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Toward the Synthesis of Phomoidride D

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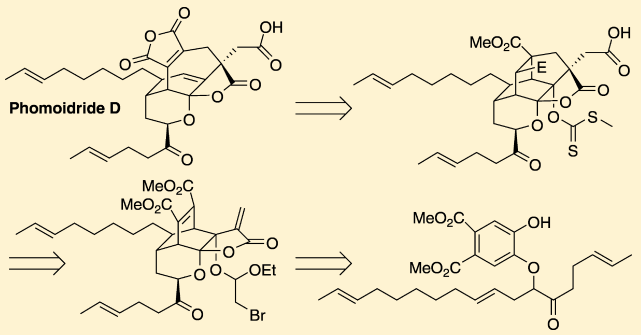
Supporting Information

ABSTRACT: An efficient and highly stereoselective approach toward the phomoidride family of natural products is described. The carbocyclic core structure was assembled using a tandem phenolic oxidation/Diels–Alder cycloaddition and a tandem 5-*exo*-*trig*/5-*exo*-*trig* radical cyclization to deliver an isotwistane intermediate that, upon a late-stage xanthate-initiated Grob fragmentation, furnishes the requisite bicyclo[4.3.1]decene.



INTRODUCTION

As part of a discovery effort toward new cholesterol-lowering and anticancer agents, researchers at Pfizer reported the isolation and structure elucidation of two novel fungal metabolites, phomoidrides A and B (**1** and **2**, a.k.a. CP-225,917 and CP-263,114, respectively).[1] Following this report, a number of synthetic chemists, intrigued by the novel structural features, initiated studies directed toward these targets,[2] efforts that culminated in not only several completed syntheses[3] but also the isolation and structural elucidation of two novel congeners, phomoidrides C and D (**3** and **4**, respectively, Figure 1).[3f,4]

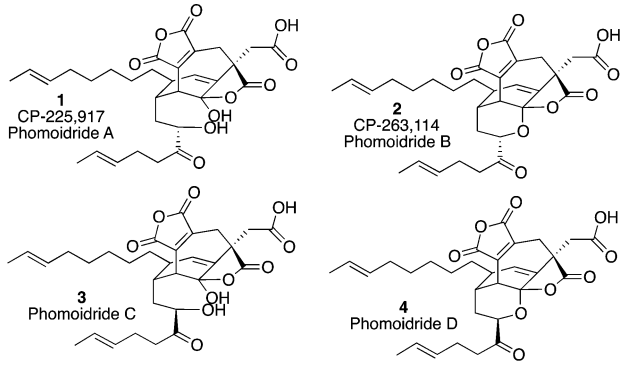
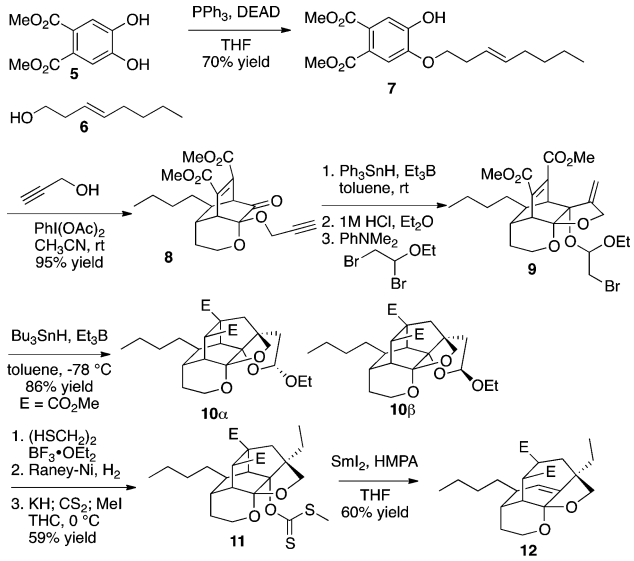


Figure 1. Structures of phomoidrides A–D.

We previously disclosed efforts toward a synthesis of the phomoidrides wherein the efficient assembly of an isotwistane skeleton was developed and set the stage for a fragmentation reaction that unveiled the carbocyclic core of the natural products.[5] The efficiency of the approach stemmed from the incorporation of two cascade sequences. As illustrated in Scheme 1, the first of these employed an intramolecular Diels–Alder (IMDA) reaction as the terminal step in a sequence that delivered **8** via the $PhI(OAc)_2$-mediated aryl oxidation of **7**, the coupling product of two readily available starting materials **5** and **6**, and the in situ incorporation of

Scheme 1. Assembly of the Phomoidride Carbocyclic Core



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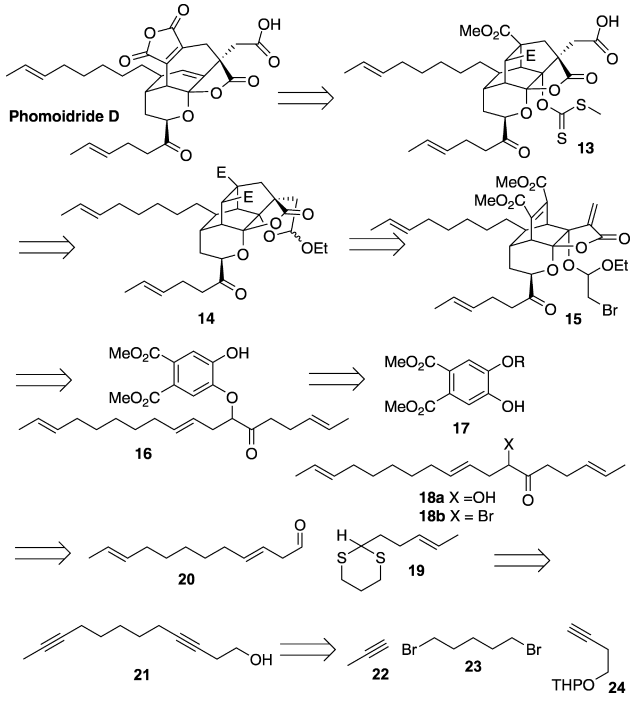
propargyl alcohol. Advancing the IMDA product (**8**) to bromoacetal **9** via a three-step sequence set the stage for a Ueno–Stork cyclization, the first step in a tandem 5-*exo*/5-*exo* radical ring-closing cascade that led to a 1:1 mixture of isotwistanes **10α**:**10β** in excellent yield.[6] Importantly, this reaction not only introduces two requisite C–C bonds but also allows for the stereocontrolled construction of the synthetically challenging phomoidride quaternary center. Acetals **10** underwent a two-step transacetalization/reductive desulfurization to provide an intermediate tertiary alcohol that, following conversion to the corresponding xanthate (**11**), was fragmented to provide **12**, a compound possessing the phomoidride carbocyclic core. Having developed an efficient access to a core structure containing the proper relative stereochemical configurations, we turned our sights to translating these efforts to a fully functionalized substrate suitable for conversion to the natural products.

As illustrated in a retrosynthetic fashion (Scheme 2) for the synthesis of phomoidride D, extending our preliminary investigations led to an approach that called for the late-stage SmI_2-promoted fragmentation of **13** to reveal the core ring system, a sequence that would conclude with introduction of the maleate double bond and dehydration to the requisite anhydride. Xanthate **13** would derive from mixed acetal **14** via transacetalization, xanthate formation, and oxidation. In direct analogy to our model study, **14** was seen as arising from a tandem radical cascade reaction applied to bromoacetal **15**, the product of an aryl oxidation/inverse electron-demand IMDA sequence employing phenol **16**. Importantly, this latter sequence held the potential for stereocontrol from the single stereogenic center resident in phenol **16**; however, a priori the extent and sense of stereochemical induction was difficult to predict. At its greatest point of convergence, the plan calls for the coupling of **17** and **18** to deliver **16**, an intermediate possessing all but five of the carbons found in the phomoidride molecules. The major carbon-containing fragment (**18**) was seen as arising from the coupling of dithiane **19**[7] and aldehyde **20**. Although numerous approaches can be envisioned as providing access to the latter, diynol **21** appeared to be a suitable precursor, which could conceivably be accessed from the simple starting materials **22**–**24**.

