a** nor **8b** were reactive under any of the basic reaction conditions investigated. For example, treatment of the diols with non-nucleophilic bases such as sodium hexamethyldisilazide, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), potassium carbonate, and potassium *tert*-butoxide even at elevated temperatures (80 °C) lead to no reaction and reisolation of starting material. Of particular note is that under these reaction conditions the *anti* and *syn* diastereomers **8a** and **8b**, respectively, did not interconvert. This observation strongly suggests that reversible elimination was not occurring. Thus, elimination of the C7 alcohol appeared to be a major obstacle to product formation.

Based on these results, we hypothesized that elimination was rate determining and that the oxetane was generated from the 6,7*E* triene intermediate **14**. Under reaction conditions that generated **16**, elimination was not reversible (no interconversion of **8a** and **8b** was observed), nor was any trieneoate intermediate (**14** or **9**) detectable by ^{1}H NMR or LCMS analysis. This suggested that as soon as the trieneoate was formed, it was converted directly into **16**. We further reasoned that if the 6,7*Z* triene **7** was formed, oxa-conjugate addition would provide the stable dihydropyran regioisomers (**10**−**13**). Conversely, formation of the high energy 6,7*E* isomer **14** could not access the desired dihydropyrans. However, this high energy intermediate **14** could access the nearly isoenergetic oxetane **16**.

Formation of the 6,7*E* intermediate **14** can be rationalized via an acid-mediated 1,8-elimination mechanism.[74] Acid-mediated formation of the enol from either **8a** or **8b** generates an enol with a 5,6*Z* bond, due to the same ring strain effects which stabilize **9** versus **14**. Orientating the leaving group perpendicular to the plane of the enol places the substitiuents on C6 and C7 in the *s-trans* conformation as shown in the Newman projection in Figure 4. Loss of water generates the 6,7*E* intermediate **14**. Because elimination occurs from the high energy enol, the transition state does not possess substantial product character, and thus, the large energetic difference between **9** and **14** does not impact the stereochemical outcome of the reaction.

SCHEME 3. E2 Elimination Accesses the *Cis* Triene 9



We thus hypothesized that the geometry of the 6,7 olefin in the trieneoate intermediate could control the regiochemistry of oxa-conjugate addition. We proposed that the 6,7*E* intermediate **14** undergoes oxa-conjugate addition providing the oxetane **14** and the 6,7*Z* intermediate **9**, if accessible, could undergo addition to generate the thermodynamically more stable dihydropyran products **10**−**13**. To test this hypothesis we needed to access **9**.

To ensure formation of **9**, an elimination mechanism with a product-like late transition state was required. The late transition state would reflect the substantial energy difference between **9** and **14**, favoring formation of **9**. An E2 mechanism, with its substantial product-like character in the transition state, is expected to provide **9** as the major product. To access an E2 mechanism, diols **8a** and **8b** were converted into the cyclic carbonates **24a** and **24b**, respectively (CDI in THF at 40 °C) (Scheme 3). Increasing the leaving group ability of the C7 substituent facilitates both leaving group departure and deprotonation in the transition state. Thus, treatment of both the *syn* and *anti* carbonate with 1,8-diazobicyclo[5.4.0]undec-7ene (DBU) in anhydrous THF afforded **7** (20% yield from **8a** and 56% yield from **8b**). The *Z*-configuration of the olefin in **9** was unambiguously defined from the ^{1}H NMR δ values and ^3J coupling constants (see the Supporting Information for trieneoate coupling constants and comparison to literature values).[75−77]

Unfortunately, triene **9** could not be converted into dihydropyran **10**−**13** under any reaction conditions investigated. Compound **9** was unreactive with Lewis and Brønsted acids at low temperatures (e.g., TsOH, 25 °C or $BF_3 \cdot OEt_2$, 25 °C) and decomposed under prolonged heating (e.g., TsOH, 80 °C, 3 d). Like diols **8a** and **8b**, triene **9** was very stable to weak and strongly basic conditions (e.g., Et_3N, 55 °C; DBU, 55 °C; KOtBu, 55 °C). Because oxa-conjugate addition is generally reversible, we were concerned that the dihydropyran product could be less stable and that we were not observing any product due to retro oxa-conjugate addition reaction predominating. To

