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Synthesis of Mulinane Diterpenoids

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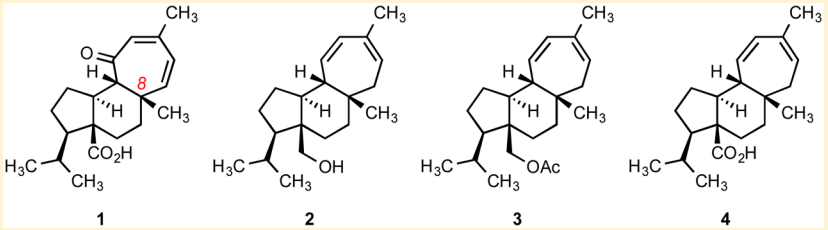
Supporting Information



ABSTRACT: The mulinane class of diterpenoids is a set of tricyclic (5-6-7), biologically active natural products whose members exhibit a variety of oxidation states. Herein, we report the inaugural synthesis of four mulinanes employing a divergent approach that relies on a diastereoselective anionic oxy-Cope rearrangement to set the relative configuration of the C8 stereocenter and an unprecedented vinylogous Saegusa dehydrogenation reaction to address C-ring functionality.

The mulinane diterpenoids comprise a family of natural products isolated from South American flowering shrubs of the *Mulinum*,[1−8] *Azorella*,[9−27] and *Laretia*[28] genera. Extracts from these plants have been used in traditional folk medicine to treat a wide variety of ailments. Preliminary biological assays indicate that several members of this class exhibit desirable physiological effects. For example, studies have shown that certain members are antitrypanosomal and thus have potential in the study or treatment of Chagas disease.[19] Also, one recent report describes the gastroprotective (antiulcer) properties of these agents.[27] Additionally, a pair of reports indicate that these secondary metabolites and synthetic derivatives thereof are potential antitubercular agents.[7,8] Other studies of bioactivity have appeared.[18,22−24]

Structurally, the mulinanes are similar to the cyathane family of natural products in that they comprise a tricyclic array of fused five-, six-, and seven-membered rings with an angular substituent at each of the ring fusions (see Figure 1).[29,30] However, the two families bear significant differences. Although both derive from geranylgeranyl diphosphate, cyathane biosynthesis is believed to involve a hydroazulene-like cation that undergoes expansion to a 6-7 bicycle and subsequent cationic cyclopentane formation.[31] In contrast, the mulinanes likely derive from labdanes via A-ring contraction and formation of the cycloheptane via cationic cyclization.[1] Consequently, the peripheral location of the isopropyl fragment differs between the families (compare the mulinanes to cyanthiwigin F, **7**). An alternative biosynthetic hypothesis involving transannular cyclization of a neodolabellane is also a possibility, although the methyl groups in the macrocyclic ring (e.g., see **8**) do not correlate with the positions of these groups in the mulinanes.[32−34]

Here, we describe the syntheses of mulinane diterpenoids **1**−**4**,[5,14,20,27] constituting the first synthesis of any member of this natural product family. Our strategy sets the relative configuration at C8 using a diastereoselective anionic oxy-Cope rearrangement and diverges at a late stage to address variable oxidation states at C20 and within the C-ring.

Our synthesis begins with the β-keto ester **9** (see Scheme 1).[35] The Michael reaction of the potassium enolate of **9** and methyl vinyl ketone (MVK) proceeded with complete diastereoselectivity (see Scheme 1). A subsequent aldol condensation under acid catalysis gave enone **10**, comprising an overall Robinson annulation and establishing one of the two all-carbon quaternary stereocenters found in structures **1**−**4**. Next, treatment of intermediate **10** with Stiles' reagent (methyl magnesium carbonate[36]) in DMF at 130 °C furnished a labile unsaturated β-keto acid[37,38] that was immediately esterified using ethereal diazomethane, giving ester **11**. All efforts to more rapidly form intermediate **11** or related structures using Nazarov's reagent[39] were unsuccessful, leading to complex mixtures. Pd-catalyzed heterogeneous hydrogenation of unsaturated ester **11** gave β-keto ester **12** with complete diastereoselectivity and established the *trans*-hydrindane core[38] of the mulinanes.

Further manipulation of diester **12** enabled the establishment of the second all-carbon quaternary stereocenter as follows. Treatment of this intermediate with sodium hydride and then diethyl chlorophosphate gave enol phosphate **13**. Subsequent nucleophilic methylation using lithium dimethylcuprate furnished enoate **14**, installing the C8 methyl group of the mulinanes.[40] Obtaining this intermediate presented the first opportunity to introduce the quaternary center at C8. However, given the well-documented difficulty of achieving nucleophilic conjugate addition to β,β-disubstituted conjugated unsaturated esters,[41] we considered other tactics. Thus, we explored setting the C8 quaternary stereocenter using an anionic oxy-Cope

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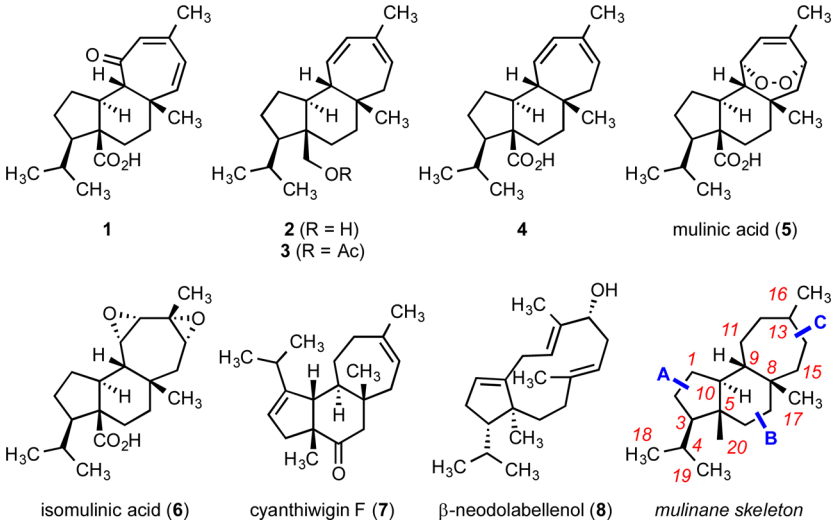
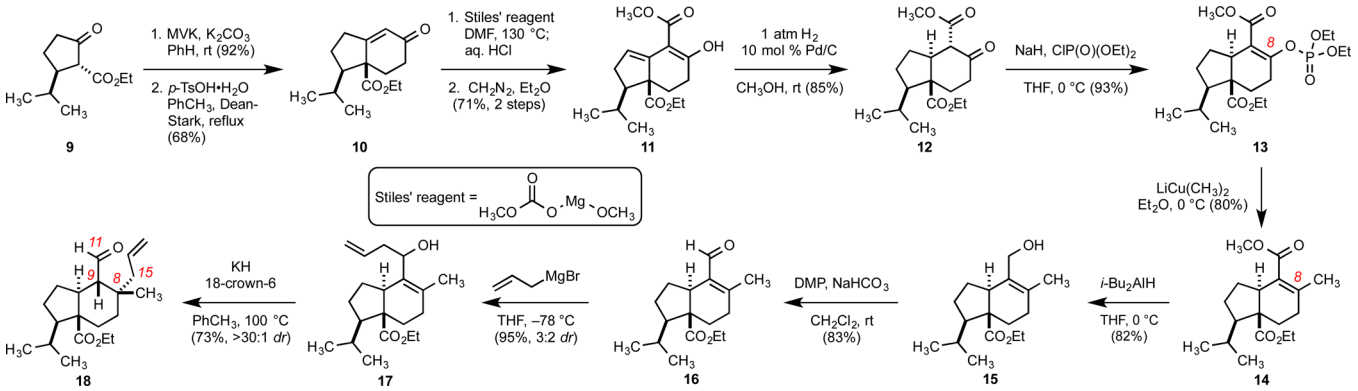


Figure 1. Representative mulinane diterpenoids, similar structures, and mulinane skeleton numbering.

Scheme 1. Synthesis of the Mulinane A-B Ring System and Anionic Oxy-Cope Rearrangement



rearrangement, reasoning that an intramolecular C−C bond forming event would stand a better chance in forming the congested C8−C15 bond.[42−45] Reduction of diester **14** gave allylic alcohol **15** with complete selectivity, and subsequent oxidation using the Dess−Martin periodinane gave aldehyde **16**. This material proved to be unstable in our hands due to facile isomerization of the alkene out of conjugation with the formyl group, presumably due to prohibitive $A^{1,3}$-strain.[46] For this reason, immediately after purification, aldehyde **16** was treated with allylmagnesium bromide, giving allylic alcohol **17** as a 3:2 mixture of diastereomers that were inseparable by flash column chromatography.

Although we were unable to assign the relative configuration of the major diastereomer, we carried intermediate **17** forward to test our hypothesis regarding the anionic oxy-Cope. Thus, addition of potassium hydride to a solution of alcohol **17** and 18-crown-6 afforded the desired aldehyde **18** as the major product in 73% yield. However, at this stage of the synthesis, we were unable to confirm the relative configuration at the newly formed all-carbon quaternary stereocenter, although NOE analysis established that the C8 methyl group and the C9 hydrogen were *cis* to each other. Indeed, the relative configurations at these two centers were confirmed only at the end of our synthesis when the ^{1}H and ^{13}C NMR spectra of the synthetic material were found to match those of the isolated natural products.

The most remarkable aspect of the anionic oxy-Cope is its stereoconvergency, giving essentially a single diastereomer (>30:1 *dr*) from two diastereomers, since a maximum of 60% isolated yield would be expected if only the major diastereomer rearranged to aldehyde **18**. Inspection of molecular models does not suggest any single preferred conformation about the C9−C11 bond of diastereomeric mixture **17**, given that the groups of atoms connected to C9 (i.e., C10,C1 and C8,C17) are roughly equally demanding in terms of $A^{1,3}$-strain. Given this scenario, it would appear that the greatest determinant of stereoselectivity in this rearrangement is the ester group of alcohol **17**, which would be expected to experience severe, unfavorable nonbonding interactions with the allyl fragment of the alkoxide derived from **17**, forcing C−C bond formation to occur on the α-face. Regardless of the factors controlling the C8 relative configuration, aldehyde **18** is produced as a single diastereomer, with the formyl group in the equatorial position.