Scheme 2. Retrosynthetic Analysis

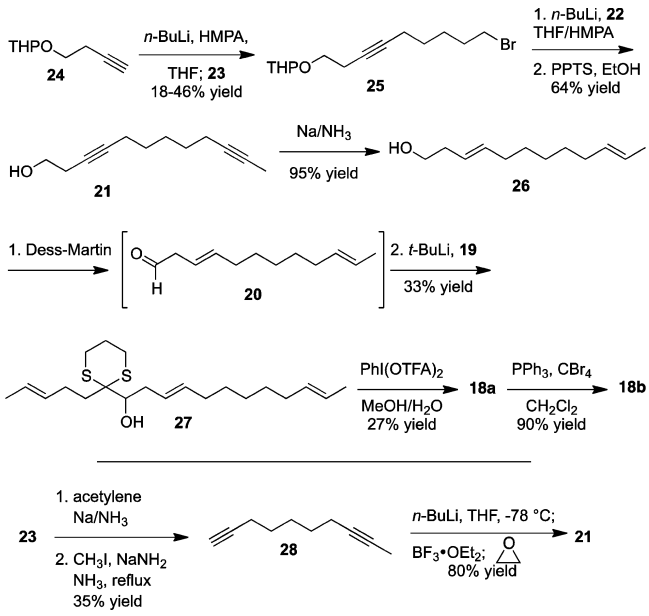


RESULTS AND DISCUSSION

In accord with the plan outlined above, our synthetic efforts commenced with the preparation of **18a**. To this end, the acetylide derived from commercially available THP-protected butynol **24** was combined with 1,5-dibromopentane (**23**) to afford bromide **25** in modest yield (Scheme 3).[8] Subsequent displacement of the remaining bromide with propynyl lithium furnished, upon deprotection, alcohol **21**. Exposure of **21** to Na/NH_3 led to the desired *trans*–*trans* dienyl alcohol **26** that, when treated with the Dess–Martin reagent, underwent oxidation to the corresponding aldehyde (**20**). Addition of the lithium anion of thioacetal **19** to a crude solution of **20** furnishes secondary alcohol **27**.[3b,c,7] Removal of the dithiane[9] by treating with $PhI(OTFA)_2$ in methanol furnished α-hydroxyketone **18a**, which could easily be converted to α-bromoketone **18b**. Unfortunately, this sequence was very low yielding (2.3% over eight steps) and was thus not synthetically useful. The very first step provided the greatest challenge in terms of scale-up, furnishing **25** with an average yield of less than 46%. As a result, we devised an improved route to **21** that calls for the reaction of 1,5-dibromopentane (**23**) with excess sodium acetylide.[10] The resulting diyne is methylated to afford a mixture of methylated products, from which monomethyl diyne **28** is recovered in 35% yield.[11] Although the yield was again modest, this route had distinct advantages, including the following: (a) the alkylation step was performed at high concentration, (b) the reagents are inexpensive, and (c) the product is easily purified by distillation. As a result, scaling the transformation to runs of greater than 2 mol was done without difficulty. Diyne **28** was next deprotonated and treated with ethylene oxide to efficiently provide alcohol **21**.[17]

Although we had improved the synthesis of **21**, this route still suffered from the instability of aldehyde **20**, and the resulting difficulty associated with the dithiane anion addition.

Scheme 3. First- and Second-Generation Syntheses of 21



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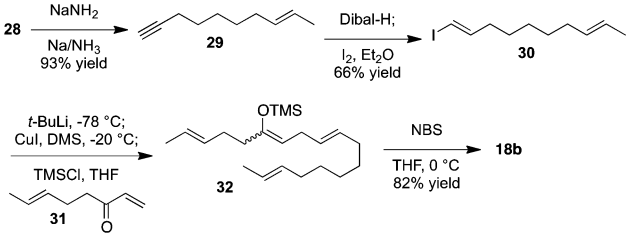
Unfortunately, all efforts to optimize these latter stages were unsuccessful; thus, a second-generation synthesis of α-bromoketone **18b** was developed. The key component of this modified approach was conjugate addition of the anion derived from diene **30** to known α,β-unsaturated ketone **31**.[3e,12] Importantly, diene **30** was readily accessible from diyne **28** via a two-step sequence involving the reduction of the internal alkyne under conditions developed by Dobson and Raphael, followed by hydroalumination/iodination of the intermediate enyne **29**.[13] Conversion of **30** to the corresponding cuprate and addition to enone **31** under TMSCl-accelerated conditions[14] led to a smooth conjugate addition that generated a 3:1 mixture of enol ethers (**32**), favoring the Z-isomer. The latter were carried on without purification into an NBS-mediated bromination that delivered α-bromoketone **18b** in 82% overall yield (Scheme 4). Importantly,

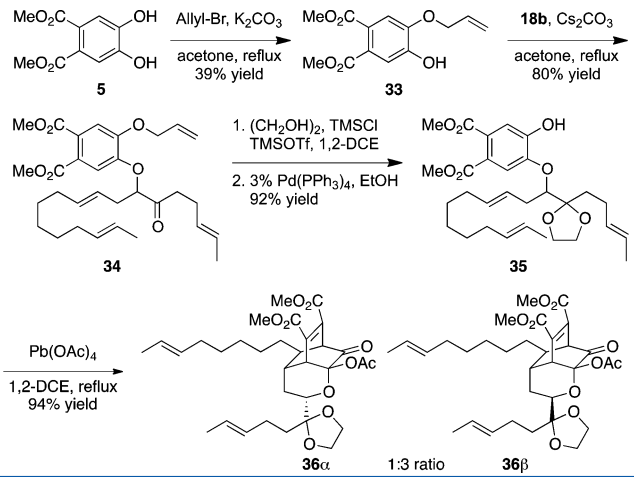
Scheme 4. Revised Synthesis of α-Bromoketone 18b



this conjugate addition reaction is very reproducible, easily performed on a 10 g scale, and allows for the regioselective preparation of substantial quantities of **18b**.

Assembly of the Phomoidride Carbocyclic Core. Having prepared the major carbon-containing fragment, we turned our focus to assembling the phomoidride carbocyclic core. To this end, catechol **5**[5] was protected as its monoallyl ether (**33**) and alkylated with bromoketone **18b** to yield **34**. Protection of the ketone under modified Noyori conditions,[15] followed by deprotection of the allyl ether, provided phenol **35**, the desired substrate for the tandem phenolic oxidation/Diels–Alder reaction.[16,17] Upon exposure to $Pb(OAc)_4$, **35** underwent smooth oxidation and cycloaddition to afford a 1:3 mixture of diastereomers **36α**:**36β** (Scheme 5). Importantly, this cascade sequence

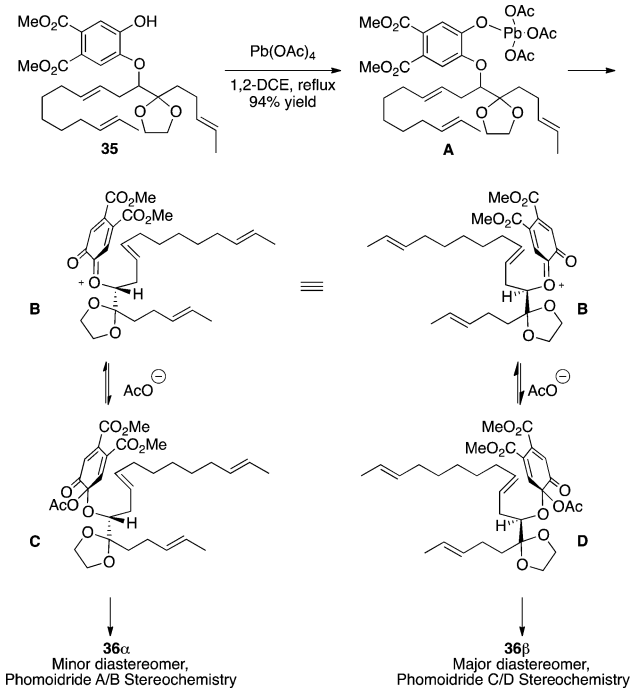
Scheme 5. Phenolic Oxidation/Diels–Alder Sequence



proved to be high yielding, and both of the derived products could potentially be advanced to members of the phomoidride family (phomoidrides A/B or C/D, respectively).

Although the mechanistic details of the Diels–Alder reaction have not been fully delineated, the diastereoselective outcome is likely attributable to a combination of two extremes: either diastereoselective acetal formation, followed by rapid Diels–Alder cycloaddition, or rapid equilibration of the initially formed acetals, followed by differential rates of the diastereomeric Diels–Alder reactions. As illustrated in Scheme 6, the cascade sequence begins

Scheme 6. Diastereoselectivity Rationale in the Phenolic Oxidation/Diels–Alder Sequence



with the formation of an oxocarbenium ion (**B**) that, in the first of the two extreme scenarios, can be envisioned as furnishing **C** and **D** in a diastereomeric ratio that is reflected in the isolated products **36α** and **36β** (i.e., 1:3, respectively). At the other extreme, **B** can be envisioned as producing a rapidly equilibrating mixture of **C** and **D** with the observed ratio of products being dictated by the differential rates of the diastereomeric Diels–Alder reactions that deliver **36α** (slow) and **36β** (fast).