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address this question, we treated **9** with strong base (NaHMDS) at low temperature (−78 °C), conditions known to access thermodynamically unstable tetrahydropyrans,[38,78] followed by a low temperature quench (−100 °C). However, this experiment did not provide any isolatable product or any detectable new products with the appropriate *m/z* by LCMS analysis. To further probe the possibility of retro oxa-conjugate addition predominating, isotope labeling experiments were carried out. Compound **9** was treated under weakly basic conditions (Et_3N, THF, 25 °C; Et_3N, THF, 55 °C) in the presence of D_2O (5% v/v). No deuterium incorporation in **9** could be detected by LCMS. This result does not support reversible transannular oxa-conjugate addition in **9**. The extended enolate formed from oxa-conjugate addition would be readily protonated by D_2O. Upon elimination, regenerating **9**, deuterium would be incorporated into the starting material. The absence of deuterium incorporation indicates that the extended enolate is not formed and that oxa-conjugate addition is not occurring.

Conclusion

This study was designed to test if an elimination oxa-conjugate addition cascade strategy could be used to access the transannular dihydropyran of the marine polyketide laulimalide. We proposed that if the chemistry occurred under mild conditions, this cascade reaction could be a biogenic mechanism for the installation of this functional group. Our results, however, demonstrate that elimination oxa-conjugate addition is not a viable route for the formation of the macrocyclic core of laulimalide. We were unable to construct transannular dihydropyran-containing systems via oxa-conjugate addition and instead formed a transannular oxetane.

This study demonstrated for the first time that highly strained oxetane systems can be generated via oxa-conjugate addition. This result is particularly surprising since the oxetane product appears to be well suited to elimination due to the 2-substituted β-electron-withdrawing group. Elimination would lead to ring opening and strain release and is clearly thermodynamically favored. The stability of **16** in conjunction with the stability of other oxetanes with 2-substituted β-electron-withdrawing groups[72,73] suggests that these oxetanes may possess unanticipated kinetic stability. Rationalization of the stability based on fundamental principles remains an unanswered question. If these oxetanes are generally stable, oxa-conjugate addition may be a viable route for their construction, complementing cyclodehydration of 1,3-diols[79] and the [2 + 2] Paternò Büchi photocycloaddition reaction.[80]

The failure of oxa-conjugate addition to access dihydropyran systems can be rationalized on the basis of orbital arguments. For dihydropyran formation, the addition must break the conjugation between olefins in a polyenoate system. There is little literature precedent for this type of reactivity. The only example of oxa-conjugate addition to a dienoate system, generating a dihydropyran, is an example where steric interactions preclude conjugation between the two olefins of the dienoate.[46] Furthermore, no examples of intermolecular addition of oxygen nucleophiles breaking conjugation in di- and trienoate,

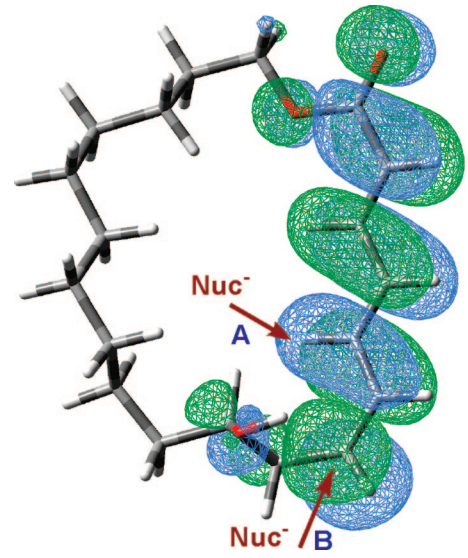

FIGURE 5. LUMO of **9** shows the approach of nucleophiles to the internal electrophilic carbon (A) to occur over top of the C−H bond, unlike approach to the terminal electrophilic carbon (B) which occurs with the expected geometry.

enone or enal systems have been reported. It thus appears that breaking of conjugation via oxa-conjugate addition is not favorable.