With aldehyde **18**, we began to examine the formation of the seven-membered ring of the mulinane skeleton via ring-closing alkene metathesis (see Scheme 2). To this end, treatment of intermediate **18** with methallylmagnesium choride led to a 3:1 mixture of diastereomeric alcohols **19** and **20**, which were separated by flash column chromatography. Independently, each diastereomer was treated with Grubbs' second-generation Ru-alkylidene catalyst at 80 °C in 1,2-dichloroethane. Notably, alcohol **20** underwent cyclization much more readily than its diastereomer and gave a higher yield of the corresponding RCM product. We attribute this difference to conformational effects; indeed, the conformation of structure **19** leading to productive

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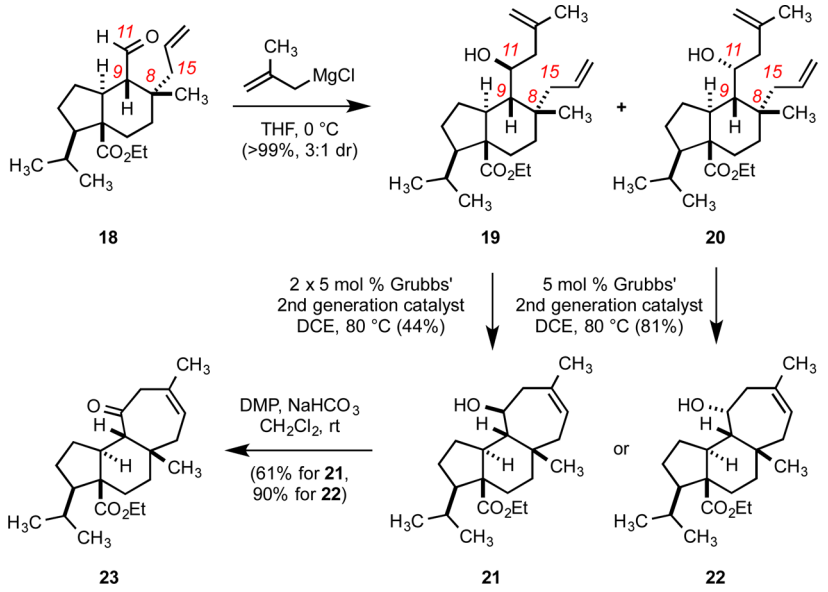
Scheme 2. C-Ring Formation by Methallylation and Ring Closing Metathesis



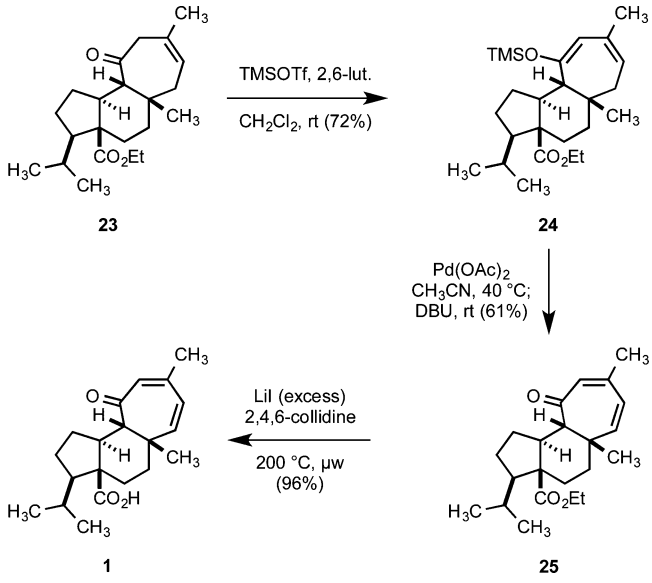
ring closure has a destabilizing steric interaction between the C-11 hydroxyl group and the C-8 methyl group, whereas this interaction is absent in the corresponding reactive conformer of structure **20**. Each alcohol diastereomer was then oxidized using the Dess–Martin periodinane, giving the same β,γ-unsaturated ketone **23** in 61% and 90% yield from alcohols **21** and **22**, respectively. As this material would slowly isomerize to the more stable, conjugated enone, it was used immediately after purification.

At this stage, we pursued the synthesis of dienone carboxylic acid **1**, a mulinane having a highly oxidized C-ring (see Scheme 3). Treatment of ketone **23** with TMSOTf and 2,6-lutidine resulted in facile, regioselective enol silane formation, giving intermediate **24**. The synthesis of **24** enabled the examination of a vinylogous Saegusa oxidation, a reaction that, to the best of our knowledge, has no precedent in the chemical literature. Thus, treatment of enol silane **24** with a stoichiometric amount of $Pd(OAc)_2$ in CH_3CN at 40 °C led to rapid consumption of substrate and the formation of an orange precipitate. Thereafter, addition of DBU at ambient temperature led to homogeneity, followed by the formation of desired dienone **25** and the precipitation of Pd black. Notably, no product formation was observed when Et_3N was used in place of DBU or when base (either DBU or Et_3N) was present in the reaction mixture prior to $Pd(OAc)_2$ addition.

With dienone **25** in hand, all that remained to complete the synthesis of mulinane **1** was conversion of the ethyl ester to the parent carboxylic acid. In practice, ester **25** proved to be very resistant to hydrolysis under forcing conditions involving aqueous base (e.g., aq. LiOH in dioxane, 100 °C) and decomposed upon exposure to strong Lewis acids (e.g., BBr_3 or TMSI). However, dealkylation could be achieved by treating compound **25** with a large excess of LiI in 2,4,6-collidine at 200 °C under microwave irradiation.[47,48] After acidification, mulinane diterpenoid **1** was isolated in 96% yield.

With mulinane **1** secured, we explored diverting advanced intermediates toward the synthesis of mulinanes bearing an isomeric C-ring diene instead of a dienone, such as structures **2**–**4** (see Scheme 4). To that end, intermediate **23** was converted to the corresponding enol triflate by initial low temperature

Scheme 3. Vinylogous Saegusa Dehydrogenation and Synthesis of Mulinane 1



enolization using $KN(TMS)_2$ and enolate trapping with $PhNTf_2$, giving triflate **26** in 99% yield. Reductive triflate removal was then achieved under Pd-catalysis with triethylsilane as the terminal reducing agent to give diene **27** in >99% yield. Finally, complete reduction of the ester function using a large excess of $LiAlH_4$ under forcing conditions (THF at reflux) furnished mulinane **2**. In accord with the attempted aqueous hydrolysis of **25**, the forcing conditions required for ester reduction attest to the extremely hindered nature of the C5-ester.

Acetylation of primary alcohol **2** was achieved under standard conditions, giving mulinane **3** in 93% yield (see Scheme 5). However, the synthesis of mulinane **4** proved to be less straightforward. In principle, the most direct path to mulinane **4** would entail the dealkylation of intermediate **27**. In practice, all attempts at hydrolysis of this intermediate met with failure, in analogy to our experience with intermediate **25**. Moreover, the previous dealkylation conditions were applied to the ethyl ester

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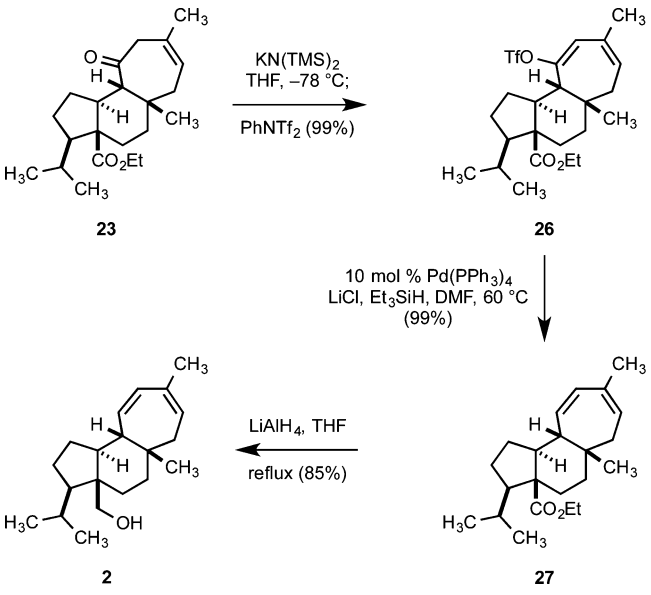
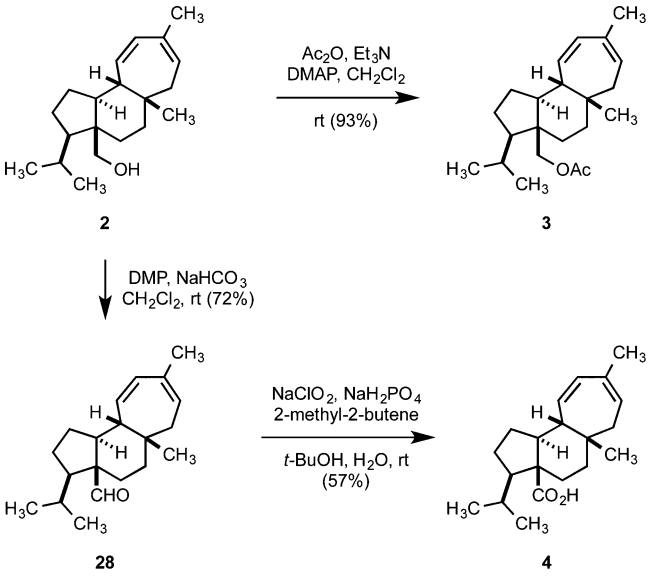
Scheme 4. Reductive Diene Formation and Synthesis of Mulinane 2



Scheme 5. Conversion of Mulinane 2 into Mulinanes 3 and 4 by Acetylation and Two-Step Oxidation, Respectively



27, but led to isomerization of the C-ring diene, presumably via a thermally allowed 1,5-hydrogen shift at this elevated reaction temperature (200 °C).[49,50]

Given the difficulty of ester hydrolysis, we pursued a slightly different approach to mulinane **4** involving stepwise oxidation of mulinane **2**. Treatment of alcohol **2** with the Jones reagent at 0 °C resulted in only partial oxidation to the corresponding aldehyde **28** in low yield, and complete decomposition was observed upon prolonged reaction at 0 °C or at higher temperatures. However, oxidation with the Dess–Martin periodinane afforded aldehyde **28** in a more preparatively useful 72% isolated yield. Finally, Lindgren–Kraus–Pinnick oxidation[51−54] with a large excess of 2-methyl-2-butene gave the desired mulinane diterpenoid **4** in 57% yield.