Regardless of the mechanistic details, the excellent efficiency of the cascade reaction put us in a good position to move forward with the synthesis. To this end, our initial attempt to advance the mixture of acetates (**36α**/**36β**) to the requisite *exo*-methylene lactones via a one-pot intramolecular lactonization/Eschenmoser olefination sequence led only to the isolation of **37β** in an unacceptably low yield (Scheme 7).[18] The latter was obtained as a crystalline solid, and single-crystal X-ray analysis confirmed the phomoidride D stereochemistry. An alternate sequence was thus developed wherein **36α**/**β** were subjected to methanolysis and reprotection as the TMS ethers to afford a chromatographically separable and stable mixture of diastereomers **38α** and **38β**.[19] The major isomer **38β** was then subjected to an intermolecular aldol reaction with the lithium enolate of 3-(dimethyl)-amino propionate (**39**) to produce amine **40** that,[20] upon oxidation, Cope elimination, and silyl deprotection, underwent spontaneous cyclization to furnish *exo*-methylene lactone **37β**.

At this stage, all but three of the carbon atoms required to complete the phomoidride synthesis had been installed; thus,

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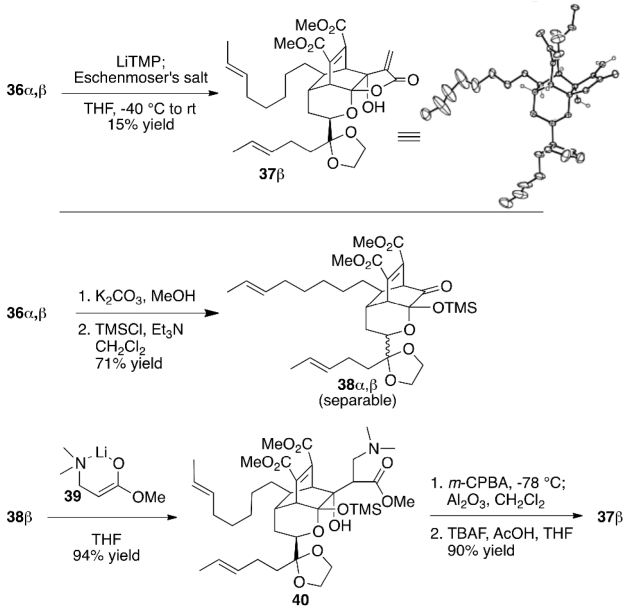
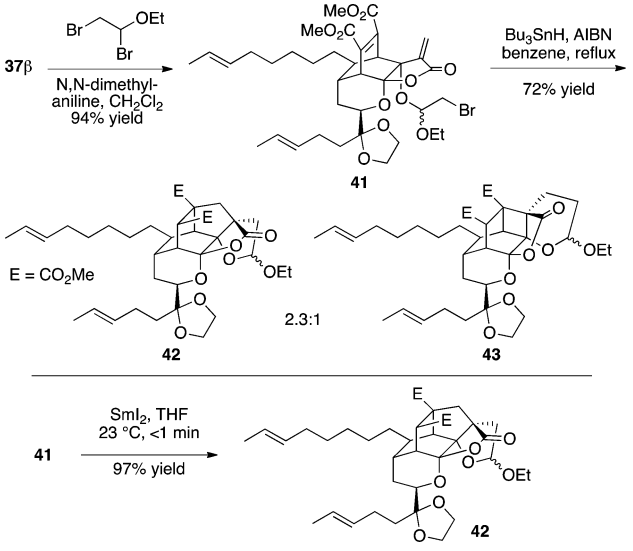
Scheme 7. *exo*-Methylene Lactone Formation



our efforts turned toward setting the stage for the stereocontrolled introduction of the remaining carbon bonds via the planned radical cascade reaction. To this end, alkylation of tertiary alcohol **37*β*** with Stork's dibromoacetal furnished mixed bromoacetal **41**, the key substrate for the radical cyclization cascade that would deliver the isotwistane carbon skeleton (Scheme 8).[6a] Gratifyingly, we found that exposure of **41** to

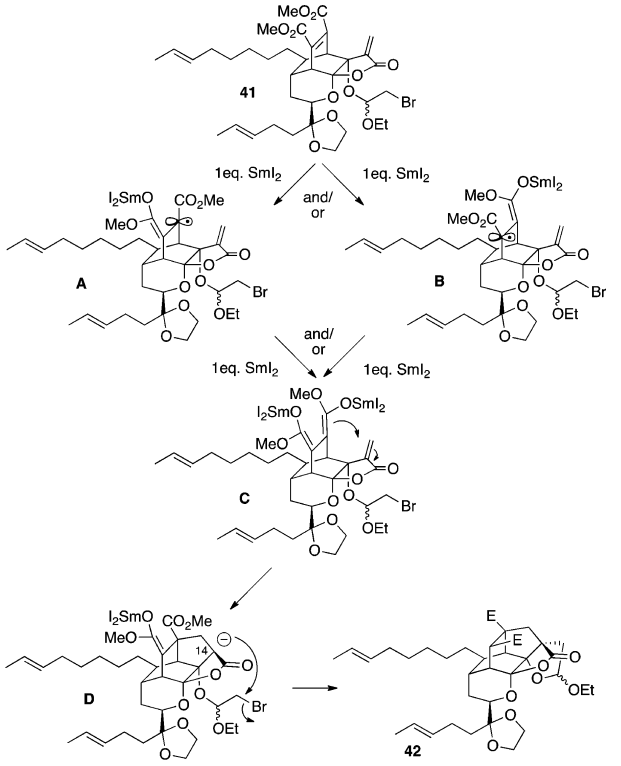
Scheme 8. Radical Cyclization Sequence



Bu_3SnH/AIBN resulted in its smooth conversion to isotwistane **42** via a 5-*exo-trig*/5-*exo-trig* cyclization; however, this desired cyclization was accompanied by a competing event leading to the formation of **43**, an isomeric product derived from a 6-*endo-trig*/4-*exo-trig* radical cyclization pathway. In an effort to improve the yield of this reaction, we explored a number of different conditions for initiating the radical cyclization, all of which were geared toward converting the bromide to the corresponding primary radical. Given the likely intermediacy of the same reactive intermediate, we were stunned to find that initiation of the reaction of bromoacetal **41** by exposure to SmI_2 rapidly produces the desired product **42** in 96% yield with no detectable sign of the undesired 6-*endo-trig*/4-*exo-trig* product![21]

Along with the superb effectiveness of this reaction, we were also surprised by the mild conditions required for its completion (i.e., ambient temperature, no additives, less than 1 min reaction time), which are contrary to that typically necessary for alkyl bromide reduction.[22] The inconsistencies in reactivity led us to suspect that SmI_2 was most likely reducing the maleate and that the observed cyclization was taking place by a different mechanism than was originally anticipated. An alternative mechanistic pathway is illustrated in Scheme 9,

Scheme 9. Proposed Mechanism for the SmI_2-Mediated Cyclization Reaction



wherein reduction of the maleate double bond in **41** delivers vinylogous ketyls **A** and **B** that, upon a second electron transfer, furnish bis-enolate **C**.[14a,23] Reaction of **C** via a 5-*endo-trig* Michael addition into the pendent *exo*-methylene lactone produces an intermediate enolate (**D**) that is poised to undergo a 5-*exo-tet* displacement of bromide to complete the cyclization and produce **42**.[24]

In support of this mechanistic hypothesis is the observation that *exo*-methylene lactone **37*β***, which lacks the bromoacetal moiety, readily undergoes cyclization to the corresponding isotwistane (**44**) upon exposure to the above reaction conditions (SmI_2, THF, rt ~1 min). Additionally, when bromoacetal **41** is treated with SmI_2 at low temperature for 30 min, one can isolate the interrupted cyclization product (**45**) (Scheme 10).

