Synthesis of the hexacyclic triterpene core of the jujuboside saponins via tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction[⋆]

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Abstract

The jujubosides are saponin natural products reported to have immunoadjuvant, anticancer, antibacterial, antifungal, and antisweet activities. The triterpene component, jujubogenin contains a unique tricyclic ketal motif comprising the DEF ring system. Herein, we describe our efforts toward the total synthesis of jujubogenin, using a sterically-demanding intermolecular Diels–Alder reaction to assemble the C-ring and a tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction to form the DF-ring system. Acid-catalyzed cyclization of the resulting bicyclic enol ether then closes the E-ring to provide the hexacyclic core of jujubogenin.

Graphical abstract
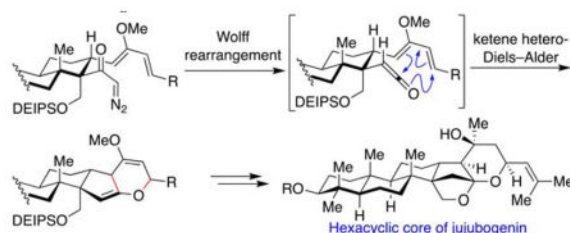
Keywords

Natural Products; Total Synthesis; Wolff rearrangement; Ketene hetero-Diels–Alder; Tandem reaction

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1. Introduction

The jujubosides are glycosylated triterpene natural products isolated mainly from Chinese and Indian herbal plants. They exhibit a wide range of bioactivities including immunoadjuvant, anticancer, antifungal, antibacterial, and antisweet activities.[1–3] In particular, jujuboside A (**2**) has been reported to generate higher antibody titers in mouse vaccinations and lower *in vitro* toxicity compared to QS-21,[2–3] another saponin immunoadjuvant that is a component of the Mosquirix (RTS,S/AS01) malaria vaccine[4] and Shingrix shingles vaccine[5] and has been investigated as the immunoadjuvant of choice in numerous other vaccine clinical trials.[6–12] Based on our laboratory's long-standing interest in saponin immunoadjvuants[13–20] we initiated a research program toward the total synthesis of jujuboside A to enable detailed structure–activity relationships studies. We recently disclosed our synthesis of the complex, doubly-branched pentasaccharide portion of jujuboside A.[21] Herein, we describe our efforts toward the total synthesis of triperpene portion of jujuboside A, called jujubogenin (**1**).[22]

Jujubogenin is a complex triterpene with nine contiguous stereocenters, six of which are quaternary, including four all-carbon quaternary centers (Figure 1). In addition, the tricyclic DEF ring system bearing a C16 ketal is unique to jujubogenin. Despite these striking structural features and numerous reported biological activities of the jujubosides, a chemical synthesis of the jujubogenin triterpene has not been reported. Developing a synthetic strategy that would address the complexity of these structural features and allow structure–activity relationship studies of this triterpene and related natural products presents a significant challenge.

2. Results and Discussion

2.1. Retrosynthetic analysis of jujubogenin (1)

Retrosynthetically, we envisioned late-stage installation of the C21 methyl group of jujubogenin (**1**) by addition of methyl lithium to the convex α-face of ketone **3** (Scheme 1). Ketone **3** could be assembled from bis(enol ether) **4** through a series of functional group interconversions including an acid-catalyzed tandem C30 alcohol deprotection, ketalization, and methyl enol ether hydrolysis.

The structural complexity of bis(enol ether) **4** could be dramatically reduced by a tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction starting from diazoketone **6** via ketene intermediate **5**. The highly functionalized C-ring of the jujubogenin would be furnished using a sterically-demanding intermolecular Diels–Alder reaction between diene **8** and dienophile **7**. Diene **8** would be prepared in enetioenriched form from the Wieland–Miescher ketone (**9**).[23]

2.2. Model study of sterically demanding Diels–Alder reaction

One of the key transformations in our synthetic plan for the synthesis of jujubogenin involved a sterically-demanding Diels–Alder reaction between diene **8** and dienophile **7**. Such sterically-demanding cycloadditions are challenging despite many advances in Diels–

Alder reaction methodology due to several reasons: 1) the diene **8** bears a C18 methyl group that hinders the adoption of s-*cis* conformation of the diene required for the Diels-Alder reaction; 2) the dienophile **7** is trisubstituted, thus the desired reaction pathway involves a highly congested transition state with two adjacent all-carbon quaternary centers; 3) the diene **8** lacks a strong electron-donating substiutent to control the regioselectivity of the reaction.

In support of the challenges highlighted above, it has been shown that dienes that are structurally similar to our proposed diene **8** react only with highly activated and sterically accessible dienophiles, such as tetracyanoethylene and acetylene dienes with an electron-withdrawing group, or under forcing condition such as high pressure.[24–25] Diactivated dienophiles such as dimethyl fumarate/maleate and maleic anhydride do not react with this type of diene. On the other hand, (carbomethoxy)maleic anhydride **7** is a highly activated dienophile.[26] Kinetic studies by Hall and coworkers revealed that it is more reactive than tetracyanoethylene. Interestingly, dienophile **7** reacts even with styrene as a diene to give the corresponding Wagner–Jauregg type[27] adduct. Despite this high reactivity, there has been limited use of this dienophile to deliver substituted cyclohexanes.[26, 28–33] In fact, only one application to natural product synthesis has appeared in the literature.[33]

We anticipated that the high reactivity of dienophile **7** would compensate for the poor reactivity of diene **8** in our proposed sterically-demanding Diels–Alder reaction. To test this hypothesis, we first conducted a model study with readily accessible diene **10**.[34] We were delighted to find that the reaction between diene **10** and dienophile **7** proceeded smoothly at ambient temperature to give tricycle **11** as a single regio- and stereoisomer (Scheme 2). Structural assignment was based on extensive 2D-NMR and nOe studies of the dicarboxylic acid derivative **12**, which was recovered after silica gel purification of anhydride **11**. Mechanistically, the cycloadduct **11** arises from an *endo* transition state relative to the anhydride portion of the dienophile.

Although this achiral model system **10** does not address the facial selectivity of dienophile approach, it validated the feasibility of this approach with respect to reactivity, setting the stage for its evaluation in the context of the more complex jujubogenin system below.

2.3. Model study of tandem Wolff rearrangement–intramolecular ketene hetero-Diels-Alder reaction

Both the C=C and C=O π-systems of ketenes can react with electron-rich dienes to produce [4+2] and [2+2] cycloaddition products and aldol-like reaction products. A literature survey suggests that, out of these possible pathways, [2+2] cycloadditions are the most common (Staudinger ketene cycloaddition).[35] In contrast, [4+2] cycloadditions involving either the C=C or C=O bonds of ketenes are rare and usually regarded as exceptions.[36–54]

In our retrosynthetic analysis, we proposed a [4+2] cycloaddition reaction between an electron-rich diene and the C=O bond of ketene intermediate **5**. Examples of such cycloaddition reactions are limited to stabilized ketenes such as dichloro-, diphenyl-, and bis(trifluoromethyl)ketenes and often result in mixtures of cycloadducts. However, in the context of our proposed approach to jujubogenin, use of the ketene intermediate **5** in a

conformationally-constrained hetero-[4+2] cycloaddition appeared promising based on the fact that the products arising from alternative undesired pathways ([2+2] and ketene C=C bond [4+2] cycloadditions) were expected to suffer from prohibitively high strain energy.

Considering that hetero-[4+2] cycloadditions of ketenes are rare and that such a cycloaddition of a simple monoalkyl substituted ketene has not been reported, we decided to test the feasibility of the proposed [4+2] cycloaddition in a model system, using diazoketone **13**, in which the cyclohexane ring mimics the C-ring of jujubogenin (Scheme 3). Thus, diazoketone **13** was prepared from readily available starting materials in nine steps (see Supporting Information). Gratifyingly, reaction of diazoketone **13** with AgOTf in the presence of triethylamine to generate corresponding ketene intermediate **14**, led to formation of tricyclic bis(enol ether) **16**, indicating that the tandem Wolff rearrangement–Diels–Alder reaction proceeded via the desired ketene C=O [4+2] cycloaddition pathway. This set the stage for investigation of this synthetic approach in the context of the more complex jujubogenin system below.

2.4. Synthesis and sterically-demanding Diel–-Alder reaction of Wieland–Miescher ketone-derived diene 8

Synthesis of diene **8** started from the Wieland–Miescher ketone (**9**) (Scheme 4), which was converted to ketone **16** through a previously described reaction sequence (see Supporting Information). Addition of vinyl magnesium bromide to ketone **16** gave allylic alcohol **17** as an epimeric mixture of vinyl carbinols (major isomer shown). Dehydration delivered the desired diene **8** in 32% overall yield from the Wieland–Miescher ketone (**9**). Importantly, the reaction sequence was easy scalable to multigram quantities, facilitating material throughput.

With diene **8** in hand, we began investigations into the envisioned sterically-demanding Diels–Alder reaction. In our initial attempt, diene **8** was reacted with triactivated dieneophile **7** in dichloromethane (Table 1, entry 1). Under these conditions, the reaction went to completion over several days to give a 1.5:1 mixture of the diastereomers **18a** and **18b** in nearly quantitative yield.

After screening a number of solvents, we found that the best diastereoselectivity was obtained in diethyl ether or benzene (entries 3, 6), although a small amount of dienophile decomposition was observed in diethyl ether. The overall reaction proceeded faster in aromatic solvents (entries 6–10) while nucleophilic solvents resulted in dienophile decomposition (entries 2, 4). The structure of the anhydride **18a** was confirmed through extensive 2D-NMR and nOe studies. We were unable to assign the stereochemistry of the second diastereomer unambiguously, but presume it to be **18b,** arising from an *endo* transition state and approach of the dienophile from the β-face of the diene **8**.

Lewis acids can dramatically alter the reactivity and stereoselectivity of Diels–Alder reactions.[55–56] Thus, we also investigated a number of Lewis-acid catalysts ($B(C_6F_5)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $Fe(OTf)_3$, $In(OTf)_3$, $SnCl_4$, Et_2AlCl, $EtAlCl_2$) in CH_2Cl_2 or PhMe, at 0 and −78 °C. Unfortunately, no clear trend or improvement in diastereoselectivity (1:1 to 2:1) was observed. Moreover, these reactions all generated

significant side products, presumably arising from product and/or dienophile decomposition. Accordingly, the optimized reaction was run in benzene without any additives (entry 6), delivering the desired anhydride **18a** in 54% isolated yield.

2.5. Elaboration of the C-ring of jujubogenin

To advance the synthesis from anhydride **18a**, several functional group manipulations were required to elaborate the Cring. We started with hydrogenation of the double bond, which we anticipated to be challenging as both the α and β faces of the double bond are hindered by functional groups present in B and C rings. In fact, all attempts to hydrogenate the double bond of anhydride **18a** using variety of heterogeneous and homogeneous catalysts, elevated hydrogen pressure (550 psi), and even heating failed. Finally, we found that directed hydrogenation could be achieved using carboxylic acid **19**, obtained by methanolysis of anhydride **18a**, affording a 90% yield of the reduced product **20** under optimized conditions (30 mol% Crabtree catalyst, 0.1 M substrate concentration) (Scheme 5). Reduction of catalyst loading or increase in olefin concentration resulted in incomplete hydrogenation.

Successful α-hydrogenation of the double bond in carboxylic acid **19** established all of the stereocenters present in the C-ring of jujubogenin. Subsequently, we turned our attention to functional group transformations of the three carbonyl groups in **20**. Thus, carboxylic acid **20** was first methylated to give trimethylester **21**, which was then converted to monoaldehyde **22** by reduction of the sterically more accessible C17 methyl ester using DIBAL, followed by Dess–Martin oxidation. Olefination of the aldehyde followed by reduction of the remaining ester groups afforded diol **23**. Several oxidants were then screened for selective monooxidation of the diol to equatorial aldehyde **24**. While Dess–Martin periodinane gave high selectivity for oxidation of the axially disposed alcohol, other oxidants (*e.g.*, $SO_3 \cdot pyr$, TEMPO, TPAP, PCC) provided large amounts of overoxidized dialdehyde product. Ultimately, we found that IBX oxidation with sonication provided a 1.2:1 mixture of monoaldehydes, favoring the desired equatorial aldehyde **24**. The undesired axial aldehyde, as well as small amount of dialdehyde, was then reduced to diol **23** and recycled, affording the desired aldehyde **24** in 74% yield based on recovered starting material.

Aldehyde **24** is a versatile intermediate, as a number of protecting groups can be put on the C30 primary alcohol at this stage of the synthesis. We found that diethylisopropylsilyl (DEIPS) was the optimal protecting group for masking the primary C30 alcohol. In later stages of the synthesis, a less-hindered triethylsilyl (TES) group was partially cleaved under strongly basic conditions, while a more-hindered *tert*-butyldimethylsilyl (TBS) group required harsh deprotection conditions that were not selective and resulted in the cleavage of the C3-TBS protecting group as well. Addition of the methyl lithium to the DEIPS-protected aldehyde derived from **24** followed by oxidation of the resulting secondary alcohol yielded methyl ketone **25**, which was then advanced to ketoaldehyde **26** through ozonolysis and reductive workup. Horner–Wadsworth–Emmons olefination of aldehyde **26** with phosphonate **27** gave triene **28** as a 2:1 mixture of *Z*- and *E*-enol ethers. Subsequent deformylative diazotransfer then delivered the α-diazoketone **29**, setting the stage for assembly of the DEF-ring system.

2.6. Tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction of diazoketone 29

Next, we explored the pivotal tandem Wolff rearrangement–ketene hetero-Diels–Alder reaction of α-diazoketone **29**. Unfortunately, under the conditions applied in our model studies above (AgOTf, Et$_3$N) (Scheme 3), no reaction was observed. It has been documented that silver-promoted Wolff rearrangement with sterically-hindered diazoketones is often sluggish.[57] On the other hand, irradiation of the α-diazoketone **29** at 310 nm in C$_6$D$_6$ delivered the desired bis(enol ether) **31** based on ^{1}H-NMR analysis of the crude reaction mixture (Scheme 6). Product formation was clearly supported by comparison of this spectrum to that of the previously synthesized model bis(enol ether) **15** (Scheme 3).