In conclusion, we have completed the synthesis of mulinane diterpenoids **1**–**4**, the first syntheses of any members of this class of diterpenoids. Our synthesis makes use of an anionic oxy-Cope rearrangement to set the relative configuration of the C8 quaternary all-carbon stereocenter. Our efforts also led to the development of a novel vinylogous Saegusa oxidation to address the highly oxidized C-ring found in mulinane **1** and may prove of further utility in other contexts.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an inert argon atmosphere with anhydrous solvents under anhydrous conditions unless otherwise stated. Anhydrous dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), and toluene ($PhCH_3$) were obtained by passing these previously degassed solvents through activated alumina columns unless otherwise stated. Organic solvents used for transfers and/or aqueous workup include ethyl acetate (EtOAc), hexanes, CH_2Cl_2, and Et_2O of ACS reagent grade specification or similar levels of purity. Yields refer to isolated material that was found to be chromatographically and spectroscopically homogeneous unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) using glass plates precoated with a 0.25 mm layer of silica gel (60 Å pore size) impregnated with a fluorescent indicator (254 nm); these were visualized by exposure to ultraviolet light and subsequent staining with acidic ethanolic anisaldehyde or acidic aqueous ceric ammonium molybdate (CAM), followed by heating on a laboratory hot plate for 5–60 s (~250 °C). Purification of intermediates was performed according to the procedures of Still and co-workers using Aldrich silica gel (catalog no. 717185, 60 Å pore size, 40–63 μm particle size, 230–400 mesh) using ACS reagent grade solvents (of aforementioned purity). Microwave heating experiments were conducted using a Biotage Initiator 2.0 microwave synthesizer. The reaction vessels used for these experiments were sealed with a two-sided PTFE/silicon disposable cap and disposable aluminum ring using a "crimper" tool. The reaction temperature was monitored using an external temperature sensor, and the reaction mixtures were irradiated at the temperature and for the times listed in the individual experimental procedure for each microwave heating experiment.

Ethyl (3*R*,3a*S*)-3-Isopropyl-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (10). To a solution of β-keto ester **9** (2.26 g, 11.40 mmol, 1.00 equiv) in 65 mL of benzene (PhH) was added anhydrous potassium carbonate (K_2CO_3, 2.21 g, 15.96 mmol, 1.40 equiv) at ambient temperature. Neat methyl vinyl ketone (MVK, 1.44 mL, 15.95 mmol, 1.40 equiv, 80% technical grade) was then added dropwise, and the reaction mixture was stirred for 6 h. An additional portion of MVK (1.44 mL, 15.95 mmol, 1.40 equiv, 80% technical grade) was added, and the reaction mixture was left to stir at ambient temperature overnight. After this time, TLC (33% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.55) and formation of the product (R_f = 0.41). The solids were removed by filtration and washed liberally with EtOAc before the solvent was removed under vacuum on a rotary evaporator. The residue was purified by column chromatography (20% EtOAc in hexanes), furnishing 2.76 g (92%) of the Michael addition product as a pale yellow oil: IR (thin film): ν_{max} = 2962, 1746, 1719, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14–4.02 (2 H, m), 2.65 (1 H, m), 2.47–2.24 (3 H, m), 2.19–2.08 (2 H, m), 2.06 (3 H, s), 1.96–1.88 (1 H, m), 1.82–1.70 (2 H, m), 1.58–1.50 (1 H, m), 1.17 (3 H, t, *J* = 7.1 Hz), 0.95 (3 H, d, *J* = 6.6 Hz), 0.86 (3 H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 208.0, 170.5, 61.5, 61.0, 53.1, 38.6, 30.6, 29.8, 27.9, 25.2, 22.2, 21.1, 14.0; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{15}H_{24}O_4$ + Na^+]: 291.1572; found: 291.1566.

To a solution of Michael addition product (2.76 g, 10.28 mmol, 1.00 equiv) in 100 mL of $PhCH_3$ was added *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 921 mg, 4.84 mmol, 0.47 equiv). The flask was equipped with a Dean–Stark trap and a water-cooled condenser, and the reaction mixture was heated at reflux overnight. After this time, the reaction mixture had taken on a dark brown color, and a small amount of water had collected in the bottom of the Dean–Stark trap. After cooling to ambient temperature, the reaction was terminated

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by the addition of saturated aqueous sodium bicarbonate ($NaHCO_3$) solution and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. TLC (33% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.35) and formation of the product (R_f = 0.43, strongly UV-active). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% to 20% to 30% EtOAc in hexanes), furnishing 1.74 g (68%) of enone **10** as a yellow oil: IR (thin film): ν_{max} = 2959, 1719, 1669, 1166 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (1 H, s), 4.27−4.09 (2 H, m), 2.96−2.81 (2 H, m), 2.54 (1 H, m), 2.47 (1 H, m), 2.36 (1 H, m), 2.09−1.99 (1 H, m), 1.81−1.71 (2 H, m), 1.64−1.49 (2 H, m), 1.27 (3 H, t, J = 7.1 Hz), 1.06 (3 H, d, J = 6.1 Hz), 0.91 (3 H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 172.6, 171.0, 123.2, 61.0, 58.5, 56.8, 34.7, 34.0, 31.0, 30.6, 27.8, 22.30, 22.27, 14.2; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{15}H_{22}O_3$ + Na^+]: 273.1467; found: 273.1461.

3a-Ethyl 7-Methyl (3*R*,3a*S*)-6-Hydroxy-3-isopropyl-2,3,4,5-tetrahydro-3a*H*-indene-3a,7-dicarboxylate (11). This procedure was adapted from a method originally reported by Covey.[38] A solution of enone **10** (5.2 g, 20.77 mmol, 1.00 equiv) in 100 mL of DMF was degassed with a stream of argon for 30 min before the addition of methyl magnesium carbonate (36.4 mL of a 2.0 M solution in DMF, 72.7 mmol, 3.5 equiv). The reaction mixture was then lowered into a preheated 130 °C oil bath and stirred at that temperature for 3 h, forming a yellow suspension. After this time, the reaction mixture was cooled to 0 °C, diluted with Et_2O, and carefully acidified with 3 M aqueous HCl solution. The layers were separated, and the aqueous phase was extracted with two additional portions of Et_2O. The combined organic layers containing the crude carboxylic acid were then treated with freshly prepared diazomethane[55] (CH_2N_2, 100 mL of an ∼0.25 M solution in Et_2O, 25 mmol, 1.20 equiv) until no additional nitrogen gas evolution was observed. Neat glacial acetic acid (AcOH, 4 mL) was then added to decompose excess CH_2N_2, and the reaction mixture was diluted with water. The layers were separated, and the aqueous phase was extracted once with Et_2O before the combined organics were dried over anhydrous $MgSO_4$. TLC (33% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.46) and formation of the product (R_f = 0.62). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 4.55 g (71% over two steps) of enol **11** as an amorphous yellow solid. ^1H NMR showed that compound **11** exists as an ∼1:1 mixture of enols in C_6D_6 solution at ambient temperature: IR (thin film): ν_{max} = 2954, 1719, 1649, 1584, 1444, 1216 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 13.65 (0.5 H, s), 13.64 (0.5 H, s), 6.30 (0.5 H, t, J = 2.6 Hz), 6.28 (0.5 H, t, J = 2.6 Hz), 3.95 (1 H, dq, J = 10.9 Hz, 7.1 Hz), 3.80 (1 H, dq, J = 10.9 Hz, 7.1 Hz), 3.25 (1.5 H, s), 3.24 (1.5 H, s), 3.11−3.02 (1 H, m), 2.59 (1 H, m), 2.55−2.49 (2 H, m), 2.33 (0.5 H, t, J = 6.6 Hz), 2.29 (0.5 H, t, J = 6.6 Hz), 1.71−1.54 (2 H, m), 1.32−1.24 (1 H, m), 1.07 (1.5 H, d, J = 6.3 Hz), 1.04 (1.5 H, d, J = 6.1 Hz), 0.87 (1.5 H, d, J = 6.1 Hz), 0.85 (3 H, t, J = 7.1 Hz), 0.84 (3 H, d, J = 6.3 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 176.19, 176.17, 174.0, 173.4, 173.24, 173.18, 135.6, 135.4, 125.1, 125.0, 99.14, 99.11, 60.4, 59.6, 59.5, 58.8, 58.6, 51.3, 51.2, 39.0, 38.8, 31.63, 31.60, 31.2, 31.1, 29.0, 28.9, 23.1, 23.0, 22.54, 22.52, 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{17}H_{24}O_5$ + Na^+]: 331.1521; found: 331.1514.

3a-Ethyl 7-Methyl (3*R*,3a*S*,7*S*,7a*S*)-3-Isopropyl-6-oxo-octahydro-3a*H*-indene-3a,7-dicarboxylate (12). To a vigorously stirred suspension of palladium on activated carbon (10% Pd/C, 2.21 g, 2.08 mmol) in 200 mL of methanol (CH_3OH) was added a solution of enol **11** (6.41 g, 20.8 mmol, 1.00 equiv) in 25 mL of CH_3OH. The flask was then evacuated and put under an atmosphere of hydrogen gas (H_2) using a balloon. After 2 h of vigorous stirring at ambient temperature, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.30, UV-active) and formation of the hydrogenated product (R_f = 0.46, not UV-active). The reaction mixture was filtered through Celite to remove the palladium on carbon, which was washed liberally with EtOAc. The solvent was then removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 5.48 g (85%) of β-keto ester **12** as a white amorphous solid. Alternatively, the crude material could be recrystallized from hexanes to afford **12** as a white microcrystalline solid: mp 66−68 °C; IR (thin film): ν_{max} = 2953, 1740, 1709, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.23 (2 H, q, J = 7.1 Hz), 3.73 (3 H, s), 3.49 (1 H, d, J = 13.7 Hz), 2.82 (1 H, ddd, J = 13.1 Hz, 5.9 Hz, 3.0 Hz), 2.50−2.41 (3 H, m), 2.06 (1 H, m), 1.86 (1 H, qd, J = 11.9 Hz, 5.0 Hz), 1.76 (1 H, m), 1.68−1.55 (2 H, m), 1.53−1.42 (2 H, m), 1.30 (3 H, t, J = 7.1 Hz), 1.02 (3 H, d, J = 6.1 Hz), 0.87 (3 H, d, J = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 173.1, 169.6, 60.7, 59.6, 57.0, 55.7, 52.1, 51.9, 38.7, 34.2, 31.9, 30.0, 25.4, 22.8, 22.3, 14.1; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{17}H_{26}O_5$ + Na^+]: 333.1678; found: 333.1670.