With ready access to **42**, we continued by performing a transacetalization with ethanedithiol to provide **46**, thus enabling derivatization of tertiary alcohol as the xanthate that would be required for fragmentation. Interestingly, during this process, the dioxolane is also converted to the dithiolane (confirmed by single-crystal X-ray analysis of **46**). Before

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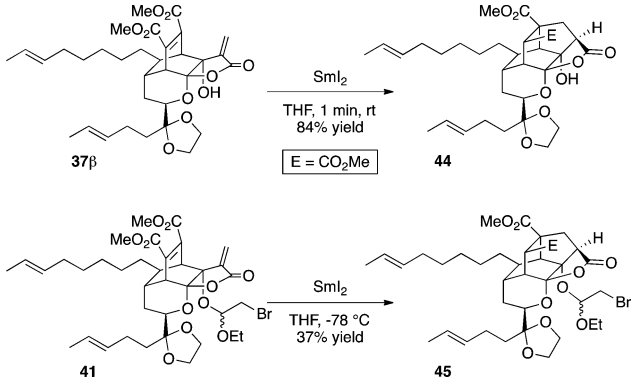
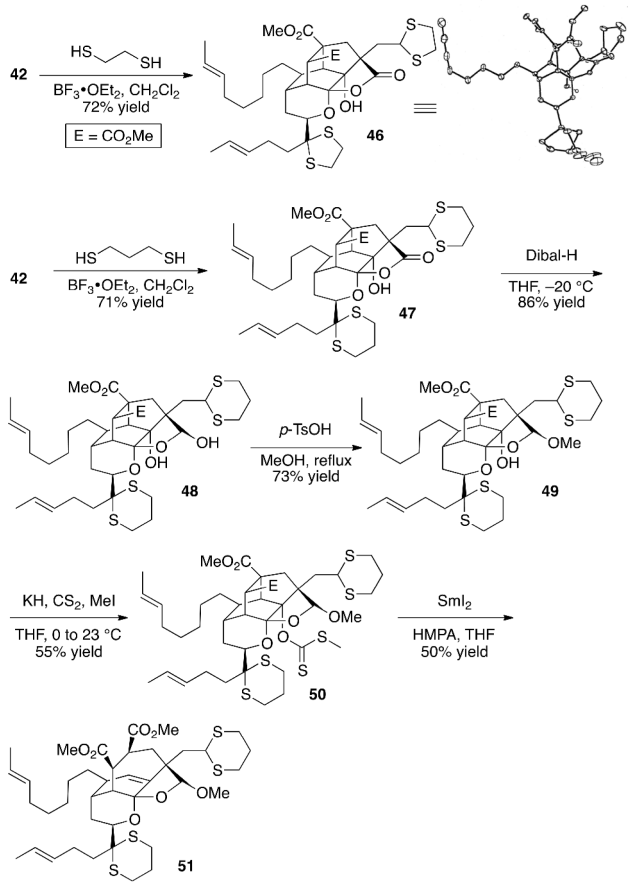
Scheme 10. Support for the "Top-Down" SmI_2-Mediated Cyclization



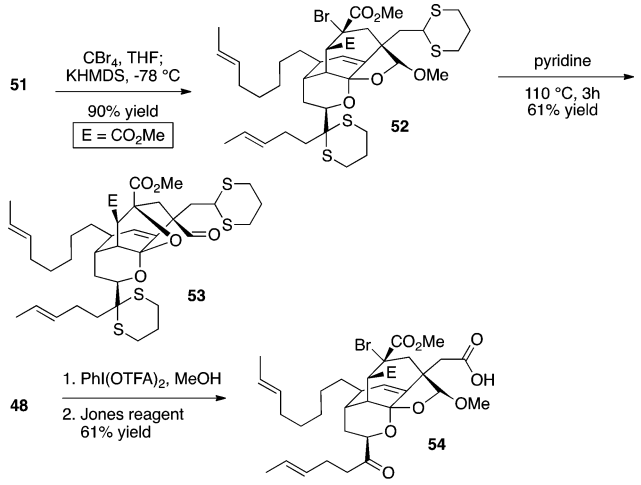
advancing further, we elected to confirm the conditions for removal of the thioacetals. Unfortunately, under a variety of standard deprotection conditions, none of the desired carbonyl products were observed. Conversely, the bis-dithiane (**47**) isolated upon treatment of **42** with propanedithiol was readily cleaved using Stork's $PhI(OTFA)_2$ conditions; thus, further efforts proceeded via the intermediacy of **47**.[9] To this end, DIBAL-H reduction of **47**, followed by protection of the resultant lactol (**48**) as the corresponding methyl acetal (**49**), set the stage for xanthate introduction and completion of key intermediate **50**. Exposure of **50** to SmI_2/HMPA delivered **51** via a Grob fragmentation that unveiled both the bridgehead olefin and the [4.3.1] bicyclic core of the phomoidrides (Scheme 11).[25]

Scheme 11. Dithiolane and Dithiane Syntheses



Successfully unraveling isotwistane **50**, after having taken advantage of the efficiency and stereocontrol that stemmed from the two cascade sequences leading to its construction, left us quite confident in our ability to access the phomoidrides via what were now seemingly minor oxidation state adjustments. Unfortunately, as is often the case in synthesis, a sense of confidence usually precedes a period of unexpected torment, which, in the case of this synthesis, came with the challenging efforts to install the maleate olefin. In what was hoped to be a very standard course of events, we explored conditions for the introduction of a leaving group adjacent to one of the ester moieties. Although decomposition proved a predominant reaction pathway, we eventually found that treating **51** with CBr_4/KHMDS efficiently furnishes the bromoester **52** (Scheme 12).[26] Unfortunately, all attempts to install the

Scheme 12. Toward Installation of the Maleate Olefin



maleate alkene by elimination of bromide failed; however, upon heating in pyridine, an interesting product (**53**) was isolated that suggested the presence of the elusive maleate. Given the unexpected difficulties associated with introducing the maleate, we chose to first address a different challenge by cleaving the dithianes and oxidizing the resulting acetal/aldehyde with Jones reagent. While the dithianes were cleanly deprotected and oxidized employing conditions we had established as effective on earlier intermediates (vide supra), the cyclic methyl acetal was unaffected, and proved resistant to oxidation. At this stage, our efforts to orchestrate a viable endgame had depleted our supply of advanced materials, so we decided to leave the synthesis at intermediate **54** and reconsider the stage at which the ester groups are introduced. To this end, as illustrated in Scheme 13, current efforts are focusing on employing the methods described herein to access intermediates poised for the concomitant introduction of an ester moiety and the maleate double bond. These efforts are underway and will be reported in due course.

CONCLUSION

In this report, we have described the continuation of our efforts to develop a synthesis of the phomoidrides that incorporates the fragmentation of an isotwistane intermediate as a key step. These current studies have demonstrated that this strategy, which incorporates two highly efficient cascade sequences to deliver the requisite isotwistane, can be readily employed on fully functionalized substrates and stereoselectively delivers

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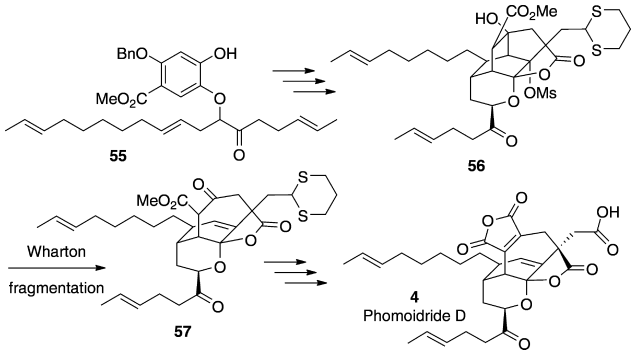
Scheme 13. Alternate Substrate Design for the Phomoidride Synthesis



intermediates possessing all of the carbon atoms and stereogenic centers required for the preparation of phomoidride D. In addition, efforts to improve efficiency resulted in the discovery of an interesting SmI_2 initiated radical cascade reaction, which furnishes **42** in 97% yield. Although we were unable to implement the final series of oxidation state changes and complete the synthesis, these efforts defined a clear path forward, the results of which will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. The NMR data are reported as follows: chemical shift in parts per million (ppm) on the δ scale, multiplicity (app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants (Hz), and integration. ^{1}H NMR spectra were recorded at ambient temperature at either 300 or 400 MHz. ^{13}C NMR spectra were recorded at ambient temperature at 100 MHz. For ^{1}H NMR spectra acquired in $CDCl_3$, chemical shifts are reported as δ values in ppm and are calibrated according to internal $CHCl_3$ (7.26 ppm). For ^{1}H NMR spectra acquired in DMSO-*d6*, chemical shifts are reported as δ values in ppm and are calibrated according to internal DMSO (2.50 ppm). For ^{13}C NMR spectra, chemical shifts are reported as δ values in ppm relative to chloroform and DMSO. Infrared spectra (IR) were obtained on an FTIR spectrophotometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were acquired on an electrospray ionization (ESI) spectrometer and were obtained by peak matching. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm precoated silica gel plates. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on silica gel (SiO_2) 60 Å (200−400 mesh). Unless otherwise noted, all reactions were carried out using flame-dried or oven-dried glassware, and inert atmosphere operations were conducted under N_2 (g) passed through a Drierite drying tube. A CEM Discover Microwave was utilized for reactions performed under microwave irradiation. Anhydrous tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), toluene, and diethyl ether (Et_2O) were filtered through two columns of activated basic alumina and transferred under Ar (g) according to the method described by Grubbs.[1] Anhydrous toluene was filtered through one column of activated basic alumina and one column of Q5 reactant, copper(II) oxide oxygen scavenger. Anhydrous acetonitrile (CH_3CN), dimethylsulfoxide (DMSO), and 1,2-dichloroethane were purchased from Aldrich and used without further purification. Triethylamine (Et_3N) was dried by distillation from CaH_2 under nitrogen. Zinc(II) chloride ($ZnCl_2$) was purchased as a 0.5 M solution in THF. All other commercial reagents were used as received, unless noted otherwise. HRMS data were collected at either the University of Illinois Urbana-Champagne or the CSU instrumentation facility using TOF and QTOF equipped instruments. Single-crystal X-ray analyses were performed by Dr. Chris Incarvito (Yale).