Unfortunately, this cycloadduct **31** readily decomposed upon attempted purification on silica gel deactivated with Et$_3$N, or basic or neutral alumina. The major product isolated after purification appeared to be triene **32**, presumably arising from fragmentation of the F-ring. However, complete characterization of **32** was difficult as a result of keto–enol tautomerization, which led to various stereoisomers.

The difference in stability between the original model bis(enol ether) **15** and the elaborated bis(enol ether) **31** was striking. Careful analysis of the structural features of **15** and **31** revealed a key difference. We noted that, compared to the model system product **15**, the elaborated product **31** bore an additional exocyclic olefin adjacent to the labile C23–O bond (Figure 2). Thus, we hypothesized that donation of electrons from the π-orbital of the additional olefin substituent into the σ*-antibonding orbital of the C23–O bond resulted in weakening of this bond in **31** compared to **15**, with this π to σ* donation promoting the observed fragmentation.

Thus, we hypothesized that masking the C24–C25 double bond, or introducing it at a later stage in the synthesis, should improve the stability of the corresponding cycloadduct. Toward this we designed two new α-diazoketones, **33** and **35** (Scheme 7), the synthesis of which involved a similar process to that of previously prepared diazoketone **29** (see Supporting Information for details). To our delight, irradiation of diazoketones **33** and **35** gave the respective bis(enol ethers) **34** and **36** in good yields. In contrast to **31**, both products were stable to the purification using basic alumina, thus supporting our hypothesis that the main source of relative instability of **31** compared to the model product **15** was the olefin substituent at C23. Of note, the stereochemical configuration of the C23 substituent in **36** remained unassigned at this stage.

2.7. Formation of the E-ring via C16 ketalization

Successful application of the tandem Wolff rearrangement–ketene hetero-Diels–Alder reaction furnished the ABCDF-ring system of jujubogenin (**1**). We then focused our attention to formation of the C16 ketal which would complete the hexacyclic core of jujubogenin (**1**). As a model system, we first advanced the C23-unsubstituted cycloadduct **34**. Selective removal of the DEIPS protecting group set the stage for acid-catalyzed ketalization (Scheme 8). Treatment of alcohol **37** with Amberlyst-15 in wet CH$_2$Cl$_2$ resulted

in formation of the desired keto-ketal **38**. Addition of MeLi at −78 °C proceeded with the desired attack from the *exo*-face to deliver the complete hexacyclic core of jujubogenin **39**.

Encouraged by the successful conversion of the C23-unsubstituted enol ether **34** to hexacycle **39**, we turned our attention to the C23-substituted enol ether **36**. While TBAF deprotection of the C30-DEIPS group proceeded smoothly, treatment of the resulting alcohol with Amberlyst-15 resulted in formation of lactone **42** and vinylogous ester **43**, with only small amount of the desired ketal **41** (Scheme 9).

Mechanistic understanding of the formation of lactone **42** lies in the innate reactivity of the jujubogenin triterpene under acidic conditions.[22] Initial isolation reports documented that treatment of jujubogenin (**1**) with acid induced ring fragmentation, yielding ebelin lactone (**45**) (Scheme 10a). We hypothesized that, in case of C23-substituted enol ether **36**, after initial cyclization and hydrolysis of the methyl enol ether, the desired ketone **41** is formed, but then undergoes further reaction with acid to generate oxocarbenium **46**, which undergoes a similar fragmentation to that of jujubogenin (**1**), yielding lactone **42** (Scheme 10b). Indeed, when isolated ketone **41** was treated with Amberlyst-15 in CH_2Cl_2, lactone **42** was produced efficiently. On the other hand, the other byproduct, vinylogous ester **43**, can be generated through C23–O bond fragmentation of the oxocarbenium generated by protonation of the C15–C16 enol ether (not shown).

Based on this mechanistic analysis, we posited that the fragmentation leading to vinylogous ester **43** would most likely happen under acidic conditions, regardless of the strength of the acid. However, the stability of the desired product **41** under the reaction conditions could depend on the strength of the acid. Accordingly, we investigated weaker acids and found that dichloroacetic acid was the optimal acid for this transformation, delivering ketone product **41** in 63% isolated yield (Scheme 11).

Stereochemical assignment of ketone **41** was then conducted using extensive 2D NMR studies. The previously published X-ray structure of jujubogenin (**1**)[58] revealed that the F-ring is in a chair conformation, putting the bulkier C21 (methyl) and C23-isobutenyl group in equatorial positions (Figure 3). Thus, if ketone **41** had the same stereochemistry, no nOe should be observed between C23-H and C17-H due to their 1,4-diaxial relationship. However, after complete structural assignment, nOe analysis indicated that these two protons reside on the same face of the F-ring. In conjunction with the lack of nOe between C17-H and bridging C15-methylene, or between the C24-methylene and bridging C15-methylene, these data were consistent with a the C23 carbon of ketone **41** having the opposite stereochemical configuration to that in jujubogenin (**1**). Furthermore, these nOe analyses indicated that the F-ring in ketone **41** adopts a boat conformation (**41b**) to avoid an unfavorable *syn*-pentane interaction between the axial C24-methylene and bridging C15-methylene groups in the corresponding chair conformation (**41a**).

This C23 stereochemical outcome, while undesired, shed light on the mechanism of the ketene hetero-Diels–Alder reaction (Scheme 12). In a concerted, pericyclic reaction mechanism, the stereochemistry observed in ketone **41** would be predicted. However, in a stepwise reaction mechanism, initial addition of the enol ether to the ketene would give

zwitterion **49**, which could then undergo 6-*endo-trig* cyclization to either face of the C22–C23 double bond to provide a mixture of C23 epimers. In our retrosynthetic analysis, we assumed that the reaction would proceed through the stepwise pathway, as both the enol ether portion of the diene and carbonyl of the ketene are highly polarized and such Mukaiyama-aldol/oxy-conjugate addition reactions are well known.[59] Unfortunately, formation of the bis(enol ether) **36** indicates that the ketene hetero-Diels–Alder reaction most likely proceeds through concerted mechanism.

Although the C23 stereochemistry was incorrect, we decided to advance ketone **41** forward, anticipating that it might be possible to correct this stereochemical configuration at a later stage in the synthesis. Thus, addition of methyl lithium followed by removal of the benzyl protecting group delivered diol **51** in good overall yield (Scheme 13). By exploiting the difference in steric hindrance between the C20 and C25 tertiary alcohols, we then selectively effected elimination of the C25 alcohol using a bulky dehydrating agent, Martin sulfurane, which gave a 1:1 mixture of olefins **52** and **53**. Olefin **52** has all of the structural features of jujubogenin (in C3-*O*-TBS protected form) except for the stereochemical configuration at C23.

2.8. Attempts to correct the C23 stereochemistry

With olefin **52** in hand, we sought to epimerize the C23 stereogenic center to finish the total synthesis of jujubogenin (**1**). Our plan involved oxidative cleavage of the olefin to form aldehyde **54**, which then would undergo epimerization under thermodynamically-controlled conditions (anticipating that the energy difference of ~5.5 kcal/mol[60] between chair and boat comformations would be sufficient to drive the equilibrium toward the desired aldehyde) to deliver the epimeric aldehyde **55** (Scheme 14). Unfortunately, ozonolysis of the olefin **52** followed by reductive workup led to hemiacetal **56** instead of the desired aldehyde **54**. Attempts to epimerize the hemiacetal **56** under basic conditions were not fruitful, leading to decomposition under forcing conditions.

3. Conclusion

In conclusion, we have developed a synthetic approach toward the total synthesis of jujubogenin (**1**) featuring two pivotal Diels–Alder reactions. First, we developed a sterically-demanding Diels–Alder reaction using a model system, which was then applied successfully to the synthesis of the C-ring of jujubogenin. The product of this reaction was then advanced to the diazoketones **28**, **33**, and **35** via several key transformations including stereoselective hydrogenation using Crabtree's catalyst, chemoselective carboxylic acid reduction, Horner–Wadsworth–Emmons olefination, and deformylative diazotransfer. Subsequently, we developed a novel tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction using a model study and successfully applied it to the construction of the DF-ring system. Finally, we developed a ketalization reaction to close the E-ring, completing the hexacyclic ring system of jujubogenin. This required us to avoid several perilous decomposition pathways via judicious choice of acid catalyst and masking of the pendant C22–C23 olefin. Although we were unable to correct the undesired stereochemical configuration at C23, this overall synthetic strategy provided expedient access to the

complete hexacyclic triterpene core of jujubogenin (**52**), and future synthetic efforts may be able to leverage the mechanistic insights derived herein to access jujubogenin (**1**), by either epimerization at C23 or direct installation of the desired configuration at the stage of the ketene hetero Diels–Alder reaction. This will enable detailed structure–activity relationship studies of the jujuboside family of natural products.

4. Experimental Section

4.1. General Materials and Methods

Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. The appropriate starting materials and reagents were dried via azeotropic removal of water with toluene. Molecular sieves were activated at 350 °C and were crushed immediately prior to use, then flame-dried under vacuum. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized under UV light (254 and 360 nm), or stained with Ceric Ammonium Molybdate in conc. H_2SO_4.

Dichloromethane, tetrahydrofuran, diethyl ether, and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[61] Methanol was distilled from magnesium at 760 Torr. Pyridine and trimethylamine were freshly distilled from CaH_2 prior to use. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Automated flash chromatography was performed with an Isco Combiflash medium-pressure liquid chromatography with Redisep silica columns (47–60 μm). Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum BX or a Bruker Tensor 27 spectrophotometer. Data are presented as the frequency of absorption (cm^{-1}). Proton and carbon-13 nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded on a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (d-chloroform: δ 7.26 for ^1H NMR, δ 77.16 for ^{13}C NMR; d6-benzene: δ 7.16 for ^1H NMR, δ 128.06 for ^{13}C NMR; d4-methanol: δ 3.31 for ^1H NMR, δ 49.00 for ^{13}C NMR; d3-acetonitrile: δ 1.94 for ^1H NMR, δ 1.32 for ^{13}C NMR; deuterium oxide: δ 4.79 for ^1H NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration, assignment.

4.2. Model bis(enol ether) 15

To a solution of diazoketone **13** (5.8 mg, 0.021 mmol, 1.0 equiv) in THF (250 μl) at 45 °C, was added Et_3N (3.4 μl, 0.021 mmol, 1.0 equiv) followed by AgOTf (1.1 mg, 0.0042 mmol, 0.20 equiv). The reaction mixture was stirred for 40 min at 45 °C, then cooled to rt and

filtered through a pad of SiO$_2$. The SiO$_2$ layer was washed with Et$_2$O five times (10 mL total). The combined THF and Et$_2$O fractions were concentrated and analyzed by ^{1}H-NMR, which indicated complete conversion and formation of the desired product (50% yield). The analytically pure bis(enol ether) **15** was obtained by flash column chromatography using basic alumina (hexanes:EtOAc 25:1). **TLC** R_f 0.14 (hexanes:EtOAc 25:1); **FTIR** (NaCl film) 2959, 1452, 1240, 1034, 835, 716; **^{1}H NMR** (600 MHz, C$_6$D$_6$) δ 5.51 (d, J = 2.0 Hz, 1H), 4.42 (dt, J = 13.9, 2.5 Hz, 1H), 4.33 (dt, J = 13.8, 2.9 Hz, 1H), 4.09 (td, J = 3.3, 1.9 Hz, 1H), 3.53 (d, J = 8.4 Hz, 1H), 3.23 (d, J = 8.6 Hz, 2H), 3.11 (s, 3H), 3.09 (s, 3H), 2.23 (ddd, J = 12.8, 4.7, 2.0 Hz, 1H), 2.17 (ddt, J = 12.7, 4.7, 2.5 Hz, 1H), 1.92 (ddd, J = 13.6, 11.3, 2.8 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.62 – 1.32 (m, 5H), 1.28 (td, J = 12.9, 4.6 Hz, 1H); **^{13}C NMR** (151 MHz, C$_6$D$_6$) δ 157.69, 157.14, 110.77, 90.07, 74.97, 67.27, 59.31, 54.40, 53.94, 46.92, 43.18, 33.21, 27.04, 24.59, 21.38; **HRMS** (ESI) m/z Calcd for C$_{15}$H$_{23}$O$_3$ [M+H]$^+$ 251.1647, found 251.1650.

4.3. Allylic alcohol 17

The known ketone **16** (5.08 g, 15.0 mmol, 1.0 equiv), prepared as previously described,[62] was azeotropically dried with PhMe (15 mL), dissolved in THF (150 mL), and cooled to −78 °C. Vinylmagnesium bromide (1 M in THF, 37.5 mL, 37.5 mmol, 2.5 equiv) was added via syringe. The cooling bath was removed and the solution was stirred for 10 h then quenched with satd aq NH$_4$Cl (200 mL) and H$_2$O (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL), and the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated to give crude allylic alcohol **17**, which was carried to the next step without further purification.

4.4. Diene 8

Crude allylic alcohol **17** (1 equiv.) was azeotropically dried with PhMe (15 mL), dissolved in pyridine (110 mL) and cooled to −30 °C. SOCl$_2$ (1.32 mL, 18 mmol, 1.2 equiv.) was added via syringe. The solution was stirred for 4 h at this temperature, diluted with pentane (1.2 L) and washed sequentially with H$_2$O (3 x 200) and satd aq CuSO$_4$ (3 x 300 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated to give crude diene **8**. Purification by flash column chromatography (hexanes) afforded diene **8** (3.56 g, 68% over 2 steps) as a white solid. **TLC** R_f 0.60 (hexanes); [α]$_D^{19}$ +38.5 (c 1.00, C$_6$H$_6$); **FTIR** (NaCl film) 2934, 2855, 1472, 1361, 1254, 1104, 1070, 1004, 934, 915, 883, 835, 772, 665; **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.07 (dddt, J = 17.7, 11.3, 2.2, 1.2 Hz, 1H), 5.20 (dd, J = 11.2, 2.8 Hz, 1H), 4.87 (dd, J = 17.6, 2.7 Hz, 1H), 3.17 (dd, J = 11.3, 4.5 Hz, 1H), 2.07 – 2.00 (m, 2H), 1.68 – 1.41 (m, 5H), 1.61 (s, 3H), 1.17 (td, J = 13.0, 3.3 Hz, 1H), 1.07 (dd, J = 12.6, 2.0 Hz, 1H), 0.96 (s, 3H), 0.89 (s, 3H), 0.86 (s, 9H), 0.74 (s, 3H), −0.00 (s, 3H), −0.01 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 141.62, 135.10, 127.18, 118.60, 79.50, 77.37, 77.16, 76.95, 50.64, 39.63, 37.44, 36.33, 33.83, 28.59, 28.30, 26.08, 21.11, 20.18, 18.91, 18.28, 16.05, −3.61, −4.79.