3a-Ethyl 7-Methyl (3*R*,3a*S*,7a*R*)-6-((Diethoxyphosphoryl)-oxy)-3-isopropyl-1,2,3,4,5,7a-hexahydro-3a*H*-indene-3a,7-dicarboxylate (13). A solution of β-keto ester **12** (1.53 g, 4.93 mmol, 1.00 equiv) in 50 mL of THF was cooled to 0 °C, and NaH (246 mg, 6.16 mmol, 1.25 equiv, 60% dispersion in mineral oil) was added in a single portion. Vigorous gas evolution was observed, and the reaction mixture immediately turned yellow. The cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperature. After 2 h, neat diethyl chlorophosphate (886 μL, 6.16 mmol, 1.25 equiv) was added dropwise, discharging the yellow color of the reaction mixture. After 15 min, TLC (50% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.64) and clean formation of the product (R_f = 0.30). The reaction was terminated by the addition of aqueous pH 7 phosphate buffer and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (33% EtOAc in hexanes), furnishing 2.04 g (93%) of enol phosphate **13** as a colorless oil. This intermediate was found to decompose upon prolonged storage and was, therefore, prepared immediately before use in the subsequent cuprate step: IR (thin film): ν_{max} = 2981, 1725, 1679, 1225, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.19−4.08 (6 H, m), 3.71 (3 H, s), 2.84 (1 H, m), 2.72 (1 H, m), 2.68−2.60 (2 H, m), 2.04 (1 H, m), 1.97−1.92 (2 H, m), 1.61−1.51 (2 H, m), 1.49−1.36 (2 H, m), 1.33 (3 H, t, J = 6 Hz), 1.32 (3 H, t, J = 6 Hz), 1.24 (3 H, t, J = 7.1 Hz), 1.02 (3 H, d, J = 6.3 Hz), 0.85 (3 H, d, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 165.9 (d, $^4J_{C-P}$ = 2.0 Hz), 149.8 (d, $^2J_{C-P}$ = 8.2 Hz), 119.1 (d, $^3J_{C-P}$ = 7.9 Hz), 64.6 (d, $^2J_{C-P}$ = 6.2 Hz), 64.5 (d, $^2J_{C-P}$ = 6.4 Hz), 60.3, 56.5 (d, $^4J_{C-P}$ = 0.7 Hz), 55.9, 51.4 (d, $^3J_{C-P}$ = 3.5 Hz), 48.2, 32.1, 32.0, 30.2, 28.2, 25.4, 25.4, 22.8, 22.3, 16.2 (d, $^3J_{C-P}$ = 2.1 Hz), 16.1 (d, $^3J_{C-P}$ = 2.2 Hz), 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{21}H_{35}O_8P$ + Na^+]: 469.1967; found: 469.1964.

3a-Ethyl 7-Methyl (3*R*,3a*S*,7a*R*)-3-Isopropyl-6-methyl-1,2,3,4,5,7a-hexahydro-3a*H*-indene-3a,7-dicarboxylate (14). A suspension of CuI (2.86 g, 15.02 mmol, 3.29 equiv) in 40.5 mL of Et_2O was cooled to 0 °C, and methyllithium (CH_3Li, 19.5 mL of a 1.54 M solution in Et_2O, 30.04 mmol, 6.57 equiv) was added dropwise. Initially, a bright yellow precipitate of methylcopper formed, and this gradually dissolved toward the end of the addition to give a nearly colorless, homogeneous solution. After stirring at 0 °C for an additional 15 min, the resulting 0.25 M stock solution of lithium dimethylcuprate ($LiCu(CH_3)_2$) was used directly in the next step.

A solution of enol phosphate **13** (2.04 g, 4.57 mmol, 1.00 equiv) in 40 mL of Et_2O was cooled to 0 °C, and a portion of the previously prepared $LiCu(CH_3)_2$ solution (22.84 mL of a 0.25 M solution in Et_2O, 5.71 mmol, 1.25 equiv) was added in a steady stream via cannula. After 30 min at 0 °C, TLC (33% EtOAc in hexanes, UV/anisaldehyde) showed roughly 60% conversion of the starting material (R_f = 0.13) to the product (R_f = 0.64). An additional portion of the $LiCu(CH_3)_2$ solution (22.84 mL of a 0.25 M solution in Et_2O, 5.71 mmol, 1.25 equiv) was then added, and after 30 min at 0 °C, TLC showed that all of the starting material had been consumed. The reaction was terminated by the dropwise addition of saturated aqueous NH_4Cl solution and diluted with water and Et_2O. The copper salts that had precipitated were removed by filtration through Celite and washed liberally with Et_2O. The layers were separated, and the aqueous phase was extracted with

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one additional portion of Et_2O before the combined organics were dried over anhydrous $MgSO_4$. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 1.13 g (80%) of α,β-unsaturated ester **14** as a colorless oil: IR (thin film): 2953, 1713, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.16−4.04 (2 H, m), 3.70 (3 H, s), 2.72 (1 H, ddd, J = 11.8 Hz, 9.4 Hz, 2.4 Hz), 2.65 (1 H, dd, J = 12.9 Hz, 8.2 Hz), 2.41 (1 H, ddd, J = 19.0 Hz, 10.5 Hz, 2.8 Hz), 2.19 (1 H, dd, J = 19.2 Hz, 8.1 Hz), 2.02 (1 H, m), 1.96−1.84 (2 H, m), 1.75 (3 H, d, J = 2.0 Hz), 1.61−1.53 (1 H, m), 1.51−1.37 (3 H, m), 1.21 (3 H, t, J = 7.1 Hz), 1.02 (3 H, d, J = 6.3 Hz), 0.85 (3 H, d, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 168.8, 140.9, 128.1, 59.9, 57.0, 56.5, 50.9, 49.1, 33.4, 32.5, 32.2, 30.0, 25.8, 22.9, 22.3, 20.3, 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{18}H_{28}O_4$ + Na^+]: 331.1885; found: 331.1878.

Ethyl (3*R*,3a*S*,7a*S*)-7-(Hydroxymethyl)-3-isopropyl-6-methyl-1,2,3,4,5,7a-hexahydro-3a*H*-indene-3a-carboxylate (15). A solution of α,β-unsaturated ester **14** (1.13 g, 3.66 mmol, 1.00 equiv) in 40 mL of THF was cooled in an ice bath, and diisobutylaluminum hydride (i-Bu_2AlH, 9.14 mL of a 1.2 M solution in $PhCH_3$, 10.97 mmol, 3.00 equiv) was added dropwise. After 30 min at 0 °C, TLC (33% EtOAc in hexanes, UV/CAM stain) showed consumption of the starting material (R_f = 0.65, UV-active) and clean formation of the product (R_f = 0.41, not UV-active). The excess i-Bu_2AlH was quenched by the dropwise addition of EtOAc, and the reaction was terminated by the addition of saturated aqueous sodium potassium tartrate solution (Rochelle's salt). After stirring vigorously at ambient temperature for 1 h, a clear biphasic solution was obtained. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (25% EtOAc in hexanes), furnishing 837 mg (82%) of allylic alcohol **15** as a colorless oil: IR (thin film): ν_{max} = 3410, 2973, 2870, 1715, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14−4.00 (4 H, m), 2.63−2.58 (2 H, m), 2.28−2.10 (3 H, m), 2.02 (1 H, m), 1.85 (1 H, dtd, J = 11.8 Hz, 9.4 Hz, 3.9 Hz), 1.69 (1 H, br s), 1.63 (3 H, d, J = 2.3 Hz), 1.59−1.44 (3 H, m), 1.40−1.31 (1 H, m), 1.19 (3 H, t, J = 7.1 Hz), 1.01 (3 H, d, J = 6.3 Hz), 0.83 (3 H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 132.0, 131.6, 60.0, 59.8, 57.7, 57.0, 50.8, 33.9, 32.2, 31.9, 29.8, 24.1, 22.8, 22.3, 18.0, 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{17}H_{28}O_3$ + Na^+]: 303.1936; found: 303.1928.

Ethyl (3*R*,3a*S*,7a*S*)-7-Formyl-3-isopropyl-6-methyl-1,2,3,4,5,7a-hexahydro-3a*H*-indene-3a-carboxylate (16). To a solution of allylic alcohol **15** (1.16 g, 4.12 mmol, 1.00 equiv) in 50 mL of CH_2Cl_2 at ambient temperature was added $NaHCO_3$ (2.08 g, 24.74 mmol, 6.00 equiv) and Dess−Martin periodinane (DMP, 2.19 g, 5.15 mmol, 1.25 equiv). After 10 min, TLC (33% EtOAc in hexanes, UV/CAM stain) showed complete consumption of the starting material (R_f = 0.41, not UV-active) and formation of the product (R_f = 0.62, strongly UV-active). The reaction was terminated by the addition of a 1:1 mixture of saturated aqueous sodium thiosulfate ($Na_2S_2O_3$) solution and saturated aqueous $NaHCO_3$, and stirring was continued until a clear biphasic solution was obtained. The layers were separated, and the aqueous phase was extracted with two additional portions of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (15% EtOAc in hexanes), furnishing 951 mg (83%) of aldehyde **16** as a colorless oil. Compound **16** was unstable to prolonged storage, and it was, therefore, prepared immediately before use in the subsequent Grignard reaction: IR (thin film): ν_{max} = 2974, 2945, 1716, 1658, 1615, 1175 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 10.00 (1 H, s), 3.93−3.80 (2 H, m), 2.62−2.53 (2 H, m), 2.49 (1 H, dd, J = 11.9 Hz, 5.3 Hz), 2.46−2.32 (2 H, m), 1.94 (1 H, ddd, J = 14.6 Hz, 9.1 Hz, 4.8 Hz), 1.84 (1 H, dd, J = 19.1 Hz, 8.1 Hz), 1.68−1.58 (1 H, m), 1.56 (3 H, d, J = 1.1 Hz), 1.47 (1 H, ddt, J = 13.1 Hz, 10.0 Hz, 6.5 Hz), 1.19−1.09 (2 H, m), 1.06 (3 H, d, J = 6.5 Hz), 0.85 (3 H, t, J = 7.2 Hz), 0.83 (3 H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 189.6, 173.4, 153.1, 135.7, 59.7, 57.1, 56.1, 48.9, 34.4, 33.8, 32.5, 31.0, 26.0, 23.1, 22.5, 17.6, 14.2; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{17}H_{26}O_3$ + Na^+]: 301.1780; found: 301.1769.