Bromide 25. To a stirred solution of THP-ether **24** (5.02 g, 32.6 mmol, 1 equiv) in THF (150 mL) at 0 °C was added *n*-BuLi (2.5 M in hexanes: 14.3 mL, 35.8 mmol, 1.1 equiv). After stirring the reaction mixture for 5 min, DMPU (15 mL) was added, followed by 1,5-dibromopentane **23** (23.7 g, 103 mmol, 3.16 equiv). After 12 h, the reaction was quenched with water (30 mL) and concentrated in vacuo. The resulting mixture was extracted with 30% EtOAc/hexanes (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo, furnishing a crude oil that was purified using silica gel chromatography employing 2−5% EtOAc/hexanes as the eluent to yield **25** (4.52 g, 46% yield) as a clear oil. FTIR (thin film/NaCl) 2936 (s), 2863 (m), 1724 (w), 1461 (w), 1452 (w), 1433 (w), 1351 (w), 1200 (w), 1135 (m), 1121 (m), 1070 (m), 1033 (s), 971 (w), 907 (w), 869 (w), 814 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (t, J = 4.0 Hz, 1H), 3.91−3.86 (m, 1H), 3.82−3.77 (m, 1H), 3.55−3.49 (m, 2H), 3.41 (t, J = 6.5 Hz, 2H), 2.48−2.44 (m, 2H), 2.19−2.15 (m, 2H), 1.89−1.80 (m, 3H), 1.74−1.69 (m, 1H), 1.62−1.49 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.9, 80.9, 66.4, 62.4, 33.8, 32.6, 30.8, 28.3, 27.6, 25.6, 20.4, 19.7, 18.8; HRMS (EI) m/z 301.0803 [calcd for $C_{14}H_{23}BrO_2$ (M − H) 301.0802].

THP-Diyne. Into a stirred solution of HMPA (0.5 mL) and THF (1.5 mL) at −78 °C was condensed an excess of propyne (**22**). The resulting solution was warmed to 0 °C, and *n*-BuLi (2.4 M in hexanes: 1.6 mL, 3.75 mmol, 1.5 equiv) was carefully added dropwise, forming a white precipitate, at which point a solution of **25** (760 mg, 2.5 mmol, 1 equiv) in HMPA (0.5 mL) was added dropwise. The reaction mixture changed from light yellow to dark, and after 2 h, it was quenched by the addition of saturated ammonium chloride (2 mL). The reaction mixture was diluted with 30% EtOAc/hexanes (20 mL) and washed sequentially with water (3 × 10 mL), saturated ammonium chloride (2 × 5 mL), and brine (3 × 5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo, to yield THP-diyne. The resulting oil was purified using silica gel chromatography to furnish THP-diyne (500 mg, 75% unoptimized yield). IR (thin film/NaCl) 2936 (s), 2859 (s), 1454 (m), 1440 (m), 1351 (m), 1260 (m), 1200 (m), 1183 (w), 1159 (w), 1136 (m), 1121 (s), 1069 (m), 1033 (s), 970 (m), 907 (m), 869 (m), 814 (m), 732 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (t, J = 4.0 Hz, 1H), 3.91−3.86 (m, 1H), 3.81−3.77 (m, 1H), 3.54−3.49 (m, 2H), 2.47−2.44 (m, 2H), 2.16−2.11 (m, 4H), 1.84−1.81 (m, 1H), 1.78 (t, J = 2.5 Hz, 3H), 1.74−1.68 (m, 1H), 1.62−1.43 (m, 10H); ^{13}C NMR (125 MHz, CDCl3) δ 98.9, 81.3, 79.4, 77.1, 75.7, 66.4, 62.4, 30.8, 28.8, 28.7, 28.3, 25.7, 20.4, 19.7, 18.9, 18.8, 3.7; HRMS (EI) m/z 261.1850 [calcd for $C_{17}H_{26}O_2$ (M − H) 261.1854].

Alcohol 21. A solution of THP-diyne (680 mg, 2.60 mmol, 1 equiv) and PPTS (65 mg, 0.26 mmol, 0.1 equiv) was heated to reflux in ethanol (35 mL) for 30 min. The reaction mixture was cooled to room temperature and concentrated in vacuo. Silica gel chromatography employing 12−14% EtOAc/hexanes as the eluent yielded **17** (393 mg, 85% yield) as a clear oil. FTIR (thin film/NaCl) 3347 (s), 2930 (s), 2858 (s), 1456 (m), 1434 (m), 1333 (m), 1185 (w), 1043 (s), 848 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (t, J = 6.5 Hz, 2H), 2.45−2.41 (m, 2H), 2.19−2.15 (m, 2H), 2.14−2.11 (m, 2H), 1.78 (t, J = 2.5 Hz, 3H), 1.52−1.46 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.8, 79.3, 76.6, 76.6, 75.7, 61.6, 28.8, 28.7, 28.3, 23.4, 18.9, 18.8, 3.6; HRMS (EI) m/z 177.1274 [calcd for $C_{12}H_{18}O$ (M − H) 177.1279].

Alternate Synthesis of 21. A 6 L three-neck flask equipped with two dry ice condensers mounted in one neck via a Claisen adapter, a mechanical stirrer, and a gas inlet was charged with NH_3, which was condensed into the flask until it had been filled to a predetermined level consistent with 3 L. Upon completion of the condensation, one of the dry ice condensers was removed and the gas inlet was transferred from NH_3 to an acetylene source. A gentle stream of acetylene was bubbled into the flask for 15 min to presaturate the ammonia. (Note: Acetylene cylinders contain significant amounts of acetone; thus it was passed through a series of four dry ice cooled traps prior to reaching the gas inlet.) At this point, sodium (117 g, 5.04 mol, 2.74 equiv) was added in small pieces (ca. 10 mm × 5 mm × 5 mm) over 90 min. Periodically during the Na addition, the reaction would turn blue, at which point the Na addition was paused until the color faded. Upon complete addition of sodium, acetylene was passed through the reaction for an additional 5 min, and the gas inlet was replaced with a dropping funnel charged with 1,5-dibromopentane (200 mL, 1.84 mmol, 1 equiv). Dibromopentane was added over

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45 min, and the reaction was then let to warm to reflux over 3 h. The reaction was quenched by slow addition of conc. NH_4OH (300 mL). (Note: This quench should be done dropwise for the first 100 mL as it is exothermic!) At this point, the reaction mixture was carefully diluted with water (1.5 L), and then the entire apparatus was left to warm to room temperature overnight, during which time the NH_3 evaporated. Once the frost on the outside of the flask had melted, the mixture was transferred to a 6 L separatory funnel, and carefully extracted with pentane (3 × 1 L). The combined organics were dried over Na_2SO_4 and then concentrated in vacuo. Distillation at 20 mmHg provided 1,8-nonadiyne as a clear liquid (206 g, 94% yield), which was consistent with commercially available material in both ^{13}C and ^1H NMR.[10]