4.5. Anhydride 18a

Diene **8** (1.60 g, 10.3 mmol, 1.0 equiv) was azeotropically dried with PhMe (5 mL) and dissolved in PhH. Dienophile **7** (1.90 g, 14.6 mmol, 1.4 equiv) was added as a solid and the

resulting bright yellow solution was stirred for 24 h, at which point the bright yellow color of the solution had disappeared. The reaction mixture was directly purified by flash column chromatography as described below. A column (22 cm length, 5.5 cm width of dry silica) was slurry packed with the aid of hexanes containing 2% AcOH. Then all of the solvent was removed using N_2 and the column was repacked with hexanes containing 2% AcOH. The reaction mixture was diluted with hexanes, loaded directly onto the column, and eluted with hexanes:PhH:AcOH (50:1:1) to yield anhydride **18a** (646 mg, 54%) and its diastereomer **18b** (275 mg, 23%) as white solids. **18a: TLC** R_f 0.21 (hexanes:PhH:AcOH 50:1:1); $[\alpha]_D^{20}$ +69.7 (*c* 1.00, C_6H_6); **FTIR** (NaCl film) 2936, 2856, 1797, 1728, 1462, 1388, 1249, 1168, 1094, 928, 885, 836, 773, 665; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.52 (dd, *J* = 7.1, 2.4 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, *J* = 11.4, 1.6 Hz, 1H), 3.21 (dd, *J* = 11.1, 4.9 Hz, 1H), 2.84 (td, *J* = 13.2, 5.1 Hz, 1H), 2.74 (ddd, *J* = 18.0, 11.5, 2.4 Hz, 1H), 2.47 (ddd, *J* = 17.9, 7.1, 1.6 Hz, 1H), 1.86 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.72 (ddt, *J* = 13.8, 4.9, 2.2 Hz, 1H), 1.65 – 1.46 (m, 4H), 1.31 – 1.22 (m, 2H), 1.29 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.62, 169.12, 167.82, 158.19, 114.91, 78.64, 77.37, 77.16, 76.95, 66.71, 53.69, 48.63, 44.09, 39.93, 39.80, 39.54, 36.71, 35.14, 28.76, 28.14, 26.04, 25.62, 25.37, 22.60, 18.23, 16.37, −3.65, −4.74; **HRMS** (ESI) *m/z* Calcd for $C_{28}H_{45}O_6Si$ [M+H]$^+$ 505.2985, found 505.2973.

18b: TLC R_f 0.20 (hexanes:PhH:AcOH 50:1:1); $[\alpha]_D^{20}$ −28.1 (*c* 1.00, C_6H_6); **FTIR** (NaCl film) 2935, 1785, 1733, 1462, 1251, 1174, 1098, 1075, 956, 884, 836, 773, 665; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.59 (dd, *J* = 7.6, 2.6 Hz, 1H), 3.89 (dd, *J* = 9.6, 1.6 Hz, 1H), 3.82 (s, 3H), 3.12 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.88 (dt, *J* = 14.2, 10.0 Hz, 1H), 2.74 (ddd, *J* = 17.3, 9.6, 2.6 Hz, 1H), 2.59 (ddd, *J* = 17.2, 7.6, 1.6 Hz, 1H), 1.82 – 1.62 (m, 5H), 1.59 – 1.52 (m, 1H), 1.33 – 1.22 (m, 2H), 1.20 (s, 3H), 1.03 (s, 3H), 0.88 (s, 9H), 0.88 (s, 3H), 0.84 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.01, 167.81, 167.53, 157.57, 115.75, 79.33, 77.37, 77.16, 76.95, 65.99, 53.72, 44.90, 43.30, 41.47, 40.47, 39.07, 38.15, 28.14, 27.88, 26.58, 26.03, 26.01, 25.01, 23.72, 22.03, 18.23, 17.33, 15.32, −3.75, −4.78; **HRMS** (ESI) *m/z* Calcd for $C_{28}H_{45}O_6Si$ [M+H]$^+$ 505.2985, found 505.2966.

4.6. Monocarboxylic acid 19

A solution of anhydride **18a** (4.00 g, 7.93 mmol, 1.0 equiv) was stirred at rt in MeOH/PhMe (250 ml/250 mL). After 24 h, the reaction mixture was concentrated to give monocarboxylic acid **19** (4.25 g, 100%). Residual PhMe was removed azeotropically with MeOH. (Note that it is important to remove all residual solvents at this stage as residual PhMe or MeOH deactivates Crabree's catalyst in the subsequent hydrogenation step.) **TLC** R_f 0.41 (hexanes:EtOAc 3:2); $[\alpha]_D^{20}$ +37.0 (*c* 1.00, C_6H_6) **FTIR** (NaCl film) 2951, 1790, 1738, 1436, 1387, 1249, 1109, 1077, 994, 925, 885, 836, 774, 738, 666; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 11.70 (bs, 1H), 5.45 (t, *J* = 3.9 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.63 (dd, *J* = 10.9, 8.2 Hz, 1H), 3.16 (dd, *J* = 11.3, 4.7 Hz, 1H), 2.68 (ddd, *J* = 18.3, 10.9, 3.5 Hz, 1H), 2.52 (ddd, *J* = 18.3, 8.3, 4.1 Hz, 1H), 2.07 (td, *J* = 12.9, 4.5 Hz, 1H), 1.80 (dt, *J* = 12.9, 3.6 Hz, 1H), 1.69 – 1.48 (m, 5H), 1.38 (td, *J* = 13.4, 3.9 Hz, 1H), 1.25 (d, *J* = 1.0 Hz, 3H), 1.14 (s, 3H), 1.04 (dd, *J* = 12.0, 1.9 Hz, 1H), 0.89 (s, 4H), 0.88 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.06, 174.55, 169.75, 151.16, 116.91, 78.69, 77.37, 77.16, 76.95, 63.59, 53.17, 52.72, 50.35, 43.13, 41.47, 39.68, 39.61, 37.74,

35.90, 28.45, 28.37, 27.49, 27.03, 26.05, 25.48, 18.46, 18.23, 16.06, −3.67, −4.80; **HRMS** (ESI) *m/z* Calcd for $C_{29}H_{49}O_7Si$ [M+H]$^+$ 559.3067, found 559.3069.

4.7. Saturated monocarboxylic acid 20

A flask containing alkene monocarboxylic acid **19** (2.700 g, 5.030 mmol, 1.0 equiv) and Crabtree's catalyst (1.333 g, 1.660 mmol, 0.3 equiv) was evacuated and backfilled with H_2 (balloon). CH_2Cl_2 (50 mL) was added and the reaction mixture was stirred for 6 h at rt, then concentrated. Purification by column chromatography (hexanes: EtOAc 5:1 with 2% AcOH) yielded the saturated carboxylic acid **20** (2.4351 g, 90%). **TLC** R_f 0.41 (hexanes:EtOAc 3:2); $[\alpha]_D^{20}$ +4.8 (*c* 1.00, C_6H_6); **FTIR** (NaCl film) 2953, 2855, 1728, 1681, 1438, 1391, 1286, 1246, 1223, 1100, 1015, 884, 836, 774, 735, 666; **^{1}H NMR** (600 MHz, CDCl$_3$) δ 12.25 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.47 (dd, *J* = 12.9, 5.6 Hz, 1H), 3.14 (dd, *J* = 11.4, 4.6 Hz, 1H), 2.45 (qd, *J* = 13.2, 4.6 Hz, 1H), 2.23 – 2.15 (m, 1H), 1.78 (dt, *J* = 12.9, 3.2 Hz, 1H), 1.72 – 1.63 (m, 2H), 1.63 – 1.51 (m, 4H), 1.51 – 1.45 (m, 1H), 1.36 – 1.26 (m, 2H), 1.01 (td, *J* = 13.6, 4.0 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 9H), 0.85 (s, 6H), 0.77 (dd, *J* = 12.1, 1.9 Hz, 1H), 0.70 (s, 3H), 0.02 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 177.34, 175.18, 170.33, 78.92, 77.37, 77.16, 76.95, 64.72, 54.70, 53.51, 52.45, 49.94, 44.62, 42.64, 39.44, 38.64, 37.89, 37.67, 28.25, 27.78, 26.05, 25.68, 20.02, 18.93, 18.40, 18.24, 16.97, 16.07, −3.68, −4.82; **HRMS** (ESI) *m/z* Calcd for $C_{29}H_{51}O_7Si$ [M+H]$^+$ 539.3404, found 539.3391.

4.8. Triester 21

To the solution of monocarboxylic acid **20** (2.71 g, 5.03 mmol, 1.0 equiv) in DMF (25 mL) was added KHCO$_3$ (1.51 g, 15.1 mmol, 3.0 equiv) and MeI (3.57 g, 25.1 mmol, 5.0 equiv). The reaction mixture was stirred at rt for 16 h then diluted with Et$_2$O (300 mL), and washed with water (50 mL), 1 N HCl (50 mL), and satd aq NaHCO$_3$ (50 mL). The Et$_2$O layer was dried over MgSO$_4$, filtered, and concentrated. Purification by automated SiO$_2$ column chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 80 g column, 1–70% EtOAc in hexanes) yielded triester **21** (2.47 g, 89%) as a white solid. **TLC** R_f 0.13 (hexanes:EtOAc 10:1); $[\alpha]_D^{20}$ +1.62 (*c* 1.00, C_6H_6); **FTIR** (NaCl film) 2951, 1738, 1434, 1390, 1361, 1257, 1197, 1171, 1101, 1071, 884, 835, 773, 737; **^{1}H NMR** (600 MHz, CDCl$_3$) δ 3.76 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.19 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.07 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.44 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.09 (dd, *J* = 12.7, 2.5 Hz, 1H), 2.04 (td, *J* = 13.3, 4.3 Hz, 1H), 1.95 (dtd, *J* = 12.9, 4.2, 2.7 Hz, 1H), 1.67 (ddt, *J* = 12.8, 7.5, 3.8 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.52 – 1.44 (m, 1H), 1.41 – 1.21 (m, 4H), 1.03 (td, *J* = 13.3, 4.0 Hz, 1H), 0.94 (s, 3H), 0.87 (s, 9H), 0.86 (s, 3H), 0.83 (s, 3H), 0.80 (dd, *J* = 11.9, 2.2 Hz, 1H), 0.71 (s, 3H), 0.02 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 175.60, 172.22, 170.62, 79.00, 77.37, 77.16, 76.95, 65.96, 54.59, 52.40, 52.33, 52.04, 50.28, 46.44, 42.72, 39.43, 38.90, 37.69, 37.34, 28.24, 27.90, 26.54, 26.06, 19.96, 18.50, 18.25, 17.64, 16.82, 15.98, −3.66, −4.78; **HRMS** (ESI) *m/z* Calcd for $C_{30}H_{52}O_7Si$ [M+H]$^+$ 553.3561, found 553.3558.

4.9. Monoaldehyde 22

To the solution of triester **21** (2.00 g, 3.62 mmol, 1.0 equiv) in PhMe (50 mL) cooled to −78 °C was added DIBAL (1 M in PhMe, 7.4 mL, 7.4 mmol, 2.1 equiv). The reaction mixture was stirred at −78 °C for 30 min, then at −50 °C for 30 min, and quenched by

adding EtOAc (10 mL). Rochelle's salt solution (20%, 100 mL) was added and the mixture stirred for 20 min. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated to give the corresponding crude alcohol, which was used in the subsequent oxidation step without further purification. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.82 – 3.74 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.21 (dd, J = 11.5, 4.6 Hz, 1H), 3.14 (dt, J = 11.6, 6.1 Hz, 1H), 2.40 (ddt, J = 13.1, 7.1, 3.5 Hz, 1H), 2.33 (dd, J = 12.6, 2.7 Hz, 1H), 2.04 (dq, J = 13.1, 3.4 Hz, 1H), 1.84 (td, J = 13.1, 4.2 Hz, 1H), 1.73 (dt, J = 13.1, 3.4 Hz, 1H), 1.68 (dt, J = 13.0, 3.6 Hz, 1H), 1.65 – 1.52 (m, 5H), 1.49 (dq, J = 13.6, 3.9 Hz, 1H), 1.36 (qd, J = 13.0, 3.5 Hz, 1H), 1.27 (qd, J = 13.0, 3.7 Hz, 1H), 1.21 – 1.12 (m, 1H), 1.03 (td, J = 13.4, 3.8 Hz, 1H), 0.92 (s, 4H), 0.88 (d, J = 3.5 Hz, 12H), 0.83 (s, 3H), 0.71 (s, 3H), 0.02 (s, 5H), 0.02 (s, 4H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.28, 170.46, 79.19, 77.37, 77.16, 76.95, 66.66, 66.51, 54.21, 51.90, 51.63, 50.64, 42.32, 41.70, 39.47, 38.98, 37.70, 36.58, 28.27, 27.94, 27.03, 26.07, 26.05, 20.30, 18.84, 18.42, 18.26, 16.91, 15.95, −3.64, −4.77.