Ethyl (3*R*,3a*S*,7a*S*)-7-(1-Hydroxybut-3-en-1-yl)-3-isopropyl-6-methyl-1,2,3,4,5,7a-hexahydro-3a*H*-indene-3a-carboxylate (17). A solution of aldehyde **16** (951 mg, 3.42 mmol, 1.00 equiv) in 50 mL of THF was cooled to −78 °C, and allylmagnesium bromide (3.76 mL of a 1.0 M solution in Et_2O, 3.76 mmol, 1.10 equiv) was added dropwise. After 15 min at −78 °C, TLC (25% EtOAc in hexanes, UV/CAM stain) showed complete consumption of the starting material (R_f = 0.55, UV-active) and formation of the product (R_f = 0.55 (copolar), not UV-active). The reaction was terminated by the addition of saturated aqueous NH_4Cl and diluted with water and EtOAc after warming to ambient temperature. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 1.05 g (95%) of allylic alcohol **17** as a colorless oil. ^1H NMR showed that **17** had been formed as a 3:2 mixture of inseparable diastereomers: IR (thin film): ν_{max} = 3484, 2974, 2870, 1714, 1640, 1177 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83−5.69 (1 H, m), 5.15−5.01 (2 H, m), 4.64 (0.6 H, td, J = 7.5 Hz, 2.1 Hz), 4.59 (0.4 H, m), 4.17−4.09 (1 H, m), 4.08−4.00 (1 H, m), 2.65−2.55 (2 H, m), 2.51−2.40 (2 H, m), 2.36−2.15 (3 H, m), 2.12−2.09 (1 H, m), 2.06−1.98 (2 H, m), 1.95−1.88 (1 H, m), 1.65 (1.8 H, d, J = 2.2 Hz), 1.59 (1.2 H, d, J = 2.2 Hz), 1.57−1.48 (1 H, m), 1.45−1.36 (2 H, m), 1.23 (3 H, t, J = 7.1 Hz), 1.05 (1.8 H, d, J = 6.1 Hz), 1.03 (1.2 H, d, J = 6.0 Hz), 0.85 (3 H, d, J = 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (starred peaks correspond to the minor diastereomer): 175.1, 174.5*, 135.6*, 135.5, 133.2*, 133.0, 130.9, 128.7*, 117.5*, 116.7, 71.5, 70.9, 60.0, 59.7*, 58.4, 57.5*, 56.12*, 56.08, 50.4*, 49.9, 41.6*, 40.0, 34.05*, 33.96, 32.7*, 32.5, 32.2*, 32.0, 29.95*, 29.91, 25.7*, 25.3, 22.93*, 22.86, 22.54, 22.47*, 18.80, 18.76*, 14.35*, 14.34; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{20}H_{32}O_3$ + Na^+]: 343.2249; found: 343.2242.

Ethyl (3*R*,3a*S*,6*S*,7*S*,7a*S*)-6-Allyl-7-formyl-3-isopropyl-6-methyloctahydro-3a*H*-indene-3a-carboxylate (18). A suspension of potassium hydride (KH, 260 mg of an ∼30% dispersion in mineral oil, 1.95 mmol, 1.25 equiv) in 10 mL of $PhCH_3$ was heated to 100 °C, and a solution of allylic alcohol **17** (500 mg, 1.56 mmol, 1.00 equiv) and 18-crown-6 (515 mg, 1.95 mmol, 1.25 equiv) in 5 mL of $PhCH_3$ was then added dropwise. Vigorous gas evolution was observed, and the initially colorless reaction mixture turned dark purple. After heating for 20 min, TLC (25% EtOAc in hexanes, anisaldehyde) showed complete consumption of the starting material (R_f = 0.55) and clean formation of oxy-Cope product **18** (R_f = 0.63). After cooling to ambient temperature, the reaction was terminated by the careful addition of pH 7 phosphate buffer and 1 M aqueous HCl solution (dark purple color discharged to yellow) and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted twice with EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (5% EtOAc in hexanes), furnishing 365 mg (73%) of aldehyde **18** as a yellow oil. ^1H NMR showed that **18** had been formed with >30:1 diastereoselectivity: IR (thin film): ν_{max} = 2957, 2932, 2870, 1715, 1178 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (1 H, d, J = 3.2 Hz), 5.77−5.68 (1 H, m), 5.07−5.01 (2 H, m), 4.15 (2 H, q, J = 7.1 Hz), 2.49−2.44 (3 H, m), 2.19 (1 H, td, J = 12.0 Hz, 8.9 Hz), 2.00−1.90 (2 H, m), 1.82−1.72 (2 H, m), 1.62 (1 H, dt, J = 14.5 Hz, 3.2 Hz), 1.43−1.31 (3 H, m), 1.27 (3 H, t, J = 7.1 Hz), 1.27−1.21 (1 H, m), 1.16−1.09 (1 H, m), 1.07 (3 H, s), 1.05 (3 H, d, J = 6.3 Hz), 0.85 (3 H, d, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 173.8, 134.1, 118.1, 60.9, 59.9, 57.3, 57.0, 45.3, 37.7, 37.4, 35.2, 32.3, 31.9, 29.1, 27.5, 24.6, 23.0, 22.4, 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{20}H_{32}O_3$ + Na^+]: 343.2249; found: 343.2245.

Ethyl (3*R*,3a*S*,6*S*,7*S*,7a*S*)-6-Allyl-7-((*S*)-1-hydroxy-3-methylbut-3-en-1-yl)-3-isopropyl-6-methyloctahydro-3a*H*-indene-3a-carboxylate (19) and Ethyl (3*R*,3a*S*,6*S*,7*S*,7a*S*)-6-Allyl-7-((*R*)-1-hydroxy-3-methylbut-3-en-1-yl)-3-isopropyl-6-methyloctahydro-3a*H*-indene-3a-carboxylate (20). A suspension of flame-dried magnesium turnings (987 mg, 40.6 mmol, 1.50 equiv) in 20 mL of THF was cooled to 5 °C, and 3-chloro-2-methyl-1-propene (2.65 mL, 27.1 mmol, 1.00 equiv) was added dropwise over the course of 10 min.

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Toward the end of the addition, the solution turned gray, and heat was evolved, indicating initiation of the Grignard reaction. After addition was complete, the cooling bath was removed, and the reaction mixture was allowed to stir at ambient temperature for 1 h. After this time, the resulting gray suspension was heated at reflux for 2 h before cooling to ambient temperature. Titration of the resulting solution of methallylmagnesium chloride with salicylaldehyde phenylhydrazone[56] gave a concentration of 0.66 M (~50% of the theoretical concentration), and this Grignard reagent was used directly in the next step.

A solution of aldehyde **18** (800 mg, 2.50 mmol, 1.00 equiv) in 25 mL of THF was cooled to 0 °C, and a portion of the previously prepared methallylmagnesium chloride solution (5.67 mL of a 0.66 M solution in THF) was added dropwise. After 15 min, TLC (25% EtOAc in hexanes, anisaldehyde) showed complete consumption of the starting material (R_f = 0.63, stains light purple) and formation of major diastereomer **19** (R_f = 0.65 (almost copolar), stains dark purple) and minor diastereomer **20** (R_f = 0.55, stains purple). The reaction was terminated by the addition of saturated aqueous NH_4Cl solution and diluted with water and EtOAc. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 705 mg (75%) of alcohol **19** and 235 mg (25%) of alcohol **20** as colorless oils. Alcohol **19**: IR (thin film): ν_{max} = 3551, 2956, 1718, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (1 H, ddt, J = 10.6 Hz, 8.1 Hz, 7.5 Hz), 5.05−5.00 (2 H, m), 4.86 (1 H, d, J = 1.4 Hz), 4.78 (1 H, d, J = 1.4 Hz), 4.16−4.10 (2 H, m), 3.99 (1 H, dd, J = 10.0 Hz, 4.4 Hz), 2.48−2.38 (3 H, m), 2.15−2.08 (3 H, m), 2.04−1.81 (3 H, m), 1.75 (3 H, s), 1.56 (1 H, dt, J = 14.4 Hz, 3.1 Hz), 1.49−1.45 (2 H, m), 1.39−1.31 (3 H, m), 1.26 (3 H, t, J = 7.1 Hz), 1.04 (3 H, d, J = 5.8 Hz), 0.86 (3 H, s), 0.83 (3 H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 143.1, 135.8, 116.9, 113.8, 67.1, 59.5, 58.4, 56.9, 51.6, 47.6, 46.3, 36.9, 36.7, 35.0, 32.5, 31.9, 29.0, 27.5, 26.8, 23.0, 22.6, 22.3, 14.4; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{24}H_{40}O_3$ + Na^+]: 399.2875; found: 399.2873. Alcohol **20**: IR (thin film): ν_{max} = 3541, 2927, 1718, 1176, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (1 H, ddt, J = 17.7 Hz, 8.5 Hz, 6.4 Hz), 5.03−4.99 (2 H, m), 4.85 (1 H, d, J = 1.4 Hz), 4.80 (1 H, d, J = 1.4 Hz), 4.17−4.10 (2 H, m), 3.98 (1 H, dt, J = 9.2 Hz, 2.7 Hz), 2.42−2.26 (4 H, m), 2.16−2.07 (2 H, m), 1.99−1.91 (2 H, m), 1.76 (3 H, s), 1.68 (1 H, dd, J = 11.9 Hz, 2.4 Hz), 1.60−1.51 (2 H, m), 1.26 (3 H, t, J = 7.1 Hz), 1.21−1.17 (1 H, m), 1.04 (3 H, d, J = 6.2 Hz), 1.03 (3 H, s), 0.83 (3 H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.8, 135.6, 117.0, 113.0, 69.9, 59.6, 58.5, 57.2, 53.1, 47.9, 44.6, 38.0, 36.9, 36.4, 32.5, 31.9, 29.0, 28.9, 25.9, 23.0, 22.5, 22.4, 14.4; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{24}H_{40}O_3$ + Na^+]: 399.2875; found: 399.2869.