A potential explanation for this phenomenon could be the lack of sufficient atomic orbital coefficient at the internal electrophilic carbon in the LUMO. Examination of the LUMOs from **9**, **14**, and simple sorbate system shows that the internal electrophilic carbon atoms contribute as much or more atomic orbital to the LUMO as compared to the terminal electrophilic carbon. Thus, based on electronic arguments, additions that break conjugation should be possible and in fact are seen for intermolecular thia[81−83] and aza-conjugate[84−87] addition reactions. The difference in reactivity between the oxygen and nitrogen and sulfur nucleophiles may however be explained by hard soft acid base theory. Softer nucleophiles such as thiols can more easily attack the soft activated polyene system, where as harder nucleophiles, such as oxygen, are less reactive.

In addition to the hard−soft incompatibility, dihydropyran formation via oxa-conjugate addition has geometrical orbital constraints. The LUMO component at the internal electrophilic carbon is positioned differently from the LUMO component at the terminal electrophilic carbon (Figure 5). At the internal electophilic carbon (A, Figure 5), the atomic orbital component of the LUMO is involved in a π-type interaction with the adjacent carbon atoms LUMO atomic orbital contribution. To maximize overlap in the transition state, the HOMO of the nucleophile must thus approach from over the top of the C−H bond, leading to a buildup of torsional strain in the transition state.[88] In contrast, at the terminal olefin (B, Figure 5), the LUMO is extending between the geminal proton and alkyl

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substituent. In this case, the incoming nucleophile minimizes torsional strain in the transition state. These orbital constraints disfavor the breaking of conjugation, and favor addition of nucleophiles to the terminal olefin of activated polyenes. We thus hypothesize that intramolecular conjugate additions to activated polyene systems that break conjugation and generate a 5-, 6-, or 7-membered ring containing an element of unsaturation will be unfavorable. To rigorously test this model, we are currently investigating intermolecular conjugate additions in linear systems.

The unsuccessful construction of the macrocyclic core of laulimalide via transannular oxa-conjugate addition has some biosynthetic implications for laulimalide and polyketide dihydropyran biosynthesis. The lack of successful chemistry to construct the laulimalide transannular dihydropyran indicated that our initial hypothesis for spontaneous nonenzyme-catalyzed dihydropyran formation is not occurring in laulimalide biogenesis. While these results do not rule out an enzyme catalyzed transannular oxa-conjugate addition biogenesis, the most reasonable mechanism for the laulimalide dihydropyran formation is an enzyme catalyzed mechanism occurring during polyketide biosynthesis. This type of mechanism is proposed for tetrahydropyran formation in the pederin biosynthetic pathway and is supported by gene cluster sequencing data.[28,89] Additionally, we propose that to enable intramolecular delivery of the nucleophilic oxygen with the least build up of torsional strain, the mechanism for enzymatic dihydropyran formation likely involves breaking of conjugation between the olefins in a enzyme bound dieneoate prior to intramolecular delivery of the oxygen. Testing of this hypothesis awaits the isolation and sequencing of the gene cluster responsible for laulimalide biosynthesis.