To the solution of the crude alcohol above (1.634 g, 3.114 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) at rt was added $NaHCO_3$ (2.62 g, 31.1 mmol, 10 equiv) followed by the Dess–Martin periodinane (1.32 g, 3.11 mmol, 1.0 equiv). The reaction mixture was stirred for 30 min, then quenched by adding a solution of $Na_2S_2O_3$ (20% w/w, 50 mL) and satd aq $NaHCO_3$ (50 mL) and stirring for 40 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 80 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by automated SiO_2 column chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 40 g column, 1–60% EtOAc in hexanes) yielded monoaldehyde **22** (1.44 g, 79% over 2 steps) as a white solid. **TLC** R_f 0.13 (hexanes:EtOAc 10:1); $[α]_D^{20}$ +18.0 (c 1.00, C_6H_6); **FTIR** (NaCl film) 2952, 1721, 1433, 1390, 1253, 1100, 1070, 884, 835, 773; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.65 (s, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.21 (dd, J = 11.4, 4.6 Hz, 1H), 3.06 (dd, J = 13.1, 3.7 Hz, 1H), 2.25 (tdd, J = 13.4, 4.8, 1.4 Hz, 1H), 2.15 – 2.08 (m, 1H), 2.00 (dd, J = 12.8, 3.0 Hz, 1H), 1.68 – 1.52 (m, 6H), 1.49 (dq, J = 13.6, 3.8 Hz, 1H), 1.45 – 1.36 (m, 1H), 1.34 – 1.24 (m, 1H), 1.13 (qd, J = 13.5, 4.3 Hz, 1H), 1.02 (d, J = 1.0 Hz, 3H), 1.01 – 0.95 (m, 2H), 0.90 (s, 3H), 0.88 (s, 9H), 0.84 (d, J = 0.9 Hz, 3H), 0.72 (s, 3H), 0.02 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.80, 170.10, 169.54, 79.10, 77.37, 77.16, 76.95, 65.84, 54.05, 52.45, 52.06, 50.55, 50.29, 42.12, 39.48, 38.77, 37.60, 35.74, 28.36, 27.84, 26.06, 22.82, 19.54, 18.84, 18.44, 18.25, 16.60, 15.94, −3.65, −4.77; **HRMS** (ESI) m/z Calcd for $C_{29}H_{51}O_6Si$ $[M+H]^+$ 523.3455, found 523.3438.

4.10. Olefin diol 23

To the slurry of Ph_3PMeBr (1.972 g, 5.520 mmol, 2.0 equiv) in THF (20 mL) cooled to 0 °C was added KHMDS (0.826 g, 4.41 mmol, 1.5 equiv). The cooling bath was removed and the orange solution was stirred for 30 min at rt. In a separate flask, aldehyde **22** (1.443 g, 2.760 mmol, 1 equiv) was azeotropically dried with toluene (5 mL), then dissolved in THF (20 mL). The phosphorous ylide solution was then added to the aldehyde solution via cannula. The resulting solution was stirred for 15 h at rt, at which time TLC analysis indicated complete conversion. The solution was poured into ice cold 1 N HCl (100 mL) and extracted with Et_2O (3 x 80 mL). The combined Et_2O extracts were washed with water (100 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by automated SiO_2 column

chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 40 g column, 1–60% EtOAc in hexanes) yielded the corresponding olefin (1.41 g, 98%) as a white solid. **TLC** R_f 0.21 (hexanes:EtOAc 10:1); $[\alpha]_D^{20}$ +13.7 (c 0.84, C_6H_6); **FTIR** (NaCl film) 2949, 1722, 1461, 1389, 1243, 1099, 1071, 884, 835, 773; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.0, 10.6, 6.0 Hz, 1H), 4.99 (dt, J = 17.3, 1.7 Hz, 1H), 4.95 (dt, J = 10.7, 1.5 Hz, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 3.21 (dd, J = 11.5, 4.6 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.38 (dd, J = 12.6, 2.6 Hz, 1H), 1.89 (dt, J = 13.1, 3.4 Hz, 1H), 1.80 – 1.65 (m, 3H), 1.65 – 1.53 (m, 4H), 1.49 (dq, J = 13.6, 3.9 Hz, 1H), 1.46 – 1.22 (m, 4H), 1.04 (td, J = 13.3, 3.8 Hz, 1H), 0.94 (d, J = 0.9 Hz, 3H), 0.92 (dd, J = 12.4, 2.1 Hz, 1H), 0.88 (s, 12H), 0.84 (s, 3H), 0.71 (s, 3H), 0.02 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.81, 170.38, 140.78, 114.25, 79.20, 77.37, 77.16, 76.95, 68.68, 54.34, 51.65, 51.01, 50.27, 42.03, 41.07, 39.47, 38.98, 37.67, 37.17, 28.24, 27.96, 27.54, 26.08, 26.06, 20.13, 18.80, 18.35, 18.27, 17.02, 15.96, −3.64, −4.77; **HRMS** (ESI) m/z Calcd for $C_{30}H_{53}O_5Si$ [M+H]$^+$ 521.3656, found 521.3662.

To the solution of olefin above (1.59 g, 3.05 mmol, 1.0 equiv) in Et_2O (50 mL) at 0 °C was added $LiAlH_4$ (0.23 g, 6.1 mmol, 2.0 equiv). The reaction mixture was allowed to warm to rt and stirred for 15 h. The reaction was cooled to 0 °C and quenched by sequential, slow addition of water (0.23 mL) then a 15% solution of NaOH (0.23 mL), then water (0.69 mL), and stirred for 2 h. The solids were removed by filtration and washed with Et_2O (2x10 mL). The combined Et_2O layers were concentrated to give diol **23** (1.36 g, 96%) as a white solid, which was analytically pure and used without further purification. **TLC** R_f 0.23 (hexanes:EtOAc 5:1); $[\alpha]_D^{20}$ +10.3 (c 1.00, C_6H_6); **FTIR** (NaCl film) 3356, 2928, 1462, 1387, 1255, 1046, 907, 883, 835, 772; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.15 (dt, J = 17.2, 9.7 Hz, 1H), 5.22 (dd, J = 17.0, 2.0 Hz, 1H), 5.08 (dd, J = 10.1, 2.0 Hz, 1H), 4.09 (dd, J = 12.6, 7.7 Hz, 1H), 3.96 (dd, J = 11.8, 8.6 Hz, 1H), 3.87 (d, J = 12.4 Hz, 1H), 3.73 (d, J = 11.7 Hz, 1H), 3.16 (dd, J = 11.4, 4.6 Hz, 1H), 3.03 – 2.92 (m, 1H), 2.36 (ddd, J = 12.9, 9.3, 3.7 Hz, 1H), 2.32 – 2.26 (m, 1H), 1.84 (td, J = 13.2, 3.9 Hz, 1H), 1.73 (dt, J = 13.4, 3.4 Hz, 1H), 1.65 (dt, J = 12.9, 3.6 Hz, 1H), 1.62 – 1.52 (m, 3H), 1.48 (dq, J = 13.7, 3.8 Hz, 1H), 1.43 (dq, J = 13.2, 3.3 Hz, 1H), 1.36 (qd, J = 13.0, 3.2 Hz, 1H), 1.32 – 1.12 (m, 4H), 0.93 (s, 3H), 0.88 (s, 12H), 0.84 (s, 3H), 0.79 (dd, J = 12.3, 2.2 Hz, 1H), 0.72 (s, 3H), 0.03 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 143.78, 116.04, 79.35, 77.37, 77.16, 76.95, 67.28, 62.01, 55.41, 52.45, 49.55, 47.73, 41.34, 39.55, 39.13, 37.50, 35.24, 29.38, 28.42, 27.92, 26.05, 20.81, 18.44, 18.24, 16.89, 16.03, 15.85, −3.63, −4.78; **HRMS** (ESI) m/z Calcd for $C_{28}H_{53}O_3Si$ [M+H]$^+$ 465.3764, found 465.3756.

4.11. Aldehyde 24

To the solution of diol **23** (1.324 g, 2.848 mmol, 1.0 equiv) in acetone/CH_3CN (25 ml/25 mL) was added IBX (0.7975 g, 2.848 mmol, 1.0 equiv) as a solid. The reaction mixture was sonicated for 8 h, then concentrated. Et_2O (20 mL) was added and the mixture was sonicated for 2 min, then filtered through a pad of celite. The celite layer was washed with additional Et_2O (2 x 20 mL) and the Et_2O layers were combined and concentrated. The residue was purified by automated SiO_2 column chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 40 g column, 1–100% CH_2Cl_2 in hexanes) to yield aldehyde **24** (422 mg, 32%) as a white solid. **TLC** R_f 0.17 (hexanes:CH_2Cl_2); $[\alpha]_D^{20}$ +10.0 (c 1.00, C_6H_6); **FTIR** (NaCl film) 3385, 2934, 1709, 1462, 1388, 1253, 1098, 1069, 884, 835, 773; **^{1}H NMR** (600

MHz, CDCl$_3$) δ 9.77 (s, 1H), 6.12 (ddd, J = 17.6, 10.6, 6.0 Hz, 1H), 5.08 (dt, J = 17.6, 1.7 Hz, 1H), 5.04 (dt, J = 10.6, 1.5 Hz, 1H), 4.36 (dd, J = 12.3, 8.3 Hz, 1H), 4.07 (dd, J = 12.4, 4.1 Hz, 1H), 3.17 (dd, J = 11.4, 4.6 Hz, 1H), 3.04 (dddd, J = 12.7, 5.8, 3.9, 1.6 Hz, 1H), 2.06 – 1.92 (m, 2H), 1.84 (dtd, J = 13.5, 4.2, 2.1 Hz, 1H), 1.70 – 1.36 (m, 11H), 1.09 (d, J = 1.1 Hz, 3H), 0.98 (dd, J = 12.6, 3.0 Hz, 1H), 0.89 (s, 4H), 0.88 (s, 10H), 0.84 (d, J = 0.9 Hz, 3H), 0.72 (s, 4H), 0.03 (s, 6H); ^{13}**C NMR** (151 MHz, CDCl$_3$) δ 208.54, 208.53, 141.90, 114.80, 79.19, 77.37, 77.16, 76.95, 61.13, 60.87, 55.26, 51.36, 42.51, 39.55, 38.77, 38.22, 37.69, 36.10, 28.52, 27.77, 26.05, 25.68, 20.35, 18.27, 18.25, 18.22, 16.57, 16.08, −3.62, −4.77; **HRMS** (ESI) m/z Calcd for C$_{28}$H$_{51}$O$_3$Si [M+H]$^+$ 463.3607, found 463.3598.

4.12. Methyl ketone 25

To the solution of aldehyde **24** (500 mg, 1.08 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (20 mL) cooled to 0 °C was added pyridine (435 µl, 5.40 mmol, 5.0 equiv) followed by DEIPSOTf (488 µl, 2.16 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 20 min, then diluted with Et$_2$O (150 mL) and washed with brine (50 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated to obtain the crude diethylisopropylsilyl ether, which was carried to the next step without further purification. **TLC** R_f 0.44 (hexanes:CH$_2$Cl$_2$ 1:1); [α]$_D^{20}$ +22.5 (c 1.12, C$_6$H$_6$); **FTIR** (NaCl film) 2951, 1718, 1462, 1388, 1252, 1097, 1008, 913, 882, 835, 773, 726; ^{1}**H NMR** (600 MHz, CDCl$_3$) δ 9.69 (s, 1H), 5.89 (ddd, J = 17.2, 10.5, 6.6 Hz, 1H), 4.99 (dt, J = 17.3, 1.6 Hz, 1H), 4.93 (dt, J = 10.5, 1.4 Hz, 1H), 4.12 (d, J = 10.8 Hz, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.16 (dd, J = 11.4, 4.6 Hz, 1H), 2.99 – 2.90 (m, 1H), 1.96 (td, J = 13.1, 12.4, 4.5 Hz, 1H), 1.80 – 1.73 (m, 1H), 1.66 (dt, J = 13.0, 3.6 Hz, 1H), 1.63 – 1.22 (m, 11H), 1.02 (s, 3H), 1.01 – 0.95 (m, 13H), 0.90 (s, 3H), 0.88 (s, 10H), 0.83 (s, 3H), 0.77 (dd, J = 11.9, 2.0 Hz, 1H), 0.72 (s, 3H), 0.68 – 0.57 (m, 4H), 0.03 (s, 6H); ^{13}**C NMR** (151 MHz, CDCl$_3$) δ 207.38, 141.35, 114.07, 79.37, 77.37, 77.16, 76.95, 61.42, 59.07, 55.39, 51.63, 42.15, 39.72, 39.53, 38.76, 37.71, 36.16, 28.57, 27.82, 27.61, 26.05, 20.34, 18.26, 18.25, 17.93, 17.52, 16.77, 16.01, 12.64, 7.29, 7.28, 3.22, 3.21, −3.63, −4.80; **HRMS** (ESI) m/z Calcd for C$_{35}$H$_{67}$O$_3$Si$_2$ [M+H]$^+$ 591.4629, found 591.4633.

The crude diethylisopropylsilyl ether above was azeotropically dried using PhMe (5 mL), dissolved in Et$_2$O, and cooled to −78 °C. MeLi (1 M in Et$_2$O, 2.16 mL, 2.16 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 2 h at −78 °C. The reaction was quenched by adding AcOH (180 µl, 3.0 mmol) then the Et$_2$O was removed using a stream of N$_2$, and the resulting crude secondary alcohol was dried under high vacuum, then used without further purification.