Ethyl (3*R*,3a*S*,5a*S*,10*S*,10a*S*,10b*S*)-10-Hydroxy-3-isopropyl-5a,8-dimethyl-2,3,4,5,5a,6,9,10,10a,10b-decahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (21). To a solution of alcohol **19** (807 mg, 2.14 mmol, 1.00 equiv) in 30 mL of 1,2-dichloroethane (1,2-DCE) was added Grubbs second-generation catalyst (91 mg, 0.11 mmol, 0.05 equiv), and the reaction was heated at 80 °C for 6 h. After this time, a second portion of catalyst (91 mg, 0.11 mmol, 0.05 equiv) was added, and the reaction mixture was heated at 80 °C for a further 18 h. After this time, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed conversion of the starting material (R_f = 0.65) to the product (R_f = 0.43) along with the formation of a byproduct (R_f = 0.65 (copolar), UV-active). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 328 mg (44%) of alcohol **21** as a brown oil: IR (thin film): ν_{max} = 3521, 2924, 1716, 1172, 1152 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.56 (1 H, m), 4.02−3.93 (2 H, m), 3.88 (1 H, m), 2.75 (1 H, d, J = 14.5 Hz), 2.50 (1 H, dt, J = 13.0 Hz, 3.3 Hz), 2.39 (1 H, d, J = 14.2 Hz), 2.16 (1 H, ddd, J = 23.5 Hz, 11.9 Hz, 4.8 Hz), 2.02 (1 H, dd, J = 12.0 Hz, 3.2 Hz), 1.93 (1 H, dd, J = 14.5 Hz, 6.7 Hz), 1.81 (3 H, s), 1.80−1.73 (2 H, m), 1.62 (1 H, m), 1.54 (1 H, ddd, J = 24.0 Hz, 12.0 Hz, 4.1 Hz), 1.47−1.37 (3 H, m), 1.30 (1 H, dd, J = 14.5 Hz, 8.5 Hz), 1.25 (3 H, s), 1.15−1.10 (2 H, m), 1.13 (3 H, d, J = 6.5 Hz), 0.96 (3 H, t, J = 7.1 Hz), 0.88 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 173.7, 136.4, 124.6, 70.1, 59.6, 58.4, 57.7, 53.0, 48.9, 44.1, 35.2, 34.8, 34.2, 33.3, 32.4, 29.8, 29.4, 27.6, 25.3, 23.2, 22.6, 14.4; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{22}H_{36}O_3$ + Na^+]: 371.2562; found: 371.2559.

Ethyl (3*R*,3a*S*,5a*S*,10*R*,10a*S*,10b*S*)-10-Hydroxy-3-isopropyl-5a,8-dimethyl-2,3,4,5,5a,6,9,10,10a,10b-decahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (22). To a solution of alcohol **20** (224 mg, 0.60 mmol, 1.00 equiv) in 12 mL of 1,2-DCE was added Grubbs second-generation catalyst (25.2 mg, 0.03 mmol, 0.05 equiv), and the reaction was heated at 80 °C for 1 h. After this time, TLC (25% EtOAc in hexanes, anisaldehyde) showed complete conversion of the starting material (R_f = 0.55) to the product (R_f = 0.39). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (15% EtOAc in hexanes), furnishing 167 mg (81%) of alcohol **22** as a brown oil: IR (thin film): ν_{max} = 3504, 2914, 1707, 1443, 1176, 1154 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.31 (1 H, m), 4.05 (1 H, dt, J = 10.1 Hz, 2.2 Hz), 3.99 (2 H, q, J = 7.1 Hz), 2.68 (1 H, d, J = 15.4 Hz), 2.61−2.54 (3 H, m), 2.03 (1 H, td, J = 11.8 Hz, 8.0 Hz), 1.95 (1 H, dd, J = 11.7 Hz, 2.8 Hz), 1.91−1.76 (3 H, m), 1.70 (3 H, s), 1.64 (1 H, dd, J = 14.7 Hz, 3.8 Hz), 1.60−1.53 (1 H, m), 1.48 (1 H, ddt, J = 13.1 Hz, 10.0 Hz, 6.5 Hz), 1.23−1.17 (3 H, m), 1.14 (3 H, d, J = 6.5 Hz), 1.11 (1 H, m), 1.03 (3 H, s), 0.98 (3 H, t, J = 7.1 Hz), 0.9 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 174.0, 136.0, 123.8, 68.1, 59.6, 59.1, 57.1, 53.3, 47.0, 42.9, 38.1, 36.6, 34.2, 33.4, 32.4, 30.0, 28.0, 26.7, 26.5, 23.3, 22.8, 14.4; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{22}H_{36}O_3$ + Na^+]: 371.2562; found: 371.2556.

Ethyl (3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-10-oxo-2,3,4,5,5a,6,9,10,10a,10b-decahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (23). To a solution of alcohol **21** (187 mg, 0.54 mmol, 1.00 equiv) in 10 mL of CH_2Cl_2 was added $NaHCO_3$ (270 mg, 3.22 mmol, 6.00 equiv) and Dess−Martin periodinane (DMP, 398 mg, 0.94 mmol, 1.75 equiv). After 10 min at ambient temperature, TLC (25% EtOAc in hexanes, anisaldehyde) showed complete conversion of the starting material (R_f = 0.43, stains blue) to the product (R_f = 0.53, stains peach). The reaction was terminated by the addition of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and the mixture was stirred until a clear, biphasic solution was obtained. The layers were separated, and the aqueous phase was extracted with two additional portions of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 114 mg (61%) of ketone **23** as a colorless oil. The same procedure was also carried out using epimeric alcohol **22** (200 mg, 0.57 mmol, 1.00 equiv), DMP (365 mg, 0.86 mmol, 1.50 equiv), and $NaHCO_3$ (289 mg, 3.44 mmol, 6.00 equiv) in 10 mL of CH_2Cl_2, furnishing 179 mg (90%) of ketone **23** as a colorless oil: IR (thin film): ν_{max} = 2928, 1718, 1697, 1444, 1178, 1150 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.32 (1 H, m), 3.91 (2 H, q, J = 7.1 Hz), 3.38 (1 H, d, J = 11.6 Hz), 2.83 (1 H, dd, J = 14.6 Hz, 3.3 Hz), 2.69 (1 H, d, J = 11.9 Hz), 2.55 (1 H, dt, J = 6.8 Hz, 3.7 Hz), 2.37 (1 H, dt, J = 11.5 Hz, 1.3 Hz), 2.17−1.98 (2 H, m), 1.85−1.75 (1 H, m), 1.72 (3 H, s), 1.61−1.37 (4 H, m), 1.32−1.18 (4 H, m), 1.13 (3 H, d, J = 6.4 Hz), 0.97 (3 H, s), 0.91 (3 H, t, J = 7.1 Hz), 0.87 (3 H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 201.3, 171.0, 130.9, 123.4, 62.7, 57.9, 55.5, 55.4, 46.1, 42.7, 39.2, 38.4, 31.9, 31.4, 30.4, 27.5, 26.1, 23.2, 22.7, 21.2, 20.6, 12.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{22}H_{34}O_3$ + Na^+]: 369.2406; found: 369.2397.

Ethyl (3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-10-((trimethylsilyl)oxy)-2,3,4,5,5a,6,10a,10b-octahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (24). A solution of ketone **23** (55 mg, 0.16 mmol, 1.00 equiv) in 3 mL of CH_2Cl_2 was cooled to 0 °C, and 2,6-lutidine (55 μL, 0.48 mmol, 3.00 equiv) was added, followed by freshly distilled trimethylsilyl trifluoromethanesulfonate (TMSOTf, 57 μL, 0.32 mmol, 2.00 equiv). After addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperature. After 3 h, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.53, not UV-active) and formation of the product (R_f = 0.75, UV-active). The reaction was terminated by the addition of aqueous pH 7 phosphate buffer and diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with one additional portion of

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CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (5% EtOAc in hexanes), furnishing 48 mg (72%) of silyl enol ether **24** as a colorless oil: IR (thin film): ν_{max} = 2955, 1718, 1619, 1252, 1183, 1152, 867, 844 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.34 (1 H, dd, J = 7.3 Hz, 1.1 Hz), 5.31 (1 H, s), 4.06−3.95 (2 H, m), 2.81 (1 H, d, J = 18.5 Hz), 2.63 (1 H, ddd, J = 23.5 Hz, 12.1 Hz, 2.5 Hz), 2.57 (1 H, dt, J = 6.4 Hz, 5.8 Hz), 2.37 (1 H, d, J = 11.2 Hz), 1.90 (1 H, m), 1.86 (3 H, d, J = 0.9 Hz), 1.82 (1 H, m), 1.74−1.66 (2 H, m), 1.62−1.53 (2 H, m), 1.50−1.43 (1 H, m), 1.35 (1 H, dt, J = 14.0 Hz, 3.1 Hz), 1.28 (1 H, td, J = 13.4 Hz, 3.6 Hz), 1.15 (3 H, s), 1.14 (1 H, m), 1.10 (3 H, d, J = 6.5 Hz), 1.01 (3 H, t, J = 7.1 Hz), 0.85 (3 H, d, J = 6.6 Hz), 0.26 (9 H, s); ^{13}C NMR (125 MHz, C_6D_6) δ 173.8, 155.4, 120.4, 110.3, 128.2, 59.6, 59.1, 58.0, 55.3, 53.2, 41.4, 36.6, 33.3, 32.60, 32.55, 29.8, 28.0, 27.6, 25.8, 23.2, 22.6, 14.4, 0.6; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{25}H_{42}O_3Si$ + Na^+]: 441.2801; found: 441.2796.