Experimental Section

***anti*-8,10-Dihydroxyoxacycloeicosa-3,5-dien-2-one (8a) and *syn*-8,10-Dihydroxyoxacycloeicosa-3,5-dien-2-one (8b).** To **22** (0.8001 g, 1.447 mmol) in ethanol (80 mL) at room temperature was added *p*-toluenesulfonic acid (1.9029 g, 10.004 mmol, 6.9 equiv) at 0 °C. The solution was warmed to room temperature and stirred vigorously for 7 h under argon atmosphere. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. The diasteromeric mixture was purified by column chromatography (silica gel, 20% acetone in toluene) to afford *syn*-**8b** as a off-white solid (0.1379 g, 0.4250 mmol) and *anti*-**8a** as a clear oil (0.1314 g, 0.4050 mmol) and a mixture of *syn* and *anti* diols (0.0845 g, 0.260 mmol) for an overall yield of 0.3538 g (1.091 mmol, 75%; 41% of **8b**, 34% of **8a**). **8b**: $R_f = 0.12$ (silica gel, 1:1 hexanes/EtOAc); IR (KBr) $\nu_{max} = 3385$, 2926, 2822, 1710, 1640, 1459, 1429, 1382, 1301, 1256, 1168, 1138, 1055, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, $J =$ 15.4, 10.7 Hz, 1H, C3), 6.21 (dd, $J = 15.2$, 10.9 Hz, 1H, C4), 6.00 (m, 1H, C5), 5.79 (d, $J = 15.4$ Hz, 1H, C2), 4.21 (t, $J = 5.9$ Hz, 2H, $-CH_2O$), 3.90 (m, 1H, $-CHOH$), 3.80 (m, 1H, $-CHOH$), 3,34 (br, 2H, $-CHOH$), 2.54 (m, 2H, $-CH_2-$, 2.24 (m, 2H, $-CH_2-$), 1.76 (2H, $-CH_2-$), 1.68 (m, 4H, $-CH_2-$), 1.26 (m, 12H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 144.6, 139.5, 131.8, 120.9, 73.3, 72.7, 64.9, 41.3, 40.1, 38.6, 30.5, 30.1, 30.0, 29.9, 29.4, 29.0, 28.7, 26.3, 25.4. The structural assignment was verified by HSQC and COSY. HRMS (ES^+): calcd for $C_{19}H_{32}O_4$ $(M + Na)^+$ 347.2193, obsd 347.2188. The a*nti* diol contains an inseparable 2*E*,4*Z* isomer. **8a**: $R_f = 0.21$ (silica gel, 1:1, hexanes/EtOAc); IR (KBr) $\nu_{max} =$ 2926, 2855, 1714, 1641, 1460, 1265, 1169, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, $J = 15.4$, 10.7 Hz, 1H, $-CH-$, C3), 6.24 (m, 1H, $-CH-$, C4), 5.91 (m, 1H, $-CH-$, C5), 5.80 (d, $J = 15.4$ Hz, 1H, $-CH-$, C2), 4.25 (m, 2H, $-CH_2-$), 4.16 (m, 1H, $-CHOH$), 4.05 (m, 1H, $-CHOH$), 3.10 (br, 2H, $-CHOH$), 2.52 (m, 4H, $-CH_2-$), 1.68 (m, 8H, $-CH_2-$), 1.28 (m, 10H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 144.6, 139.4, 131.5, 121.0, 70.1, 69.0, 65.1, 40.4, 37.8, 37.4, 30.4, 29.8, 29.3, 28.6, 28.1, 27.6, 26.4, 26.0; HRMS (ES^+) calcd for $C_{19}H_{32}O_4$ $(M + Na)^+$ 347.2193, obsd 347.2183.