The crude secondary alcohol above was dissolved in CH$_2$Cl$_2$ (25 mL). NaHCO$_3$ (910 mg, 10.8 mmol, 10 equiv) and Dess–Martin periodinane (458 mg, 1.08 mmol, 1.0 equiv) were added promptly. The reaction mixture was stirred for 30 min and quenched by addition of 20% aq Na$_2$S$_2$O$_3$ (25 mL) and saturated NaHCO$_3$ (25 mL). The mixture was stirred for 40 min, then extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined CH$_2$Cl$_2$ extracts were dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by automated SiO$_2$ column chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 40 g column, 1–60% EtOAc in hexanes) to yield methyl ketone **25** (554 mg, 87%) as a white solid. **TLC** R_f 0.28 (hexanes:CH$_2$Cl$_2$ 1:1); [α]$_D^{22}$ +4.7 (c 1.00, C$_6$H$_6$); **FTIR** (NaCl film) 2876, 1632,

1430, 1359, 1215, 1069, 974, 835, 813, 726, 716; **^{1}H NMR** (600 MHz, CDCl$_3$) δ 5.88 (ddd, J = 17.1, 10.5, 6.4 Hz, 1H), 4.90 (dt, J = 17.4, 1.7 Hz, 1H), 4.80 (dt, J = 10.5, 1.7 Hz, 1H), 4.25 (dd, J = 10.7, 1.2 Hz, 1H), 4.16 (d, J = 10.7 Hz, 1H), 3.18 (dd, J = 11.4, 4.6 Hz, 1H), 3.13 – 3.03 (m, 1H), 2.13 (s, 3H), 1.91 (td, J = 13.0, 4.0 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.67 (dt, J = 13.0, 3.6 Hz, 1H), 1.61 – 1.34 (m, 10H), 1.05 (dd, J = 12.6, 2.9 Hz, 1H), 1.02 – 0.95 (m, 12H), 0.93 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.82 (s, 3H), 0.72 (s, 3H), 0.70 – 0.61 (m, 5H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 210.82, 142.68, 112.55, 79.30, 77.37, 77.16, 76.95, 64.08, 61.06, 55.12, 51.58, 41.32, 39.97, 39.51, 38.93, 37.81, 37.33, 31.97, 28.55, 27.88, 27.64, 26.04, 20.46, 18.77, 18.25, 18.12, 17.64, 17.63, 16.59, 16.08, 12.63, 7.41, 7.40, 3.28, −3.61, −4.76; **HRMS** (ESI) m/z Calcd for C$_{36}$H$_{69}$O$_3$Si$_2$ [M +H]$^+$ 605.4785, found 605.4796.

4.13. Keto-aldehyde 26

Keto-alkene **25** (160 mg, 0.282 mmol, 1 equiv) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue color appeared (~3 min). The reaction mixture was stirred for 15 min, then N$_2$ was bubbled through the solution to remove excess ozone. Solid Ph$_3$P (81.4 mg, 0.310 mmol, 1.1 equiv) was then added and reaction was stirred for 24 h at rt, then concentrated. Purification by automated SiO$_2$ column chromatography (Isco CombiFlash Rf: 10 g solid loading cartridge, 40 g column, 1–60% EtOAc in hexanes) yielded keto-aldehyde **26** (100 mg, 65%) as a white solid. **TLC R$_f$** 0.17 (CH$_2$Cl$_2$) [α]$_D^{19}$ +39.1 (c 1.00, C$_6$H$_6$); **^{1}H NMR** (600 MHz, CDCl$_3$) δ 9.40 (s, 1H), 4.42 (d, J = 10.2 Hz, 1H), 4.09 (d, J = 10.2 Hz, 1H), 3.20 (dd, J = 11.4, 4.6 Hz, 1H), 3.12 (dd, J = 12.1, 4.1 Hz, 1H), 2.29 (s, 3H), 2.13 (ddd, J = 10.1, 4.3, 2.6 Hz, 1H), 1.67 (dtq, J = 20.2, 7.9, 4.2 Hz, 4H), 1.62 – 1.47 (m, 5H), 1.47 – 1.23 (m, 4H), 1.04 – 0.98 (m, 1H), 0.98 – 0.93 (m, 17H), 0.91 (s, 3H), 0.88 (s, 10H), 0.83 (s, 3H), 0.72 (s, 3H), 0.68 (dd, J = 12.3, 2.0 Hz, 1H), 0.62 (dqd, J = 10.3, 7.9, 2.2 Hz, 4H), 0.03 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 211.31, 203.00, 79.11, 77.37, 77.16, 76.95, 65.58, 60.80, 55.32, 52.55, 48.30, 41.07, 39.54, 39.02, 37.97, 37.77, 30.78, 28.49, 27.82, 26.03, 21.29, 19.89, 18.76, 18.34, 18.25, 17.46, 17.45, 16.81, 16.07, 12.37, 7.24, 7.13, 3.02, 3.00, −3.59, −4.74; **HRMS** (ESI) m/z Calcd for C$_{35}$H$_{67}$O$_4$Si$_2$ [M+H]$^+$ 607.4578, found 607.4562.

4.14. Triene 28

To a solution of phosphonate **27** (150 mg, 0.63 mmol, 2.5 equiv) in THF (8 mL) cooled to −78 °C was added LiHMDS (85 mg, 0.51 mmol, 2.0 equiv). The resulting orange solution was stirred for 35 min at −78 °C. In a separate flask, aldehyde **26** (150 mg, 0.25 mmol, 1.0 equiv.) was azeotropically dried with toluene (5 mL), then dissolved in THF (7 mL) and cooled to −78 °C. The phosphorous ylide solution was added to the aldehyde solution via cannula. The resulting solution was stirred for 4 h at −78 °C, by which time TLC analysis indicated complete conversion. The reaction was quenched by addition of satd aq NaHCO$_3$ (3 mL). The resulting mixture was diluted with Et$_2$O (100 mL), washed with brine (20 mL), dried over MgSO$_4$, filtered, and concentrated. The residue was purified by automated column chromatography (Isco CombiFlash Rf: basic Al$_2$O$_3$, 10 g solid loading cartridge, 40 g column, 1–15% EtOAc in hexanes) to yield triene **28** (220 mg, 63%) as a colorless oil. **TLC R$_f$** 0.44 (hexanes:EtOAc 25:1); **FTIR** (NaCl film) 2951, 1696, 1462, 1388, 1359,

1253, 1100, 1068, 1009, 956, 884, 835, 774, 732; **^{1}H NMR** (600 MHz, C_6D_6) *For (Z)-eno lether isomer:* δ 6.89 (dd, J = 15.2, 11.2 Hz, 1H), 6.09 (d, J = 15.1 Hz, 1H), 6.01 (d, J = 11.2 Hz, 1H), 5.94 (d, J = 9.7 Hz, 1H), 4.54 (s, 2H), 3.95 (ddd, J = 13.5, 9.8, 4.4 Hz, 1H), 3.80 (s, 3H), 3.12 (dd, J = 11.5, 4.3 Hz, 1H), 2.27 (s, 3H), 2.04 – 1.89 (m, 2H), 1.84 (qd, J = 13.2, 4.9 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.65 (s, 2H), 1.63 (s, 4H), 1.61 (d, J = 3.2 Hz, 1H), 1.56 – 1.35 (m, 6H), 1.27 (ddd, J = 12.4, 8.9, 3.3 Hz, 2H), 1.10 – 1.00 (m, 30H), 0.98 (s, 3H), 0.89 (s, 1H), 0.86 (s, 3H), 0.76 (s, 1H), 0.73 (s, 3H), 0.71 – 0.57 (m, 5H), 0.09 (s, 4H), 0.07 (s, 3H); **^{13}C NMR** (151 MHz, C_6D6) *For (Z) enol ether isomers*: δ 209.38, 154.14, 135.43, 128.35, 128.22, 128.14, 128.06, 127.98, 127.90, 126.62, 125.96, 125.10, 122.74, 79.64, 63.01, 62.44, 59.11, 55.71, 52.20, 42.03, 39.69, 39.09, 37.97, 37.96, 37.07, 35.54, 31.67, 30.81, 28.73, 28.27, 26.22, 26.21, 26.15, 21.38, 18.98, 18.63, 18.42, 18.39, 17.78, 17.73, 16.76, 16.37, 13.00, 7.58, 7.56, 7.54, 3.58, 3.52, −3.58, −3.59, −4.67; **HRMS** (ESI) m/z Calcd for $C_{43}H_{79}O_4Si_2$ [M+H]$^+$, 715.5517 found 715.5524.

4.15. Diazoketone 29

Methyl ketone **28** (50 mg, 0.071 mmol, 1.0 equiv) was dissolved in THF (8 mL) in a sealed tube and cooled to 0 °C. NaH (12 mg, 0.20 mmol, 7.0 eqiuv) and ethyl formate (250 μL, 3.10 mmol, 44 equiv.) were added and the reaction vessel was sealed and heated to 45 °C for 24 h, by which point TLC analysis (basic alumina, hexanes:EtOAc 5:1) indicated complete conversion. The volatiles were removed under high vacuum. The residue was dissolved in EtOH/CH_3CN (8 mL/6 mL) and $AcNHPhSO_2N_3$ (72 mg, 2.840 mmol, 4.0 equiv.) was added at rt. The reaction mixture was stirred for 3 h, diluted with Et_2O (100 mL), and washed with brine (2x 20 mL) and water (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (toluene then toluene:EtOAc 10:1) afforded diazoketone **29** (37 mg, 71%) as a yellow oil. **TLC R_f** 0.43 (hexanes:EtOAc 25:1); **FTIR** (NaCl film) 2952, 2096, 1625, 1462, 1359, 1251, 1100, 1070, 884, 835, 773, 725; **^{1}H NMR** (600 MHz, C_6D_6) δ 6.88 (dd, J = 15.1, 11.2 Hz, 1H), 6.16 (s, 1H), 6.07 (d, J = 15.1 Hz, 1H), 5.97 (t, J = 11.3 Hz, 2H), 4.62 (d, J = 10.6 Hz, 1H), 4.58 (d, J = 10.5 Hz, 1H), 3.61 (s, 3H), 3.47 (ddd, J = 12.4, 10.5, 4.3 Hz, 1H), 3.17 (dd, J = 11.4, 4.8 Hz, 1H), 2.13 – 1.73 (m, 5H), 1.67 – 1.64 (m, 3H), 1.63 (s, 3H), 1.61 – 1.40 (m, 3H), 1.38 (s, 3H), 1.15 (s, 3H), 1.12 – 1.05 (m, 15H), 1.03 (s, 10H), 0.99 (s, 3H), 0.88 (s, 3H), 0.85 – 0.62 (m, 10H), 0.11 (s, 3H), 0.09 (s, 3H); **^{13}C NMR** (151 MHz, C_6D6) δ 196.58, 153.22, 136.15, 128.35, 128.22, 128.14, 128.06, 127.98, 127.90, 126.00, 125.73, 125.42, 123.05, 79.75, 62.99, 61.58, 59.74, 55.76, 55.53, 52.39, 42.40, 39.72, 39.16, 38.06, 36.76, 35.05, 31.73, 30.49, 28.71, 28.35, 26.27, 26.22, 26.20, 26.14, 21.42, 18.98, 18.81, 18.43, 18.38, 17.80, 17.77, 17.69, 16.98, 16.38, 13.09, 13.08, 7.58, 7.52, 7.47, 7.45, 3.64, 3.57, 3.47, −3.58, −4.65, −4.66; **HRMS** (ESI) m/z Calcd for $C_{43}H_{77}O_4Si_2$ [M+H]$^+$ 763.5241 found 763.5240.

4.16. Bis(enol ether) 31

A solution of diazoketone **29** (3.5 mg, 0.0048 mmol, 1.0 equiv) in C_6D_6 (0.6 mL) was irradiated in a photobox using UV-B lights (centered at 310 nm) for 20 min, by which time ^{1}H-NMR analysis of the crude reaction mixture indicated complete conversion. The resulting bis(enol ether) **31** was not stable to purification and was not fully characterized.

4.17. Bis(enol ether) 34

A solution of diazoketone **33** (11.5 mg, 0.0167 mmol, 1.0 equiv) (see Supporting Information) in C_6D_6 (1.5 mL) was irradiated in a photobox using UV-B lights (centered at 310 nm) for 20 min, by which time ^{1}H-NMR analysis of the crude reaction mixture indicated complete conversion. The reaction mixture was concentrated and purified by basic Al_2O_3 column chromatography (hexanes:EtOAc 100:1) to give bis(enol ether) **34** (7.4 mg, 67 %) as a colorless oil. **TLC R$_f$** 0.24 (hexanes:EtOAc 100:1); **FTIR** (NaCl film) 2935, 1641, 1462, 1386, 1221, 1064, 883, 835, 772, 728; **^{1}H NMR** (600 MHz, C_6D_6) δ 5.23 (d, J = 1.8 Hz, 1H), 4.47 (dt, J = 13.7, 2.5 Hz, 1H), 4.37 (ddd, J = 13.8, 3.5, 2.2 Hz, 1H), 4.18 (d, J = 10.3 Hz, 1H), 4.13 (q, J = 2.9 Hz, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.40 (dt, J = 10.9, 2.1 Hz, 1H), 3.15 (s, 3H), 3.15 (m, 1H), 2.36 (td, J = 13.2, 12.5, 7.6 Hz, 2H), 1.94 (td, J = 13.0, 3.8 Hz, 1H), 1.74 – 1.54 (m, 6H), 1.54 – 1.15 (m, 9H), 1.13 – 1.04 (m, 18H), 1.03 (s, 9H), 1.00 (s, 3H), 0.98 – 0.91 (m, 1H), 0.90 (s, 3H), 0.89 – 0.79 (m, 5H), 0.76 (s, 3H), 0.72 – 0.60 (m, 4H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (151 MHz, C$_6$D6) δ 157.54, 156.89, 128.44, 128.36, 128.32, 128.20, 128.07, 127.99, 127.96, 127.91, 127.86, 127.83, 127.75, 127.58, 127.46, 106.19, 89.98, 79.68, 67.17, 63.75, 56.53, 56.31, 53.88, 52.14, 47.81, 43.17, 40.31, 39.74, 38.85, 37.66, 36.18, 31.84, 28.66, 28.24, 26.08, 25.61, 22.93, 22.59, 18.93, 18.86, 18.28, 17.64, 17.60, 16.28, 16.14, 14.24, 13.10, 7.42, 3.52, 3.47, −3.70, −4.80; **HRMS** (ESI) m/z Calcd for $C_{39}H_{71}O_4Si_2$ [M+H]$^+$ 659.4891 found 659.4883.