1,8-Decadiyne (28). A 3 L, three-neck, round-bottom flask was equipped with two dry ice condensers and a gas inlet. The flask was charged with NH_3 (1.5 L) via the gas inlet, which was then removed and replaced with a powder funnel. One of the dry ice condensors was removed to allow for efficient venting while the sodium amide (95.8 g, 2.46 mol, 1.5 equiv) was added through the powder funnel. Next, an addition funnel was attached, and 1,8-nonadiyne (198.5 g, 1.65 mol, 1 equiv) was added over 20 min. The funnel was rinsed with ether (50 mL) and then charged with iodomethane (113 g, 1.82 mol, 1.82 equiv), and the iodomethane was added slowly over a period of 1.5 h. The mixture was allowed to stir for an additional 2 h, at which time NH_4Cl (44.1 g, 0.825 mol, 0.5 equiv) was added with care. Next, water (500 mL) was slowly added via the dropping funnel. The flask was allowed to warm to room temperature, and after the NH_3 had evaporated, the remaining mixture was transferred to a 2 L separatory funnel, and carefully extracted with pentane (3 × 200 mL). The organic layer was washed with 6 N HCl until it remained acidic. The combined organics were washed successively with aqueous $NaHCO_3$ (200 mL), and brine (200 mL). The solvent was removed in vacuo to give 190 g of a mixture of 1,8-nonadiyne, 1,8-decadiyne, and 2,9-undecadiyne that was distilled through a Vigreux column at 6 mmHg to give recovered 1,8-nonadiyne (first fraction, 71.2 g, 36% yield), mixed fractions (second fraction, 37.2 g, 17% yield), and the title compound **28** (81.0g, 37% yield), both ^{13}C and ^1H NMR consistent with the literature reports.[11]

Alcohol 21. To a stirred solution of **28** (6.7 g, 50 mmol, 1 equiv) in THF (500 mL) at −78 °C was added a 2.5 M solution of *n*-BuLi in hexane (24 mL, 60 mmol, 1.2 equiv). This mixture was allowed to stir for 1.5 h at this temperature, at which time $BF_3{\cdot}Et_2O$ (7.8 mL, 55 mmol, 1.1 equiv) was added. After an additional 20 min, ethylene oxide (9 g, 204 mmol, 4.1 equiv) was added slowly by cannula over 35 min. (Note: The ethylene oxide was measured by condensing into a tared flask maintained at −78 °C. It was then transferred to the reaction mixture by placing the tip of a cannula just *above* the surface of the liquid, with the other tip of the cannula *below* the surface of the reaction mixture. In this manner, the ethylene oxide is slowly added to the reaction mixture as it warms from −78 to 0 °C. If the addition was not sufficiently rapid, a 25 °C water bath was used to accelerate the process.) Following the addition, the mixture was stirred for an additional 3 h at −78 °C, at which time the mixture was quenched by the addition of aqueous NH_4Cl (200 mL). The mixture was transferred to a separatory funnel and extracted with EtOAc (3 × 200 mL). The combined organics were washed with brine (200 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to provide an oil that was purified by silica gel chromatography (20−30% EtOAc/hexanes eluent) to furnish **21** (6.8 g, 80% yield) as a clear oil.

Alcohol 26. To liquid NH_3 (50 mL) at −78 °C was added Na metal (1.4 g, 60.9 mmol, 6 equiv). The dark blue solution was warmed to −40 °C, and a solution of **21** (1750 mg, 9.83 mmol, 1 equiv) in a mixture of THF (10 mL) and *t*-BuOH (3 mL) was added dropwise. The reaction mixture was stirred for 1 h and quenched by the addition of MeOH (10 mL), diluted with water (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and chromatographed to provide **26** (1.70 g, 95% yield) as a clear oil. FTIR (thin film/NaCl) 3339 (s), 3021 (m), 2924 (s), 2853 (s), 1461 (m), 1440 (m), 1377 (m), 1260 (w), 1187 (w), 1045 (s), 964 (s), 726 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.55−5.50 (m, 1H), 5.43−5.32 (m, 3H), 3.59 (t, J = 6.5 Hz, 2H), 2.24 (dq, J = 6.5, 1.0 Hz, 2H), 2.01−1.92 (m, 4H), 1.76 (s, 1H), 1.63−1.61 (m, 3H), 1.35−1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 131.7, 125.9, 124.8, 62.2, 36.1, 32.8, 32.6, 29.6, 29.5, 28.8, 18.0; HRMS (EI) m/z 182.1669 [calcd for $C_{12}H_{22}O$ (M^+) 182.1671].

Alcohol 27. To a stirred solution of **26** (196 mg, 1.08 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added Dess−Martin reagent (502 mg, 1.19 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 10 min, then poured onto a silica gel column and eluted rapidly using 10% EtOAc/hexanes. Concentration of the filtrate in vacuo yielded an aldehyde (190 mg, 98% yield) that was carried on directly to the next step. In a separate flask, dithiane **19** (505 mg, 2.69 mmol, 2.5 equiv) in THF (2 mL) at −25 °C was treated with *t*-BuLi (1.6 M in pentane: 1.68 mL, 2.69 mmol, 2.5 equiv) and stirred for 1.5 h. The reaction mixture was cooled to −78 °C before adding a solution of the previously prepared aldehyde in THF (2 mL). After stirring the reaction mixture for 20 min, it was quenched with saturated ammonium chloride (5 mL), extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification using silica gel chromatography employing 2−4% EtOAc/hexanes as the eluent yielded **27** (130 mg, 33% unoptimized yield over the 2 steps). FTIR (thin film/NaCl) 3491 (w), 3014 (w), 2923 (s), 2852 (m), 1434 (m), 1378 (m), 1277 (m), 1061 (m), 965 (s), 909 (w), 806 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57−5.55 (m, 2H), 5.46−5.38 (m, 4H), 3.98 (dt, J = 10.0, 1.5 Hz, 1H), 3.03−2.95 (m, 2H), 2.71−2.63 (m, 4H), 2.34−1.80 (m, 10H), 1.68−1.61 (m, 7H), 1.40−1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5, 131.8, 130.8, 127.6, 125.6, 124.8, 72.7, 58.7, 34.8, 34.0, 32.8, 29.7, 29.5, 29.0, 27.9, 26.3, 25.4, 24.7, 18.1; HRMS (EI) m/z 368.2216 [calcd for $C_{21}H_{36}OS_2$ (M^+) 368.2208].

Alcohol 18a. To a stirred solution of **27** (83 mg, 0.23 mmol, 1 equiv) in a mixture of MeOH (0.9 mL) and water (0.1 mL) was added BTIB (145 mg, 0.34 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min, diluted with water (1 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. Purification using silica gel chromatography employing 5−9% EtOAc/hexanes as the eluent yielded **18a** (17 mg, 27% unoptimized yield) as a clear oil. FTIR (thin film/NaCl) 3473 (m), 3021 (m), 2926 (s), 2854 (s), 1712 (s), 1439 (m), 1403 (w), 1358 (w), 1063 (m), 966 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57−5.44 (m, 3H), 5.41−5.30 (m, 3H), 4.20 (t, J = 5.5 Hz, 1H), 3.42 (s, 1H), 2.57−2.45 (m, 3H), 2.37−2.27 (m, 3H), 2.00−1.93 (m, 4H), 1.64−1.61 (m, 6H), 1.35−1.23 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 135.2, 131.7, 129.3, 126.6, 124.8, 123.7, 76.5, 38.4, 38.2, 37.2, 37.2, 32.7, 29.6, 29.4, 28.8, 26.6, 18.1; HRMS (EI) m/z 278.2245 [calcd for $C_{18}H_{30}O_2$ (M^+) 278.2246].

Dec-8-ene-1-yne (29). A dry, three-neck, 1 L flask was equipped with a dry ice condenser (with a KOH drying tube) and charged with sodium amide (14.6 g, 375 mmol, 2.5 equiv), followed by ammonia (500 mL). Diyne **28** (20.1 g, 150 mmol, 1 equiv) was added in one portion, and the mixture was allowed to stir at reflux for 1 h. Sodium (6.9 g, 300 mmol, 2.0 equiv) was added over 1 h. After the addition was complete, stirring continued for 5 min, at which time the blue color had disappeared. The reaction was quenched by careful addition of methanol (50 mL), followed by water (100 mL). Once the flask had warmed to room temperature, the mixture was transferred to a separatory funnel, and carefully extracted with pentane (3 × 100 mL). The combined organics were dried over Na_2SO_4 and then concentrated in vacuo. Distillation at 20 mmHg provided **29** as a clear liquid (19 g, 93% yield).[3e]

TMS-Enol Ethers 32. To a stirred solution of **30** (6.6 g, 18.9 mmol, 1.0 equiv) in THF (95 mL) at −78 °C was added *t*-BuLi (1.7 M in pentane: 35 mL, 59.5 mmol, 3.15 equiv) slowly until the color of the mixture turned yellow. At this time, a few drops of additional **30** were added until the yellow color of the reaction mixture disappeared. Stirring at −78 °C continued for 20 min, at which time the reaction was warmed to −40 °C and maintained at that temperature for 30 min. The mixture was then recooled to −78 °C and kept at that temperature for 10 min. A solution of CuI (5.71 g, 22.7 mmol, 1.2 equiv) in DMS (36.7 mL, 378 mmol, 20 equiv) was then added over 10 min. Stirring and the reaction temperature (−78 °C) were maintained for an additional 10 min, followed by warming again to −40 °C and keeping the reaction at that temperature for 30