***syn*-21,21-Dimethyl-8,20,22-trioxabicyclo[17.3.1]tricosa-3,5-dien-7-one (23b).** To **8b** (0.0075 g, 0.023 mmol) was added acetone (150 μL) followed by 2,2-dimethoxypropane (70 μL, 0.57 mmol, 24 equiv) and camphorsulfonic acid (0.0030 g, 0.013 mmol, 0.6 equiv) and the mixture stirred at room temperature under argon atmosphere for 5 h. The reaction was quenched with triethylamine (5 μL) and concentrated to dryness in vacuo. The compound was purified by column chromatography (silica gel, 30% EtOAc in hexanes) to afford *syn*-**23b** as an off-white solid (0.0044 g, 0.012 mmol, 52%). **23b**: $R_f = 0.74$ (silica gel, 1:1, hexanes/EtOAc); IR (KBr) $\nu_{max} =$ 2991, 2926, 2855, 2360, 2341, 1717, 1645, 1617, 1460, 1378, 1333, 1298, 1257, 1199, 1171, 1139, 1112, 1041, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, 1H, $J = 15.4$, 10.8 Hz, $-CHCO_2R$, C3), 6.24 (dd, 1H, $J = 15.3$, 10.8 Hz, $-CHCHCH-$), 6.06 (dt, 1H, $J = 15.2$, 7.5 Hz, $-CH_2CHCH-$), 5.83 (d, 1H, $J = 15.5$ Hz, $-CH-$, C2), 4.35 (m, 1H, $-CH_2O$, ester), 4.17 (m, 1H, $-CH_2O$, ester), 3.90 (m, 2H, $-CHO-$, acetonide, C7, C9) 2.49 (m, 1H, $-CH-$, C6), 2.28 (m, 1H, $-CH-$, C6), 1.64 (m, 4H, $-CH_2-$), 1.44−1.01 (m, 8H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 139.0, 132.1, 120.7, 99.0, 68.7, 68.2, 64.8, 39.5, 35.5, 34.3, 30.6, 30.5, 30.4, 30.1, 30.0, 29.9, 29.2, 29.1, 26.5, 23.6, 20.2; HRMS (ES^+) calcd for $C_{22}H_{36}O_4$ $(M + Na)^+$ 387.2506, obsd 387.2496.

3-*trans*,5-*trans*-8,20-Dioxa-*trans*-bicyclo[17.1.1]heneicosa-3,5-dien-7-one (16). Amberlyst 15 H^+ resin (0.0821 g) and anhydrous dichloroethane (5 mL) were added to a dry round-bottom flask equipped with a reflux condenser containing **8b** (0.0425 g, 0.131 mmol) under argon atmosphere. The reaction mixture was stirred and heated to 80 °C for 48 h. The mixture was cooled to room temperature, filtered over Celite, and concentrated to dryness in vacuo. The crude residue was purified by column chromatography (silica gel, 5% EtOAc in hexanes) to afford **16** as an off-clear oil (0.0254 g, 0.0829 mmol, 63.0%). Following an identical procedure, **8a** could be converted into **16** in 42% yield. **16**: $R_f = 0.42$ (silica gel, 1:3, EtOAc/hexanes); IR (KBr) $\nu_{max} = 3420$, 2926, 2854, 1715, 1644, 1462, 1377, 1257, 1170, 1170, 1059, 1001 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 1H, $CHCHCH-$, C3), 6.24 (m, 2H, $-CH-$, C4, C5), 5.78 (d, 1H, $J = 15.4$ Hz, $-CHCO_2R$, C2), 4.31 (m, 1H, $-CH_2O-$, C19), 4.20 (m, 1H, $-CHO-$, C7), 4.14 (m, 1H, $-CH_2O-$, C19), 4.01 (m, 1H, $-CHO-$, C9), 2.75 (m, 1H, $-CH_2-$, C6), 2.23 (m, 1H, $-CH_2-$, C6), 2.00 (m, 1H, $-CH_2-$, C8) 1.78−1.55 (m, 5H, $-CH_2-$), 1.43−1.28 (m, 14H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 140.5, 131.2, 120.0, 79.6, 78.5, 64.0, 36.8, 36.4, 31.5, 30.1, 29.9, 28.9, 28.8, 28.3, 28.2, 26.1, 25.3. The structural assignment was verified by HSQC, HMBC, and COSY. The *trans* stereochemistry of the oxetane was determined by NOESY: MS (ESI) $C_{19}H_{30}O_3$ $(M + H)^+ = 307.05$, $(M + Na)^+$ 329.00, $(M + K^+) = 345.05$; HRMS (ES^+) calcd for $C_{19}H_{30}O_3$ $(M + Na)^+$ 329.2087, obsd 329.2087.