4.18. Bis(enol ether) 36

A solution of diazoketone **35** (10.6 mg, 0.0125 mmol, 1.0 equiv) (see Supporting Information) in C_6D_6 (1.5 mL) was irradiated in a photobox using UV-B lights (centered at 310 nm) for 20 min, by which time ^{1}H-NMR analysis of the crude reaction mixture indicated complete conversioon. The reaction mixture was concentrated and purified by basic Al_2O_3 column chromatography (hexanes:EtOAc 100:1) to give bis(enol ether) **36** (7.2 mg, 70 %) as a colorless oil. **TLC R$_f$** 0.11 (hexanes:EtOAc 100:1); [α]$_D^{20}$ +39.7 (c 0.95, C_6H_6); **FTIR** (NaCl film) 2950, 1651, 1463, 1386, 1250, 1218, 1187, 1146, 1103, 1062, 883, 835, 773, 730; **^{1}H NMR** (600 MHz, C_6D_6) δ 7.41 – 7.37 (m, 2H), 7.21 (t, J = 7.7 Hz, 2H), 7.13 – 7.10 (m, 1H), 5.20 (d, J = 2.1 Hz, 1H), 5.14 – 5.08 (m, 1H), 4.46 (dd, J = 3.2, 1.9 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.33 (d, J = 11.3 Hz, 1H), 4.19 (d, J = 10.4 Hz, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.40 – 3.33 (m, 1H), 3.17 (s, 3H), 3.17 (m, 1H), 2.39 – 2.30 (m, 2H), 2.10 (dd, J = 14.7, 7.9 Hz, 1H), 1.97 (td, J = 13.1, 3.8 Hz, 1H), 1.89 (dd, J = 14.6, 3.6 Hz, 1H), 1.74 – 1.43 (m, 11H), 1.41 (s, 4H), 1.25 (s, 3H), 1.17 – 1.04 (m, 18H), 1.02 (s, 10H), 1.00 (s, 3H), 0.98 – 0.92 (m, 1H), 0.90 (s, 3H), 0.89 – 0.80 (m, 3H), 0.77 (s, 3H), 0.72 – 0.58 (m, 4H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** (151 MHz, C$_6$D6) δ 158.07, 155.92, 140.50, 128.47, 128.35, 128.22, 128.14, 128.10, 128.06, 127.98, 127.90, 127.59, 127.28, 107.00, 96.27, 79.83, 74.59, 73.86, 63.88, 56.89, 56.69, 54.05, 52.32, 48.08, 48.04, 43.36, 40.41, 39.89, 39.00, 37.83, 36.40, 28.81, 28.38, 27.07, 26.23, 25.72, 25.34, 22.74, 19.10, 19.01, 18.43, 17.80, 17.78, 16.43, 16.29, 13.26, 7.59, 3.70, 3.64, −3.55, −4.65; **HRMS** (ESI) m/z Calcd for $C_{50}H_{85}O_5Si_2$ [M+H]$^+$ 821.5936 found 821.5959.

4.19. Keto-ketal 38

To the solution of bis(enol ether) **34** (7 mg, 0.0106 mmol) in THF (1 mL) was added TBAF (1 M in THF, 16 μl, 0.016 mmol, 1.5 equiv). The reaction mixture was stirred at rt for 16 h, then diluted with Et_2O (100 mL), washed with satd aq $NaHCO_3$ (5 x 10 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concentrated to give the crude alcohol **37** (6.9 mg, 100%), which was used without further purification.

To the solution of the crude alcohol **37** above (3.6 mg, 0.0068 mmol, 1.0 equiv) in wet CH_2Cl_2 (1 mL) was added Amberlyst-15 (1 mg). The reaction mixture was stirred for 20 min at rt then quenched by addition of Et_3N (10 μl). The mixture was diluted with Et_2O (100 mL), washed with satd aq $NaHCO_3$ (5x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes:EtOAc 5:1) to afford keto-ketal **38** (1.8 mg, 50%) as a white solid. **TLC** *Rf* 0.26 (hexanes:EtOAc 10:1); **FTIR** (NaCl film) 2949, 1721, 1463, 1387, 1253, 1108, 1003, 883, 836, 773, 737; **^{1}H NMR** (600 MHz, C_6D_6) δ 4.04 (dd, *J* = 7.8, 2.1 Hz, 1H), 4.00 (d, *J* = 7.7 Hz, 1H), 3.99 – 3.94 (m, 1H), 3.48 (dt, *J* = 12.0, 5.0 Hz, 1H), 3.12 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.68 (dddd, *J* = 12.3, 7.0, 4.6, 2.1 Hz, 1H), 2.18 (dd, *J* = 7.3, 1.6 Hz, 1H), 2.09 (ddd, *J* = 17.1, 8.9, 5.4 Hz, 1H), 1.91 (dtd, *J* = 11.9, 4.6, 2.1 Hz, 1H), 1.82 (dt, *J* = 17.0, 4.5 Hz, 1H), 1.64 – 1.55 (m, 2H), 1.52 – 1.08 (m, 17H), 1.04 (s, 9H), 0.96 (s, 3H), 0.86 (s, 3H), 0.82 (s, 3H), 0.65 (s, 3H), 0.58 (ddd, *J* = 22.6, 13.1, 3.5 Hz, 2H), 0.45 (dt, *J* = 9.4, 2.3 Hz, 1H), 0.13 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.47, 112.13, 79.59, 66.46, 62.89, 59.25, 55.87, 53.18, 52.90, 40.43, 39.76, 39.33, 38.58, 38.01, 37.31, 37.11, 35.80, 31.99, 28.73, 28.19, 27.07, 26.21, 23.08, 21.29, 18.60, 18.53, 18.43, 16.35, 16.30, 14.39, −3.50, −4.61.

4.20. Jujubogenin hexacyclic core (39)

To the solution of ketone **38** (0.5 mg, 0.001 mmol, 1.0 equiv) in Et_2O (0.3 mL) cooled to −78 C was added MeLi (1M, 5 μl, 0.005 mmol, 5.0 equiv). The reaction mixture was stirred for 30 min then diluted with Et_2O (100 mL) and washed with satd aq $NaHCO_3$ (30 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography to afford tertiary alcohol **39** (0.4 mg, 73%) as a white solid. **TLC** *Rf* 0.25 (hexanes:EtOAc 5:1); **^{1}H NMR** (600 MHz, C_6D_6) δ 4.09 (d, *J* = 1.7 Hz, 2H), 3.92 – 3.87 (m, 2H), 3.79 (ddd, *J* = 11.4, 4.7, 3.2 Hz, 1H), 3.13 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.40 – 2.31 (m, 1H), 2.05 (d, *J* = 8.5 Hz, 1H), 1.54 – 1.15 (m, 24H), 1.05 (s, 9H), 1.02 (s, 3H), 0.96 (s, 3H), 0.88 (s, 4H), 0.86 (s, 3H), 0.84 (s, 3H), 0.72 (s, 3H), 0.72 – 0.69 (m, 1H), 0.67 – 0.59 (m, 1H), 0.50 (dd, *J* = 11.5, 2.2 Hz, 1H), 0.14 (s, 3H), 0.13 (s, 3H); **HRMS** (ESI) *m/z* Calcd for $C_{32}H_{56}O_4SiNa$ [M+Na]$^+$ 555.3846, found 555.3852.

4.21. Keto-ketal 41

To a solution of bis(enol ether) **36** (12 mg, 0.015 mmol, 1 equiv) in THF (1 mL) was added TBAF (1M, 29 μl, 0.029 mmol, 2.0 equiv). The reaction mixture was stirred at rt for 16 h, then diluted with Et_2O (100 mL), and washed with satd aq $NaHCO_3$ (5 x 10 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concentrated to give the crude alcohol **40**, which was used without further purification.

To a solution of the crude alcohol **40** above (2.6 mg, 0.0038 mmol, 1.0 equiv) in wet CH_2Cl_2 (1 mL) was added dichloroacetic acid (0.1 mg, 0.0004 mmol, 0.1 equiv). The reaction mixture was stirred for 20 min at rt, then quenched by addition of Et_3N (10 µl). The mixture was diluted with Et_2O (100 mL), washed with satd aq $NaHCO_3$ (5x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography (hexanes:EtOAc 5:1) to afford keto-ketal **41** (1.6 mg, 63%) as a white solid. **TLC** *Rf* 0.26 (hexanes:EtOAc 7:1); $[\alpha]_D^{18}$ +17.0 (*c* 0.18, C_6H_6) **FTIR** (NaCl film) 2929, 2855, 1775, 1720, 1462, 1387, 1297, 1254, 1185, 1106, 930, 884, 836, 773, 735, 697 **¹H NMR** (600 MHz, C_6D_6) δ 7.42 – 7.36 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.86 (ddt, *J* = 11.1, 7.8, 3.2 Hz, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.24 (d, *J* = 11.4 Hz, 1H), 4.11 (dd, *J* = 7.8, 2.2 Hz, 1H), 4.03 (d, *J* = 7.7 Hz, 1H), 3.09 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.76 – 2.64 (m, 1H), 2.31 (dd, *J* = 7.4, 1.5 Hz, 1H), 2.18 (dd, *J* = 18.3, 11.1 Hz, 1H), 2.09 (dd, *J* = 18.3, 3.7 Hz, 1H), 1.89 (ddt, *J* = 11.1, 5.3, 2.6 Hz, 1H), 1.81 (dd, *J* = 9.3, 1.5 Hz, 1H), 1.76 (dd, *J* = 14.7, 7.8 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.49 – 1.30 (m, 9H), 1.30 – 1.18 (m, 3H), 1.16 (s, 4H), 1.04 (s, 9H), 0.93 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.65 (s, 3H), 0.63 – 0.53 (m, 2H), 0.44 (dd, *J* = 11.7, 2.5 Hz, 1H), 0.41 (s, 4H), 0.12 (d, *J* = 1.4 Hz, 6H); **¹³C NMR** (151 MHz, C_6D6) δ 207.01, 140.45, 128.50, 128.47, 128.35, 128.22, 128.14, 128.06, 127.98, 127.90, 127.73, 127.70, 127.61, 127.57, 127.46, 127.37, 111.50, 79.54, 74.46, 70.39, 66.53, 63.99, 58.57, 55.84, 53.18, 52.89, 47.31, 46.49, 40.82, 39.74, 38.59, 37.75, 37.30, 37.14, 35.81, 28.68, 28.19, 27.03, 26.79, 26.21, 25.06, 21.30, 18.57, 18.53, 18.43, 16.36, 16.33, −3.51, −4.60; **HRMS** (ESI) *m/z* Calcd for $C_{42}H_{66}O_5SiNa$ [M+Na]⁺ 701.4577, found 701.4543.

4.22. Diol 51

To the solution of ketone **41** (1.5 mg, 0.0022 mmol, 1.0 equiv) in Et_2O (0.3 mL) cooled to −78 C was added MeLi (1.2 M, 9.2 µl, 0.011 mmol, 5.0 equiv). The reaction mixture was stirred for 30 min then diluted with Et_2O (100 mL) and washed with satd aq $NaHCO_3$ (30 mL). The Et_2O layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by SiO_2 column chromatography to afford the corresponding tertiary alcohol (1.1 mg, 73%) as a white solid. **TLC** *Rf* 0.21 (hexanes:EtOAc 5:1); $[\alpha]_D^{18}$ +28.0 (*c* 0.12, C_6H_6) **FTIR** (NaCl film) 3427, 2927, 2855, 1670, 1458, 1387, 1255, 1095, 932, 884, 836, 773, 735, 969, 668; **¹H NMR** (600 MHz, C_6D_6) δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 4.49 – 4.41 (m, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.31 (d, *J* = 11.5 Hz, 1H), 4.15 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.03 (d, *J* = 7.7 Hz, 1H), 3.10 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.33 (dtd, *J* = 12.4, 4.9, 2.5 Hz, 1H), 1.91 – 1.82 (m, 2H), 1.78 – 1.66 (m, 3H), 1.66 – 1.49 (m, 4H), 1.49 – 1.19 (m, 17H), 1.03 (d, *J* = 8.1 Hz, 13H), 0.96 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.70 (s, 3H), 0.63 (dd, *J* = 12.6, 2.9 Hz, 2H), 0.51 – 0.47 (m, 1H), 0.13 (s, 6H); **¹³C NMR** (151 MHz, C_6D6) δ 140.70, 128.47, 128.44, 128.35, 128.22, 128.14, 128.11, 128.06, 127.98, 127.90, 127.73, 127.61, 127.57, 127.23, 109.92, 79.55, 74.86, 69.99, 68.42, 65.94, 63.92, 55.83, 53.32, 53.14, 53.11, 47.98, 47.63, 40.28, 39.76, 38.66, 38.44, 37.34, 37.32, 36.01, 28.69, 28.34, 28.23, 27.23, 26.96, 26.22, 25.12, 21.52, 18.70, 18.62, 18.43, 16.43, 16.40, −3.52, −4.59; **HRMS** (ESI) *m/z* Calcd for $C_{43}H_{71}O_5Si$ [M+H]⁺ 695.5071, found 695.5056.

To a solution of the tertiary alcohol above (1.1 mg, 0.0016 mmol, 1 equiv) in THF/EtOAc (0.5 mL/0.5 mL) was added Pd/C (10%, 2 mg, 0.0019 mmol, 1.2 equiv). The reaction was stirred under H_2 (balloon) atmosphere for 12 h, then filtered through a pad of celite and concentrated to give diol **51** (0.7 mg, 75%). **TLC** *Rf* 0.11 (hexanes:EtOAc 5:1); **FTIR** (NaCl film); 3412, 2949, 2853, 1433, 1218, 1109, 1087, 867 **^{1}H NMR** (600 MHz, Benzene-d_6) δ 4.33 (dddd, *J* = 11.5, 9.4, 6.9, 2.3 Hz, 1H), 4.07 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.98 (d, *J* = 7.7 Hz, 1H), 3.38 (s, 1H), 3.11 (dd, *J* = 11.5, 4.4 Hz, 1H), 2.28 (dddd, *J* = 9.4, 7.0, 4.9, 2.3 Hz, 1H), 1.81 – 1.74 (m, 2H), 1.68 – 1.52 (m, 4H), 1.49 – 1.15 (m, 18H), 1.04 (s, 9H), 1.03 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.88 (s, 3H), 0.70 (s, 3H), 0.66 – 0.57 (m, 2H), 0.50 (dd, *J* = 11.8, 2.3 Hz, 1H), 0.13 (s, 6H); **^{13}C NMR** (151 MHz, C$_6$D6) δ 109.56, 79.53, 70.13, 69.98, 69.60, 66.06, 55.84, 53.35, 53.10, 53.08, 48.27, 46.84, 39.95, 39.77, 38.66, 38.42, 37.31, 37.30, 36.03, 31.15, 28.97, 28.70, 28.34, 28.23, 27.35, 26.22, 21.50, 18.63, 18.62, 18.43, 16.43, 16.40, −3.52, −4.59; **HRMS** (ESI) *m/z* Calcd for $C_{36}H_{65}O_5Si$ [M+H]$^+$ 605.4601, found 605.4611.