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min, at which point it was again recooled to −78 °C. After stirring at −78 °C for 10 min, a solution of **31** (2.79 g, 17 mmol, 0.9 equiv) and TMSCl (7.19 mL, 42.7 mmol, 2.25 equiv), in THF (10 mL) was added. The reaction was kept at −78 °C for 2 h, warmed to −40 °C, kept at −40 °C for 1 h, warmed to 0 °C, kept at 0 °C for 2 h, warmed to rt, and kept at rt for 2 h. At this time, the reaction was again cooled to −78 °C, and treated with Et_3N (15 mL) and water (10 mL) and pentane (100 mL). The layers were separated, and the organic layer was washed with brine (2 × 100 mL), dried over Na_2SO_4, filtered, concentrated in vacuo, and kept under vacuum for 1 h to remove all traces of DMS (DMS solubilizes the Cu salts, making work up difficult). At this time, pentane (100 mL) was added and the mixture was filtered through Celite. The Celite was then washed with pentane (4 × 50 mL) and concentrated. At this point, an analytical sample of **32** could be obtained by silica gel chromatography (hexanes eluent) to afford **32** in a 3:1 ratio, as an inseparable mixture. FTIR (thin film/NaCl) 3021 (w), 2959 (m), 2925 (s), 2854 (m), 1673 (w), 1451 (w), 1438 (w), 1252 (s), 1163 (m), 1008 (w), 965 (s), 844 (s), 753 (w) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.39−5.21 (m, 6H), 4.82 (t, J = 7.7 Hz, 0.25H), 4.65 (t, J = 7.2 Hz, 0.75H), 2.96−2.92 (m, 1.5H), 2.75−2.71 (m, 0.5H), 2.35−2.21 (m, 2.5H). 2.16−2.11 (m, 1.5H), 2.05−1.95 (m, 4H), 1.63−1.55 (m, 6H), 1.4−1.25 (m, 6H), 0.20 (s, 2.25H), 0.17 (s, 6.75H); ^{13}C NMR (125 MHz, C_6D_6) δ 152.2, 150.6, 131.97, 131.95, 131.3, 131.1, 130.5, 130.4, 129.9, 129.7, 128.6, 125.3, 125.3, 124.9, 124.8, 107.0, 105.4, 37.3, 33.1, 33.1, 32.99, 32.95, 31.9, 30.8, 30.7, 30.5, 29.99, 29.97, 29.95, 29.87, 29.3, 29.2, 29.1, 18.1, 18.1, 0.8, 0.5.

α-Bromoketone 18b. The unpurified foregoing mixture of **32** was dissolved in THF (100 mL) and cooled to 0 °C, and NBS (5 g, 28.3 mmol, 1.5 equiv) was added in one portion. The reaction was stirred at 0 °C for 5 min, and then treated with pentane (150 mL) and water (25 mL). The phases were separated, and the organic layer was washed with water (2 × 25 mL). The combined organics were dried over Na_2SO_4, and then concentrated in vacuo. Purification by silica gel chromatography (0−10% EtOAc/hexanes) gave α-bromoketone **18b** (6.28 g, 81.9% yield) as a clear oil. FTIR (thin film/NaCl) 3021 (w), 2926 (s), 2854 (w), 1717 (s), 1438 (m), 1407 (w), 1376 (w), 1360 (w), 1070 (w), 985 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.57−5.28 (m, 6H), 4.20 (t, J = 15.5 Hz, 1H), 2.80−2.56 (m, 4H), 2.31−2.26 (m, 2H), 2.03−1.93 (m, 4H), 1.64−1.62 (m, 6H), 1.36−1.24 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 135.7, 131.7, 129.3, 126.4, 124.9, 124.7, 52.6, 39.5, 36.9, 32.7, 32.6, 29.6, 29.3, 28.8, 27.1, 18.1, 18.0; HRMS (CI) m/z 341.1470 [calcd for $C_{18}H_{29}BrO$ (M + H) 341.1481].

Alternate Synthesis of 18b. To a stirred solution of **18a** (30 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) was added PPh_3 (40 mg, 0.15 mmol, 1.4 equiv) and CBr_4 (44 mg, 0.13 mmol, 1.2 equiv). After stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and saturated $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The resulting oil was purified using silica gel chromatography to give pure bromide **18b** (33 mg, 90% yield) as a clear oil.

Phenol 33 and Bisallyl Ether. To a solution of catechol **5** (50 g, 221.2 mmol, 1 equiv) in acetone (221 mL, 1.0 M) was added K_2CO_3 (30.6 g, 221.2 mmol, 1.0 equiv) and allyl bromide (19.2 mL, 221.2 mmol, 1.0 equiv). The reaction mixture was heated to reflux for 6 h and then cooled to rt, filtered, and concentrated in vacuo. Purification by silica gel chromatography (10−33% EtOAc/hexanes eluent) gave bisallyl ether (21.4 g, 31.6% yield, eluting first) and monoallyl phenol **33** (23.1 g, 39.3% yield, eluting second) as white crystalline solids. FTIR (thin film/NaCl) 3408 (br), 2952 (m), 1722 (s), 1612 (m), 1580 (m), 1437 (s), 1361 (w), 1306 (s), 1201 (s), 1125 (s), 994 (m), 783 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.21 (s, 1H), 6.1−5.98 (m, 2H), 5.14 (ddd, J = 17.2, 2.8, 1.4 Hz, 1H), 5.35 (dd J = 10.5, 1.1 Hz, 1H), 4.66 (dt, J = 5.49, 1.4 Hz, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.7, 148.3, 147.0, 131.9, 126.9, 123.9, 119.5, 115.4, 112.7, 70.2, 52.79, 52.77. HRMS (ESI) m/z 267.0869 [calcd for $C_{13}H_{15}O_6$ (M + H) 267.0869]. Bisallyl ether: FTIR (thin film/NaCl) 2951 (w), 1724 (s), 1648 (w), 1598 (m), 1517 (m), 1435 (m), 1407 (w), 1353 (m), 1288 (s), 1196 (s), 1131 (m), 1054 (w), 993 (m), 931 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.02 (dddd, J = 17.25, 10.46, 5.3, 5.3 Hz,1H), 5.39 (dt, J = 17.25, 1.3 Hz, 1H), 5.27 (dt, J = 10.46, 1.3 Hz, 1H), 4.62 (dt, J = 5.3, 1.3 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 150.2, 132.4, 125.3, 118.4, 113.6, 69.9, 52.6. HRMS (ESI) m/z 307.1183 [calcd for $C_{16}H_{19}O_6$ (M + H) 307.1182].

To a solution of bisallyl ether (1.14 g, 3.72 mmol, 1 equiv) in EtOH (37 mL) was added $Pd(PPh_3)_4$ (43 mg, 0.04 mmol, 0.01 equiv), The mixture was then cooled to 0 °C, and $NaBH_4$ (70.4 mg, 1.9 mmol, 0.5 equiv) was added. The reaction was stirred at 0 °C for 2 h, and then quenched with water (5 mL), and extracted with EtOAc (3 × 5 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (20−50% EtOAc/hexanes eluent) furnished recovered bisallyl ether (304 mg, 26.7% yield, eluted first), and **33** (595 mg, 60.2% yield, eluted second) as white solids.

Ketone 34. A stirred solution of bromoketone **18b** (3.3 g, 9.67 mmol, 1.0 equiv), phenol **33** (2.60 g, 9.67 mmol, 1.0 equiv), and $CsCO_3$ (3.15g, 9.67 mmol, 1.0 equiv) in acetone (25 mL, 0.39 M) was heated to reflux and maintained at that temperature for 4 h. At that time, the mixture was cooled to room temperature and the solids were removed by filtration. The organics were diluted with EtOAc (200 mL), washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished **34** (4.03 g, 80% yield). FTIR (thin film/NaCl) 2962 (s), 2854 (s), 1725 (s), 1599 (m), 1579 (m), 1514 (m), 1435 (m), 1405 (w), 1290 (m), 1192 (m), 1128 (m), 1056 (m), 968 (m), 934 (m), 800 (w), 784 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 7.12 (s, 1H), 6.03 (dddd, J = 17.4, 10.5, 5.3, 5.3 Hz, 1H), 5.6−5.25 (m, 8H), 4.62 (dt J = 5.3, 1.3, 1.3 Hz, 2H), 4.57 (t, J = 5.78, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.71−253 (m, 4H), 2.2 (dd, J = 13.3, 6.7) 2H, 1.64−1.56 (m, 6H), 1.35−1.19 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 168.0, 167.4, 151.0, 149.4, 135.5, 132.4, 131.7, 129.6, 127.1, 126.2, 125.0, 124.8, 123.3, 118.5, 116.6, 114.1, 85.0, 70.0, 52.9, 52.8, 38.4, 35.8, 32.7, 29.6, 29.3, 29.3, 28.90, 28.9, 25.9, 18.1, 18.0; HRMS (ESI) m/z 527.3021 [calcd for $C_{31}H_{43}O_7$ (M + H) 527.3009].