Ethyl (3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-10-oxo-2,3,4,5,5a,10,10a,10b-octahydrocyclohepta[*e*]indene-3a-(1*H*)-carboxylate (25). To a solution of silyl enol ether **24** (52 mg, 0.12 mmol, 1.00 equiv) in 4 mL of CH_3CN was added palladium(II) acetate (56 mg, 0.25 mmol, 2.00 equiv) at ambient temperature. The reaction mixture was then heated to 40 °C, and after 10 min, an orange solid had precipitated from solution. TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.75). After the reaction mixture had cooled to ambient temperature, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 112 μL, 0.75 mmol, 6.00 equiv) was added. The reaction mixture immediately became homogeneous, and stirring was continued at ambient temperature for 18 h. After this time, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed clean formation of the product (R_f = 0.48, weakly UV-active, stains pink). The reaction was terminated by the addition of 1 M aqueous HCl solution and diluted with EtOAc. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 26 mg (61%) of dienone **25** as a colorless oil: IR (thin film): ν_{max} = 2954, 2924, 2868, 1717, 1648, 1182, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (1 H, m), 5.79 (1 H, dd, J = 12.2 Hz, 1.5 Hz), 5.74 (1 H, d, J = 12.8 Hz), 4.17 (2 H, q, J = 7.1 Hz), 2.58 (1 H, dt, J = 13.1 Hz, 3.2 Hz), 2.44 (1 H, dt, J = 12.2 Hz, 1.7 Hz), 2.25 (1 H, td, J = 12.1 Hz, 8.6 Hz), 1.97 (3 H, d, J = 1.3 Hz), 1.94−1.84 (2 H, m), 1.60 (1 H, dt, J = 13.5 Hz, 3.5 Hz), 1.46−1.30 (6 H, m), 1.28 (3 H, t, J = 7.1 Hz), 0.99 (3 H, s), 0.98 (3 H, d, J = 6.5 Hz), 0.82 (3 H, d, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.6, 173.8, 147.6, 145.3, 128.9, 127.5, 60.6, 60.1, 57.5, 57.1, 47.0, 40.6, 39.5, 34.0, 32.1, 29.4, 27.3, 24.7, 24.4, 23.0, 22.3, 14.4; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{22}H_{32}O_3$ + Na^+]: 367.2249; found: 367.2242.

Mulin-12,14-dien-11-on-20-oic Acid (1). This procedure was adapted from a method originally reported by Sebahar and Williams.[48] To an oven-dried microwave tube equipped with a magnetic stirring bar was added a solution of dienone **25** (33 mg, 96 μmol, 1.00 equiv) in 1 mL of freshly distilled 2,4,6-collidine. Lithium iodide (LiI, 641 mg, 4.79 mmol, 50 equiv) was then added in a single portion, the tube was tightly sealed, and the reaction mixture was heated at 200 °C for 1 h under microwave irradiation. After cooling to ambient temperature, the reaction mixture was partitioned between CH_2Cl_2 and aqueous 3 M HCl solution. The layers were separated, and the aqueous phase was extracted with one additional portion of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. TLC (33% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.50, stains pink) and clean formation of the product (R_f = 0.11, stains pink). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (33% to 50% to 66% EtOAc in hexanes), furnishing 29 mg (96%) of mulin-12,14-dien-11-on-20-oic acid (**1**) as an off-white amorphous solid: IR (thin film): ν_{max} = 2953, 2923, 2866, 1716, 1693, 1645, 1613, 1186, 1159 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.96 (1 H, s), 5.81 (1 H, dd, J = 12.3 Hz, 1.0 Hz), 5.77 (1 H, d, J = 12.4 Hz), 2.60−2.56 (2 H, m), 2.27 (1 H, m), 1.98 (3 H, d, J = 1.2 Hz), 1.93−1.87 (2 H, m), 1.63 (1 H, m), 1.56−1.47 (3 H, m), 1.45−1.37 (2 H, m), 1.28 (1 H, m), 1.03 (3 H, s), 1.00 (3 H, d, J = 6.2 Hz), 0.84 (3 H, d, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 178.0 (weak), 147.9, 146.2, 128.7, 127.5, 60.3, 57.5, 57.0 (weak), 46.9, 40.5, 39.5, 33.8, 31.8, 29.0, 27.3, 24.6, 24.3, 22.8, 22.5; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{20}H_{28}O_3$ + Na^+]: 339.1936; found: 339.1929.

Ethyl (3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-10-(((trifluoromethyl)sulfonyl)oxy)-2,3,4,5,5a,6,10a,10b-octahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (26). A solution of ketone **23** (179 mg, 0.52 mmol, 1.00 equiv) in 6 mL of THF was cooled to −78 °C, and potassium bis(trimethylsilyl)amide (KN(TMS)$_2$), 1.29 mL of a 0.5 M solution in toluene, 0.65 mmol, 1.25 equiv) was added dropwise. The reaction mixture immediately turned yellow, and stirring was continued at −78 °C for 45 min. After this time, a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (PhNTf$_2$, 231 mg, 0.65 mmol, 1.25 equiv) in 2 mL of THF was added, and the yellow color of the enolate solution was immediately discharged. After 15 min, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.53, not UV-active) and clean formation of the product (R_f = 0.70, UV-active). The reaction was terminated by the addition of aqueous pH 7 phosphate buffer, diluted with water and EtOAc, and allowed to warm to ambient temperature. The layers were separated, and the aqueous phase was extracted with one additional portion of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (5% to 10% EtOAc in hexanes), furnishing 245 mg (99%) of enol triflate **26** as a colorless oil: IR (thin film): ν_{max} = 2958, 1720, 1673, 1416, 1209, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (1 H, s), 5.62 (1 H, d, J = 6.7 Hz), 4.28−4.20 (1 H, dq, J = 10.8 Hz, 7.1 Hz), 4.16−4.09 (1 H, dq, J = 10.8 Hz, 7.1 Hz), 2.79 (1 H, d, J = 18.5 Hz), 2.51−2.45 (2 H, m), 2.22 (1 H, qd, J = 12.1 Hz, 5.3 Hz), 1.99−1.90 (1 H, m), 1.82 (3 H, s), 1.80−1.73 (2 H, m), 1.61−1.35 (7 H, m), 1.29 (3 H, t, J = 7.1 Hz), 1.00 (3 H, d, J = 5.6 Hz), 0.96 (3 H, s), 0.83 (3 H, d, J = 5.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 151.5, 128.8, 125.4, 122.1, 118.5 (q, $^1J_{C-F}$ = 319 Hz), 60.3, 58.7, 57.8, 53.3, 53.1, 40.4, 36.5, 32.9, 32.1, 32.0, 29.1, 26.8, 26.3, 25.1, 22.9, 22.3, 14.3; HRMS (ESI-TOF): [M + Na^+] calcd for [$C_{23}H_{33}F_3O_5S$ + Na^+]: 501.1898; found: 501.1889.

Ethyl (3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-2,3,4,5,5a,6,10a,10b-octahydrocyclohepta[*e*]indene-3a(1*H*)-carboxylate (27). A solution of enol triflate **26** (245 mg, 0.51 mmol, 1.00 equiv) in 5 mL of DMF was degassed with a stream of argon for 15 min before the addition of anhydrous lithium chloride (LiCl, 65.1 mg, 1.54 mmol, 3.00 equiv), triethylsilane (Et_3SiH, 245 μL, 1.54 mmol, 3.00 equiv), and Pd(PPh$_3$)$_4$ (59 mg, 51 μmol, 0.10 equiv) at ambient temperature. The reaction mixture was then heated at 60 °C for 1 h, at which point the reaction mixture had turned black. After cooling to ambient temperature, the reaction mixture was partitioned between water and Et_2O. The layers were separated, and the organic phase was washed four times with water (to remove DMF), twice with 3% aqueous hydrogen peroxide (to oxidize any residual triphenylphosphine), and once with brine before drying over anhydrous $MgSO_4$. TLC (10% EtOAc in hexanes, UV/anisaldehyde) showed clean spot-to-spot conversion of the starting material (R_f = 0.47, UV-active) to the product (R_f = 0.59, UV-active, stains blue). The solvent was removed under vacuum on a rotary evaporator to afford crude diene **27**, which was contaminated with Et_3SiH. Therefore, the crude mixture was dissolved in 5 mL of THF at ambient temperature and treated with tetrabutylammonium fluoride (3.07 mL of a 1.0 M solution in THF, 3.07 mmol, 6.00 equiv). After 10 min, the reaction was terminated by the addition of saturated aqueous NH_4Cl solution and diluted with water and EtOAc. The layers were separated, and the aqueous phase was extracted with two additional portions of EtOAc before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (5% EtOAc in hexanes), furnishing 168 mg (99%) of pure diene **27** as a colorless oil: IR (thin film): ν_{max} = 2951, 1719, 1180, 1153 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.62 (1 H, dd, J = 12.7 Hz, 1.5 Hz), 5.57 (1 H, dd, J = 12.5 Hz, 5.8 Hz), 5.45 (1 H, d, J =

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7.1 Hz), 4.15 (2 H, q, J = 7.1 Hz), 2.67 (1 H, d, J = 17.3 Hz), 2.43 (1 H, dt, J = 6.2 Hz, 2.8 Hz), 2.15 (1 H, ddd, J = 10.4 Hz, 5.8 Hz, 1.9 Hz), 2.04 (1 H, m), 1.96−1.88 (1 H, m), 1.78 (3 H, d, J = 2.2 Hz), 1.71−1.59 (4 H, m), 1.48−1.33 (5 H, m), 1.28 (3 H, t, J = 7.1 Hz), 1.01 (3 H, d, J = 6.0 Hz), 0.81 (3 H, d, J = 6.4 Hz), 0.82 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 133.1, 131.8, 127.7, 125.4, 59.7, 58.6, 57.7, 55.3, 50.4, 41.3, 36.4, 34.9, 32.9, 32.1, 29.2, 27.2, 25.8, 24.8, 23.0, 22.4, 14.4; HRMS (ESI-TOF): [M + H$^+$] calcd for [$C_{22}H_{34}O_2$ + H$^+$]: 331.2637; found: 331.2631.