4.23. 3-O-TBS-23-epi-jujubogenin (52)

To a solution of diol **51** (0.7 mg, 0.0012 mmol, 1 equiv) in CH_2Cl_2 (0.3 mL) cooled to 0 °C, was added Martin sulfurane (1.1 mg, 0.0014 mmol, 1.2 equiv). The reaction was stirred for 30 min then quenched with satd aq NaHCO$_3$ (3 drops) and 20% aq Na$_2$S$_2$O$_3$ (3 drops). The mixture was diluted with CH_2Cl_2 (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by SiO$_2$ column chromatography (CH_2Cl_2) to afford 3-*O*-TBS-23-*epi*-jujubogenin **52** (0.3 mg, 43%). **TLC** *Rf* 0.18 (CH_2Cl_2); **FTIR** (NaCl film) 3422, 2953, 1653, 1447, 1226, 1128 1015, 9, 821 **^{1}H NMR** (600 MHz, C$_6$D$_6$) δ 5.32 (d, *J* = 8.0 Hz, 1H), 4.90 (q, *J* = 8.1 Hz, 1H), 4.16 (dd, *J* = 7.8, 2.1 Hz, 1H), 4.06 (d, *J* = 7.7 Hz, 1H), 3.13 (dd, *J* = 11.6, 4.3 Hz, 1H), 2.37 (dt, *J* = 12.2, 5.7 Hz, 1H), 1.86 (d, *J* = 8.8 Hz, 1H), 1.80 (d, *J* = 13.3 Hz, 1H), 1.71 (d, *J* = 8.7 Hz, 1H), 1.68 (s, 0H), 1.62 (s, 4H), 1.59 (s, 3H), 1.55 – 1.13 (m, 58H), 1.09 (s, 3H), 1.05 (s, 10H), 0.97 (s, 4H), 0.95 (s, 3H), 0.88 (s, 3H), 0.71 (s, 3H), 0.64 (dtd, *J* = 12.7, 7.5, 6.6, 3.8 Hz, 2H), 0.50 (d, *J* = 11.5 Hz, 1H), 0.13 (d, *J* = 2.7 Hz, 6H); **^{13}C NMR** (151 MHz, C$_6$D6) δ 109.73, 79.62, 70.01, 68.47, 66.07, 55.88, 53.69, 53.13, 53.08, 46.81, 40.34, 39.78, 38.68, 38.56, 37.32, 37.31, 35.95, 32.38, 30.25, 28.74, 28.45, 28.24, 27.15, 26.23, 25.66, 21.53, 18.68, 18.60, 18.51, 18.44, 16.43, 16.38, 14.43, −3.50, −4.59; **HRMS** (ESI) *m/z* Calcd for $C_{36}H_{63}O_4Si$ [M+H]$^+$ 587.4496, found 587.4501.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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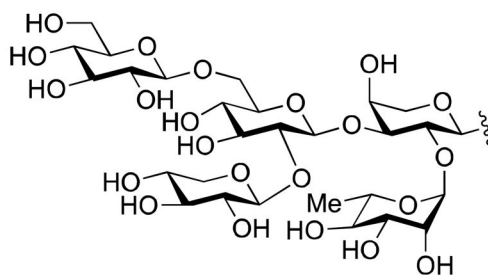62. Jung ME, Duclos BA. Tetrahedron. 2006; 62(40):9321–9334.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https\\:. These data include experimental details of synthesis of ketone **16** from Wieland Miescher ketone **9** and synthesis of the diazoketones **13**, **33** and **35**.
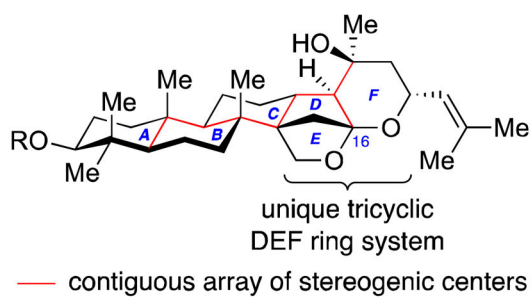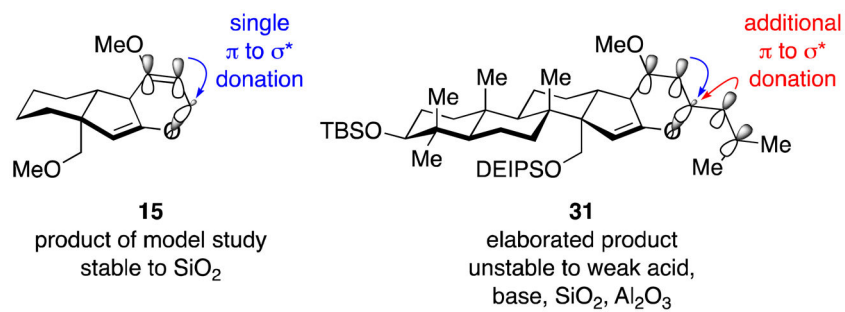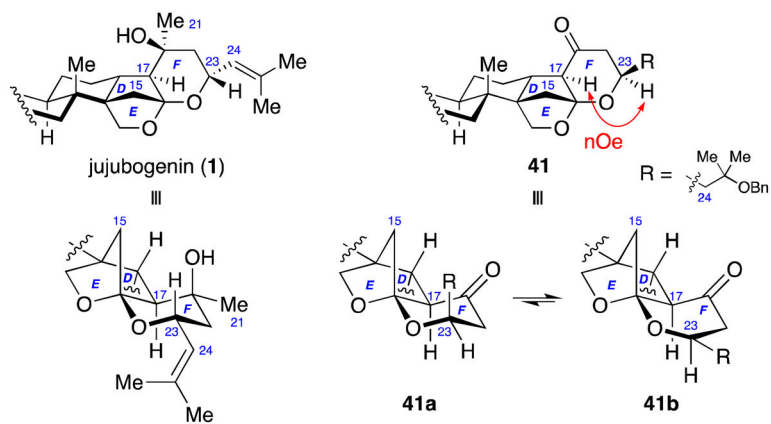
Figure 1.
Structures of jujubogenin (**1**) and jujuboside A (**2**).
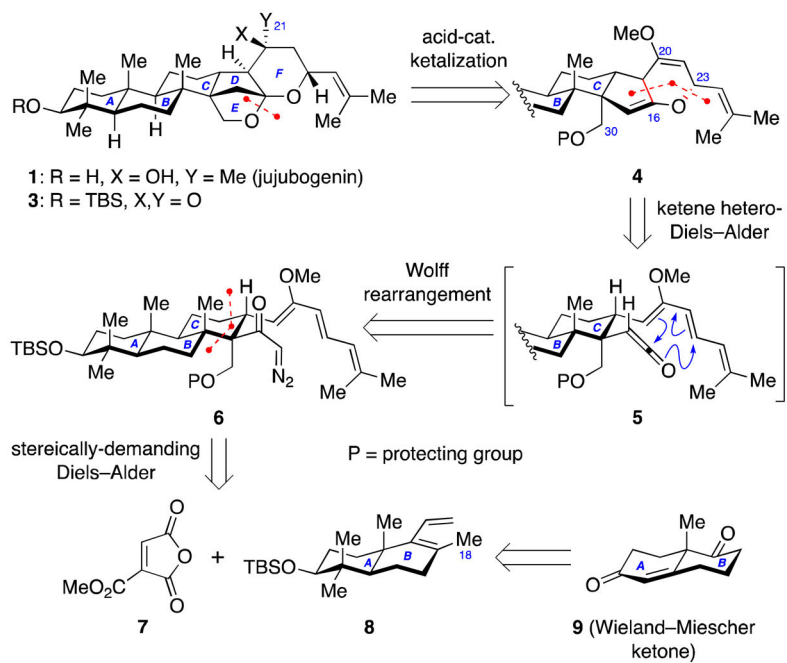
Figure 2.
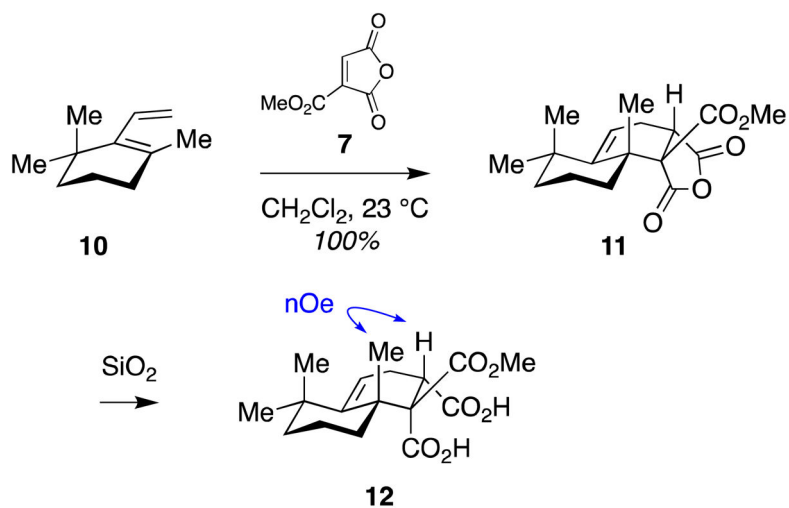Comparison of tandem Wolff rearrangement–ketene hetero-Diels–Alder products **15** and **31**.

Figure 3.
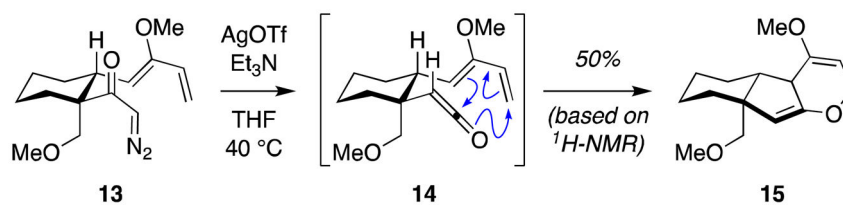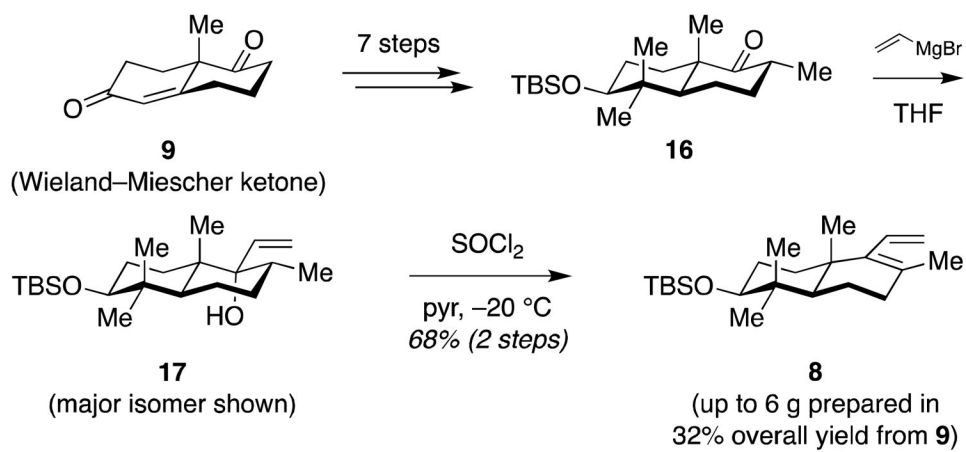Stereochemical assignment of ketone **41**.

Scheme 1.
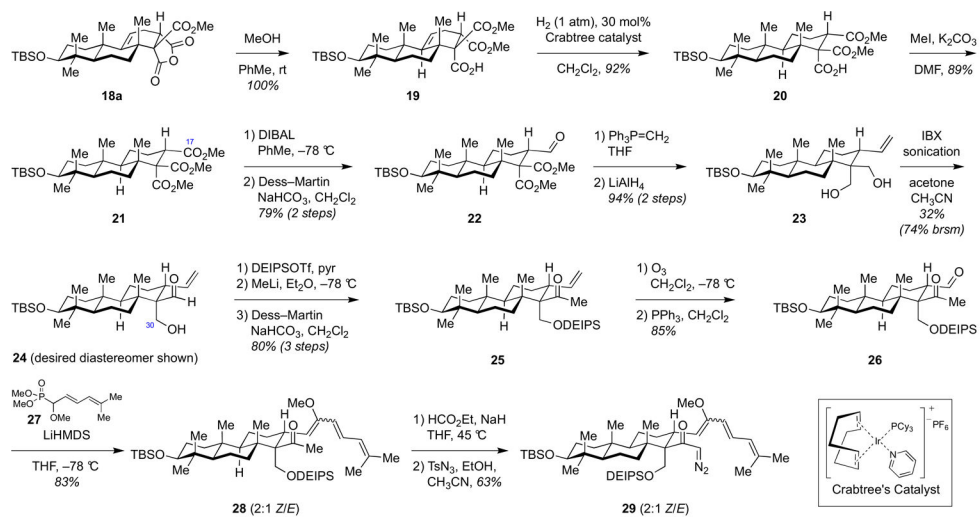Retrosynthetic analysis of jujubogenin (**1**).