***syn*-8,20,22-Trioxabicyclo[17.3.1]tricosa-3,5-diene-7,21-dione (24b).** To **8b** (0.0157 g, 0.0484 mmol) was added anhydrous THF (1 mL) at 55 °C under argon atmosphere. Carbonyldiimidazole (0.0121 g, 0.0740 mmol, 1.5 equiv) was added and the mixture stirred overnight. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. The compound was purified by column

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chromatography (silica gel, 20% EtOAc in hexanes) to afford **23b** as a clear oil (0.0143 g, 0.0408 mmol, 84%). **23b**: $R_f = 0.44$ (silica gel, 3:2, EtOAc/hexanes); IR (KBr) $\nu_{max} = 2926, 2854, 1751, 1710, 1645, 1617, 1460, 1403, 1380, 1254, 1192, 1114, 1051, 1005\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, 1H, $J = 15.5, 10.8$ Hz, $-CHCHCHCO_2R$, C3), 6.32 (dd, 1H, $J = 15.2, 10.9$ Hz, $-CHCHCH-$, C4), 6.05 (m, 1H, $-CH_2CHCH-$, C5), 5.87 (d, 1H, $J = 15.5$ Hz, $-CHCHCO_2R$, C2), 4.59 (m, 2H, $-CHO$-carbonate, C7, C9), 4.35 (m, 1H, $-CH_2O$, C19), 4.18(m, 1H, $-CH_2O$, C19), 2.70 (m, 1H, CH_2CHO-, C6), 2.57 (m, 1H, CH_2CHO-, C6), 1.88−1.57 (m 6H, $-CH_2-$), 1.29 (m, 14H, $-CH_2-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 149.7, 143.5, 135.2, 135.2, 133.9, 122.3, 78.4, 46.8, 37.6, 34.0, 30.2, 30.1, 30.0, 29.8, 29.7, 29.6, 29.1, 28.9, 26.3, 22.6; MS (ESI) $C_{30}H_{23}O_5$ $(M + H)^+ = 351.00$, $(M + Na^+)$ 373.00, $(M + K)^+ = 388.95$.

***E,E,Z*-10-Hydroxyoxacycloeicosa-3,5,7-trien-2-one (9).** To **24b** (0.0157 g, 0.0484 mmol) were added THF (0.5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 10 μL, 0.067 mmol, 1.4 equiv) at room temperature under argon atmosphere and the mixture stirred at 55 °C overnight. The reaction mixture was quenched with saturated NH_4Cl (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness in vacuo. The compound was purified by column chromatography (silica gel, 20% EtOAc in hexanes) to afford **9** as a clear oil (0.0119 g, 0.0340 mmol, 74%). **9**: $R_f = 0.33$ (silica gel, 1:3, EtOAc/hexanes); IR (KBr) $\nu_{max} =$ 3026, 2925, 2854, 1710, 1616, 1462, 1410, 1381, 1260, 1157, 1053, 1002; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (dd, 1H, $-CH-$, C3), 6.79 (dd, 1H, $J = 14.52, 11.56$ Hz, $-CH-$, C5), 6.35 (dd, 1H, $J = 14.70, 11.05$ Hz, $-CH-$, C6), 6.27 (dd, 1H, $J = 11.04, 11.04$ Hz, $-CH-$, C4), 5.90 (dt, 1H, $J = 8.70$ Hz, $-CH-$, C7), 5.84 (d, 1H, $J = 15.42$, $-CH-$, C2), 4.18 (m, 2H, $-CH_2-$, C19), 3.83 (m, 1H, $-CHOH$, C9), 2.65 (m, 1H, $-CH_2-$, C6), 2.27 (m, 1H, $-CH_2-$, C6), 1.68 (m, 2H, $-CH-$), 1.51−1.26 (m, 16H, $-CH-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 145.1, 136.0, 133.3, 130.6, 130.4, 121.7, 72.4, 65.1, 36.7, 34.0, 30.5, 30.1, 29.5, 29.1, 29.0, 28.5, 26.3, 25.3; HRMS (ES^+) calcd for $C_{19}H_{30}O_3$ $(M + Na)^+$ 329.2087, obsd 329.2086.

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Supporting Information Available: Full experimental details and characterization for all compounds, tabulated ^1H NMR chemical shift for literature trienoates and **9**, ^1H and ^{13}C NMR spectra for all compounds, and NOESY, COSY, HSQC, and HMBC for oxetane **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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