Mulin-11,13-dien-20-ol (2). To a solution of ethyl ester **27** (63 mg, 0.19 mmol, 1.00 equiv) in 5 mL of THF was added lithium aluminum hydride ($LiAlH_4$, 817 μL of a 3.5 M solution in $PhCH_3$, 2.86 mmol, 15.00 equiv) at ambient temperature. The flask was equipped with a water-cooled condenser, and the reaction mixture was heated at reflux for 2.5 h. After this time, the reaction mixture was cooled in an ice bath, and EtOAc was added dropwise to consume the excess $LiAlH_4$. Aqueous 3 M HCl solution was then added dropwise, and the reaction mixture was diluted with water and EtOAc until a clear, biphasic solution was obtained. The layers were separated, and the aqueous phase was extracted with two portions of dichloromethane before the combined organics were dried over anhydrous Na_2SO_4. TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.70) and clean formation of the product (R_f = 0.48). The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 47 mg (85%) of mulin-11,13-dien-20-ol (**2**) as a colorless oil: IR (thin film): ν_{max} = 3403, 2946, 2867, 1455, 1038 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (1 H, d, J = 12.6 Hz), 5.49−5.43 (2 H, m), 3.79 (1 H, d, J = 11.6 Hz), 3.57 (1 H, d, J = 11.5 Hz), 2.73 (1 H, d, J = 17.2 Hz), 2.16 (1 H, dt, J = 13.4 Hz, 3.5 Hz), 2.05 (1 H, dd, J = 11.0 Hz, 6.1 Hz), 1.88 (1 H, dtd, J = 13.6 Hz, 9.5 Hz, 6.2 Hz), 1.79 (3 H, dd, J = 2.5 Hz, 1.4 Hz), 1.72−1.58 (4 H, m), 1.47 (1 H, m), 1.40 (1 H, m), 1.30 (1 H, dt, J = 11.5 Hz, 4.1 Hz), 1.24 (1 H, td, J = 12.5 Hz, 3.5 Hz), 1.17−1.08 (2 H, m), 1.03 (3 H, d, J = 6.4 Hz), 0.87 (3 H, s), 0.85 (3 H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 131.7, 127.9, 125.7, 60.2, 58.1, 54.1, 49.3, 48.3, 39.2, 36.4, 35.0, 31.8, 30.0, 28.4, 27.3, 25.7, 23.9, 23.5, 23.3; HRMS (ESI-TOF): [M + H$^+$] calcd for [$C_{20}H_{32}O$ + H$^+$]: 289.2531; found: 289.2523.

20-Hydroxymulin-11,13-dienyl Acetate (3). To a solution of alcohol **2** (7.5 mg, 26 μmol, 1.00 equiv) in 1 mL of CH_2Cl_2 at ambient temperature was added Et_3N (7.25 μL, 26 μmol, 2.00 equiv), followed by solid 4-(dimethylamino)pyridine (DMAP, 0.3 mg, 2.6 μmol, 0.10 equiv) and acetic anhydride (Ac_2O, 4 μL, 39 μmol, 1.5 equiv), and the reaction mixture was stirred at ambient temperature for 2.5 h. After this time, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed complete consumption of the starting material (R_f = 0.48) and clean formation of the product (R_f = 0.65). The reaction was terminated by the addition of aqueous pH 7 phosphate buffer and diluted with CH_2Cl_2. The layers were separated, and the aqueous phase was extracted with one additional portion of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 8 mg (93%) of 20-hydroxymulin-11,13-dienyl acetate (**3**) as a colorless oil: IR (thin film): ν_{max} = 2923, 1741, 1237, 1037 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (1 H, dd, J = 12.5 Hz, 1.0 Hz), 5.46 (1 H, d, J = 7.9 Hz), 5.36 (1 H, dd, J = 12.5 Hz, 6.3 Hz), 4.27 (1 H, d, J = 11.9 Hz), 3.90 (1 H, d, J = 11.8 Hz), 2.66 (1 H, d, J = 17.2 Hz), 2.08 (1 H, dt, J = 13.5 Hz, 3.1 Hz), 1.91 (1 H, dd, J = 11.0 Hz, 6.7 Hz), 1.79 (3 H, s), 1.68 (3 H, s), 1.65−1.59 (2 H, m), 1.53−1.45 (3 H, m), 1.32 (1 H, m), 1.18−1.13 (3 H, m), 1.03 (3 H, d, J = 6.4 Hz), 0.95 (3 H, s), 0.93 (1 H, m), 0.83 (1 H, m), 0.82 (3 H, d, J = 6.6 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 169.9, 132.7, 131.6, 127.5, 125.4, 61.6, 57.7, 53.7, 48.9, 46.6, 38.8, 36.4, 34.6, 31.5, 30.5, 28.1, 27.0, 25.6, 23.5, 23.3, 22.7, 20.2; HRMS (ESI-TOF): [M + Na$^+$] calcd for [$C_{22}H_{34}O_2$ + Na$^+$]: 353.2457; found: 353.2450.

(3*R*,3a*S*,5a*S*,10a*S*,10b*S*)-3-Isopropyl-5a,8-dimethyl-2,3,4,5,5a,6,10a,10b-octahydrocyclohepta[*e*]indene-3a(1*H*)-carbaldehyde (28). To a solution of alcohol **2** (53 mg, 184 μmol, 1.00 equiv) in 5 mL of CH_2Cl_2 was added $NaHCO_3$ (93 mg, 1.10 mmol, 6.00 equiv) and Dess−Martin periodinane (117 mg, 276 μmol, 1.50 equiv). After 25 min at ambient temperature, TLC (25% EtOAc in hexanes, anisaldehyde) showed complete consumption of the starting material (R_f = 0.48) and formation of the product (R_f = 0.69). The reaction was terminated by the addition of a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and the mixture was stirred until a clear, biphasic solution was obtained. The layers were separated, and the aqueous phase was extracted with two additional portions of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by column chromatography (10% EtOAc in hexanes), furnishing 38 mg (72%) of aldehyde **28** as a colorless oil: IR (thin film): ν_{max} = 3397, 2953, 2928, 2871, 1715, 1456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.83 (1 H, s), 5.63 (1 H, dd, J = 12.4 Hz, 0.8 Hz), 5.54 (1 H, dd, J = 12.5 Hz, 6.3 Hz), 5.45 (1 H, d, J = 7.1 Hz), 2.70 (1 H, d, J = 17.7 Hz), 2.36 (1 H, dt, J = 6.6 Hz, 3.6 Hz), 2.15−2.04 (1 H, dtd, J = 13.7 Hz, 9.2 Hz, 6.6 Hz), 1.99 (1 H, ddd, J = 11.7 Hz, 6.6 Hz, 2.0 Hz), 1.97−1.90 (2 H, m), 1.79 (3 H, s), 1.78 (1 H, m), 1.64 (1 H, ddd, J = 17.6 Hz, 8.3 Hz, 2.0 Hz), 1.50−1.42 (3 H, m), 1.36−1.25 (3 H, m), 0.93 (3 H, d, J = 5.9 Hz), 0.85 (3 H, d, J = 6.0 Hz), 0.83 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 132.1, 131.6, 128.3, 125.6, 61.2, 57.3, 53.9, 50.7, 40.0, 36.1, 34.8, 31.8, 29.8, 29.1, 27.1, 26.0, 24.3, 23.2, 22.2; HRMS (ESI-TOF): [M + H$^+$] calcd for [$C_{20}H_{30}O$ + H$^+$]: 287.2375; found: 287.2364.

Mulin-11,13-dien-20-oic Acid (4). To a solution of aldehyde **28** (10 mg, 35 μmol, 1.00 equiv) in 1.5 mL of *tert*-butanol (*t*-BuOH) and 1 mL of water was added sodium dihydrogen phosphate monohydrate ($NaH_2PO_4{\cdot}H_2O$, 21 mg, 175 μmol, 5.00 equiv) and 2-methyl-2-butene (1 mL, 9.44 mmol, 270 equiv). The resulting biphasic mixture was stirred vigorously at ambient temperature, and sodium chlorite ($NaClO_2$, 20 mg, 175 μmol, 5.00 equiv, 80% technical grade) was added in a single portion. After 30 min, TLC (25% EtOAc in hexanes, UV/anisaldehyde) showed unreacted starting material (R_f = 0.69) and ∼15% conversion to the product (R_f = 0.43, UV-active). Additional 20 mg portions of $NaH_2PO_4{\cdot}H_2O$ and $NaClO_2$ were added periodically (every 30 min, 200 mg of each, in total), and the progress of the reaction was monitored by TLC. After 6 h, essentially all of the starting material had been consumed to give the desired carboxylic acid as the major product along with two slightly more polar byproducts that were not UV-active. The reaction was diluted with EtOAc and brine, and the layers were separated. The aqueous phase was then extracted with two portions of CH_2Cl_2 before the combined organics were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum on a rotary evaporator, and the residue was purified by preparative TLC (sample loaded in CH_2Cl_2, eluted in 20% EtOAc in hexanes, silica washed with EtOAc), furnishing 6 mg (57%) of mulin-11,13-dien-20-oic acid (**4**) as an off-white amorphous solid: IR (thin film): ν_{max} = 2953, 2928, 2871, 1690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (1 H, d, J = 12.6 Hz), 5.57 (1 H, dd, J = 12.5 Hz, 6.0 Hz), 5.46 (1 H, d, J = 8.0 Hz), 2.68 (1 H, d, J = 17.2 Hz), 2.42 (1 H, dt, J = 13.1 Hz, 3.1 Hz), 2.18 (1 H, dd, J = 10.0 Hz, 6.1 Hz), 2.05−1.98 (1 H, m), 1.95−1.91 (1 H, m), 1.79 (3 H, s), 1.74−1.70 (2 H, m), 1.68−1.64 (1 H, m), 1.60 (1 H, m), 1.50−1.35 (5 H, m), 1.02 (3 H, d, J = 5.7 Hz), 0.86 (3 H, d, J = 5.0 Hz), 0.85 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 132.8, 131.8, 127.9, 125.4, 58.5, 57.6, 55.1, 50.4, 41.1, 36.4, 34.9, 32.7, 31.9, 28.9, 27.2, 25.8, 24.7, 22.9, 22.5; HRMS (ESI-TOF, negative ion mode): calcd for [$C_{20}H_{30}O_2$ − H$^+$]: 301.2173; found: 301.2178.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds and full NMR assignments for compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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