Scheme 2.
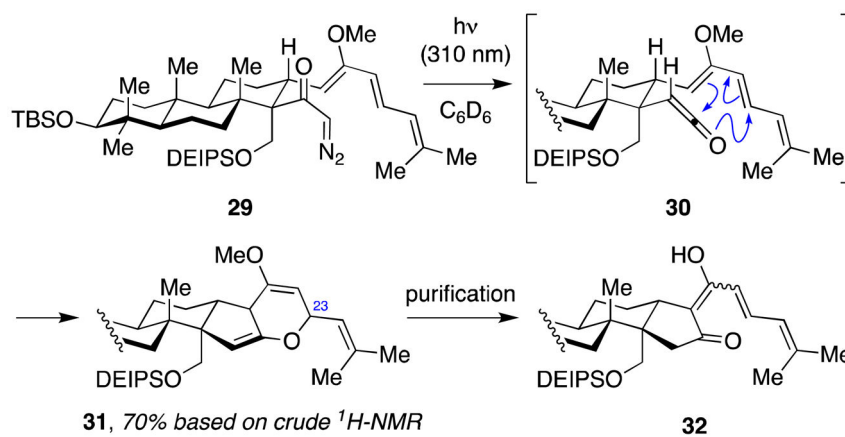Model study of sterically-demanding Diels–Alder reaction.

Scheme 3.
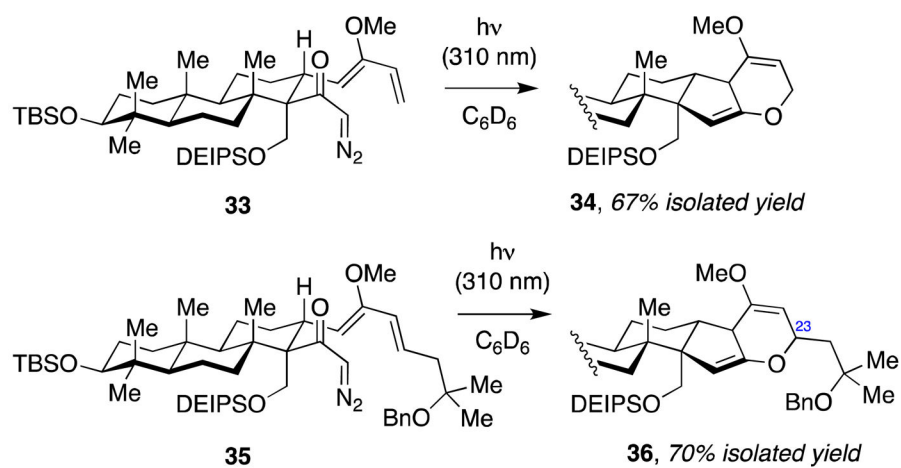Model study of tandem Wolff rearrangement–intramolecular hetero-[4+2] cycloaddition across ketene C=O bond.

Scheme 4.
Synthesis of diene **8** from the Wieland–Miescher ketone (**9**).

Scheme 5.
Elaboration of jujubogenin C-ring from anhydride **18a** to generate α-diazoketone **29**.

Scheme 6.
Tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reaction of α-diazoketone **29**

Scheme 7.
Tandem Wolff rearrangement–intramolecular ketene hetero-Diels–Alder reactions of
alternative α-diazoketone substrates **33** and **35**
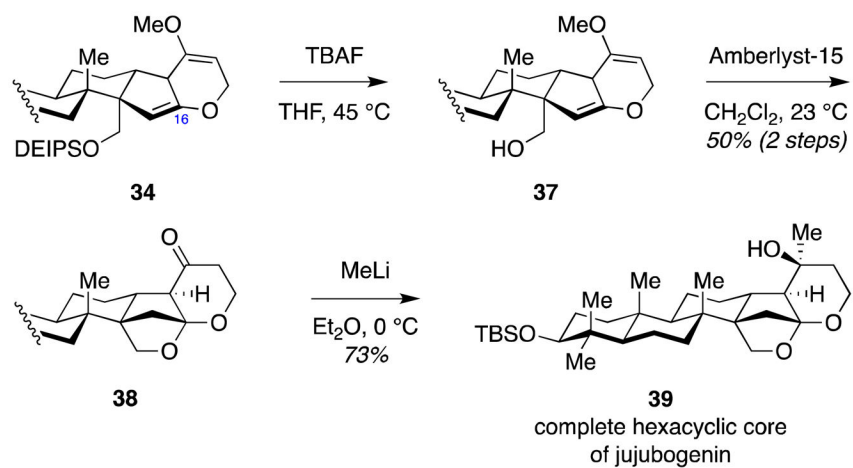
Scheme 8.
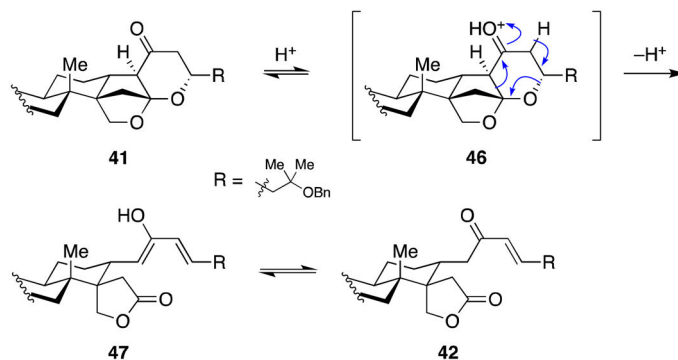Completion of the hexacyclic core of jujubogenin via formation of the C16 ketal.
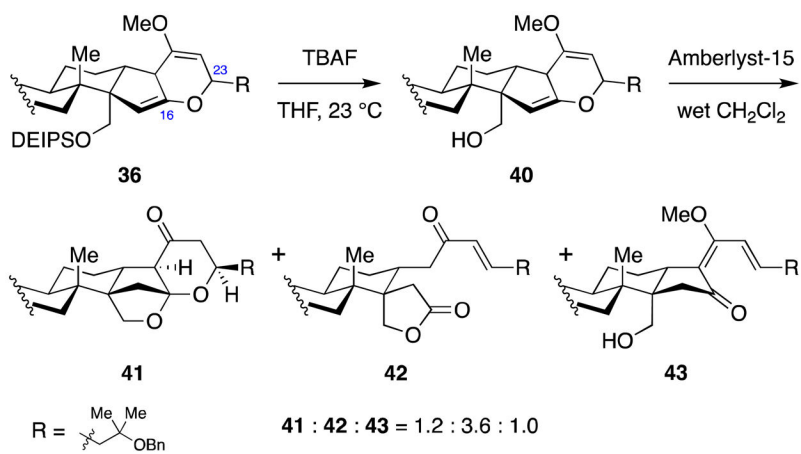
Scheme 9.
Attempted C16-ketalization of C23-substituted enol ether substrate **36**.

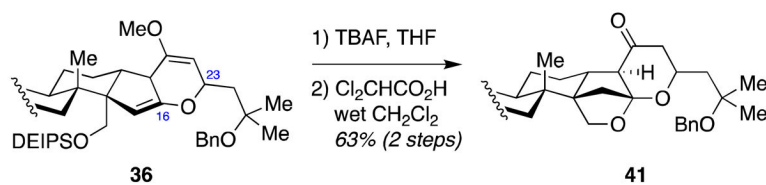**a)** Acid-catalyzed fragmentation of jujubogenin (**1**) reported by Kawai and coworkers (ref. 22)

jujubogenin (**1**)   **44**

ebelin lactone (**45**)

b) Proposed acid-catalyzed fragmentation of ketone **41**
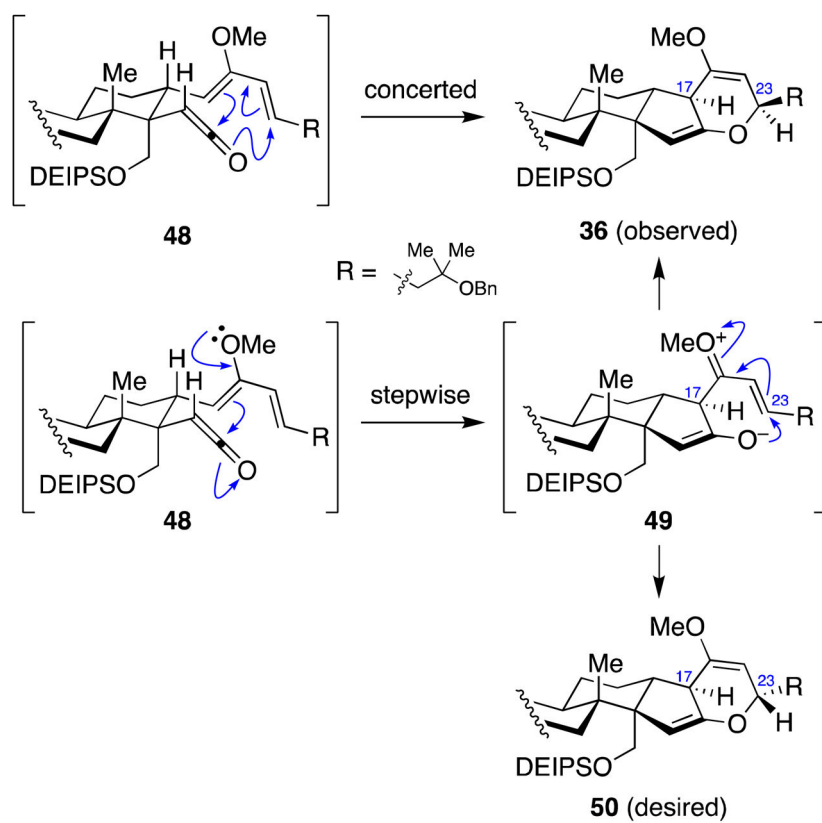
41   **46**

47   **42**
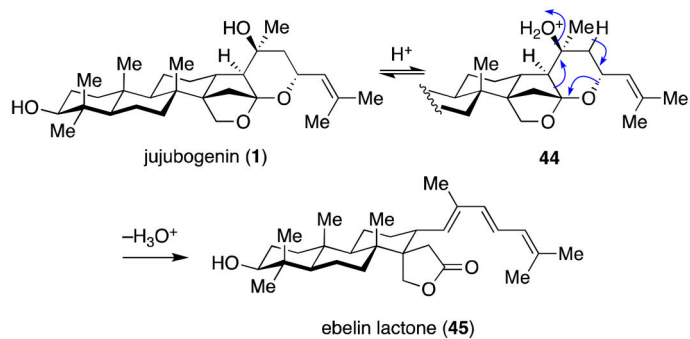
Scheme 10.

(a) Acid-catalyzed fragmentation of jujubogenin (**1**). (b) Proposed acid-catalyzed fragmentation of ketone **41**.
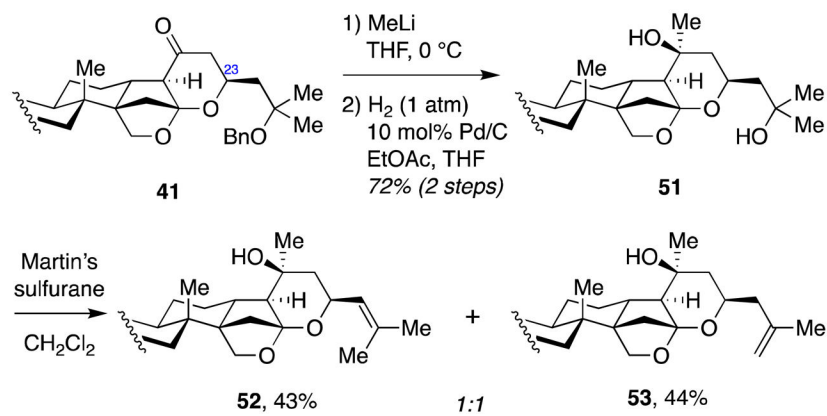
Scheme 11.
Sucessful C16-ketalization of C23-substituted enol ether substrate **36** with dichloroacetic acid (DCA).
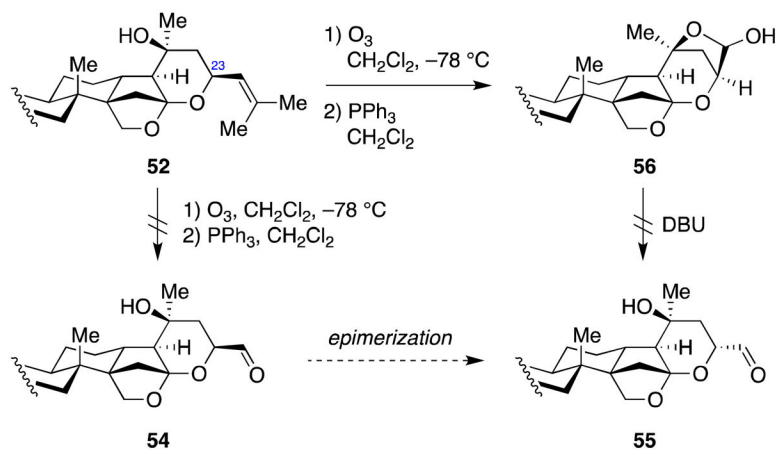
Scheme 12.
Predicted stereochemical outcomes at C23 depending on mechanism of the ketene hetero-Diels–Alder reaction.

Scheme 13.
Synthesis of C3-*O*-TBS protected 23-*epi*-jujubogenin (**52**)

Scheme 14.
Attemped epimerization of the C23 stereocenter via aldehyde **54**.

Table 1

Effect of solvents on diastereoselectivity of sterically-demanding Diels–Alder reaction of **7** and **8**.[a]

entry	solvent	18a: 18b
1	CH_2Cl_2	1.5: 1
2	THF	decomposition
3	Et_2O	2.2: 1
4	acetone	decomposition
5	EtOAc	2: 1
6	**PhH**	**2.2: 1**[b]
7	PhMe	2: 1
8	CF_3Ph	1.8: 1
9	C_6F_6	1.85: 1
10	mesytylene	2: 1
11	pentane	2: 1

[a]All reactions were carried out with 0.2 mmol of diene **8** and 0.22 mmol of dienophile **7** in 1mL of the solvent at ambient temperature. Ratios of products was determined by 1H NMR analysis of the crude reaction mixtures.

[b]54% isolated yield of **18a**.