Phenol 35: Ketal. To a stirred mixture of ketone **34** (8.0 g, 15.19 mmol, 1.0 equiv), TMSCl (25 mL, 197 mmol, 12.9 equiv), and ethylene glycol (12 mL, 197 mmol, 12.9 equiv) in 1,2-dichloroethane (120 mL, 0.126 M) at 0 °C was added TMSOTf (0.4 mL, 2.2 mmol, 0.15 equiv). The mixture was heated to reflux and maintained at that temperature for 3 h, at which time it was cooled to 0 °C and quenched by the addition of Et_3N (50 mL), then water (200 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organics were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished the ketal (8.0 g, 92% yield) as a clear oil. FTIR (thin film/NaCl) 3083 (w), 3018 (m), 2926 (s), 2854 (s), 1727 (s), 1597 (s), 1575 (m), 1515 (s), 1435 (s), 1405 (m), 1346 (s), 1281 (s), 1193 (s), 1129 (s), 1051 (m), 968 (m), 926 (m), 880 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.15 (s, 1H), 6.03 (dddd, J = 17.14, 10.4, 5.2, 5.2 Hz, 1H), 5.56−5.35 (m, 8H), 5.28 (dd, J = 10.4, 1.3 Hz, 1H), 4.6 (dd, J = 5.2, 1.0 Hz, 2H), 4.51 (t, 5.2 Hz, 1H), 4.27 (dd, J = 7.6, 4.5 Hz, 1H), 4.09−4.03 (m, 1H), 4.0−3.85 (m, 10H), 2.47−2.43 (m, 2H), 2.05−2.03 (m, 2H), 1.98−1.87 (m, 6H), 0.78−1.58 (m, 8H), 1.30−1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 151.5, 150.7, 133.9, 132.9, 131.8, 131.8, 131.0, 131.0, 125.8, 125.2, 125.1, 124.7, 118.1, 115.9, 114.0, 111.4, 83.7, 83.7, 69.8, 66.4, 66.1, 52.7, 52.7, 34.3, 34.0, 32.7, 32.7, 29.6, 29.3, 28.9, 26.0, 18.1; HRMS (ESI) m/z 571.3273 [calcd for $C_{33}H_{47}O_8$ (M + H) 571.3271].

A stirred mixture of the ketal (1.3 g, 2.28 mmol, 1.0 equiv) and $Pd(PPh_3)_4$ (100 mg, 0.087 mmol, 0.038 equiv) in EtOH (25 mL) was lightly degassed by repeating cycles of vacuum(∼1−2 s) and N_2 four times. This was then heated to reflux for 3 h and the cooled to room temperature and concentrated in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished **35** (1.2 g, 99% yield) as a clear oil. FTIR (thin film/NaCl) 3422 (br), 2925 (s), 2854 (s), 1724 (s), 1613 (m), 1578 (s), 1511 (s), 1436 (s), 1364 (m),

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1312 (w), 1258 (m), 1200 (m), 1121 (m), 1051 (m), 968 (m), 925 (m), 854 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.47 (s, 1H), 7.14 (s, 1H), 5.61−5.28 (m, 6H), 4.08−3.92 (m, 4H), 3.88 (s, 3H), 3.85 (s 3H), 2.49 (t, J = 6.6 Hz, 2H), 2.16−2.02 (m, 2H), 2.0−1.85 (m, 6H), 1.8−1.55 (m, 6H), 1.35−1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.2, 150.9, 147.9, 134.8, 131.7, 130.9, 130.5, 129.3, 125.6, 125.3, 124.8, 123.8, 122.7, 120.9, 116.5, 111.6, 86.0, 66.3, 66.2, 52.8, 52.6, 34.9, 34.1, 32.7, 32.6, 29.6, 29.6, 29.2, 29.2, 29.0, 28.9, 26.9, 25.9, 18.1; HRMS (ESI) m/z 531.2958 [calcd for $C_{30}H_{43}O_8$ (M + H) 531.2958].

Acetates 36α and 36β. To a stirred solution of phenol **35** (3.18 g, 5.99 mmol, 1.0 equiv) at reflux in 1,2-dichloroethane (32 mL) was added a solution of $Pb(OAc)_4$ (3.99 g, 8.99 mmol, 1.5 equiv) in 1,2-dichloroethane (40 mL; total concentration of reaction, 0.083 M). The solution was maintained at reflux for 10 min and then cooled to rt and concentrated in vacuo. Purification via silica gel chromatography (short plug ∼4 cm, 25% EtOAc/hexanes eluent) furnished an inseparable mixture of acetates **36α** and **36β** (3.31 g, 94% yield) as a clear oil. Acetate **36β**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.45−5.38 (m, 4H), 4.00−3.92 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.82−3.78 (m, 1H), 3.73 (d, J = 3.6 Hz, 1H), 3.61 (dd, J = 12.4, 2.6 Hz, 1H), 2.15−1.80 (m, 12H), 1.70−1.55 (m, 9 H), 1.4-.12 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 168.5, 166.6, 164.0, 140.7, 131.7, 131.5, 131.1, 131.0, 125.2, 125.1, 125.1, 124.2, 110.4, 110.3, 92.0, 75.1, 66.9, 65.9, 53.9, 53.0, 52.8, 52.7, 45.2, 41.2, 36.1, 35.1, 34.1, 32.6, 29.6, 29.2, 29.2, 28.9, 27.1, 26.0, 21.5, 18.1; HRMS (ESI) m/z 589.3020 [calcd for $C_{32}H_{45}O_{10}$ (M + H) 589.3013]. Acetate **36α**: FTIR (thin film/NaCl) 2929 (m), 1749 (s), 1725 (s), 1434 (m), 1368 (m), 1283 (s) 1229 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45−5.35 (m, 4H), 4.67−4.62 (m, 1H), 4.09 (d, J = 3 Hz, 1H), 4.08−3.82 (m, 4H), 3.86 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.78−3.74 (m, 1H), 3.63 (d, J = 1.5 Hz, 1H), 2.15−1.8 (m, 10H), 1.85−1.78 (m, 1H), 1.72−1.55 (m, 9H), 1.46−1.24 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 170.0, 165.5, 164.7, 139.4, 133.3, 131.5, 131.0, 125.2, 125.1, 124.8, 118.6, 113.6, 110.4, 93.0, 75.9, 69.9, 66.8, 66.2, 53.9, 53.1, 52.9, 52.9, 52.8, 44.2, 39.4, 35.7, 35.4, 34.1, 32.7, 30.8, 29.6, 29.2, 27.2, 15.9, 21.9, 20.7, 18.1, 18.1; HRMS (ESI) m/z 589.3022 [calcd for $C_{32}H_{45}O_{10}$ (M + H) 589.3013].

Preparation of Silyl Ethers 38α and 38β: Lactols. To a cooled solution (0 °C) of acetates **36α,β** (56.2 mg, 0.106 mmol, 1.0 equiv) in MeOH (5 mL) was added K_2CO_3 (29.3 mg, 0.212 mmol, 2.0 equiv). The reaction mixture was warmed to rt, and stirred for 40 min. The reaction was then cooled to 0 °C, quenched with 1 N HCl (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by preparative TLC (33% EtOAc/hexanes eluent) gave lactol-α (11.2 mg, 19.4% yield, higher band) and lactol-β (33.7 mg, 58.3% yield, lower band) as clear oils. Lactol-α: FTIR (thin film/NaCl) 3436 (br), 2930 (s), 2856 (m), 1725 (s), 1634 (w), 1435 (m), 1364 (w), 1225 (s), 1172 (m), 1085 (m), 1043 (m), 967 (m), 925 (w), 736 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (m, 4H), 4.4−3.9 (m, 5H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 1H), 3.57 (d, J = 1.2 Hz, 1H), 3.37 (d J = 2.9 Hz, 1H), 2.12−1.9 (m, 8H), 1.78−1.55 (m, 10H), 1.35−1.22 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 165.2, 165.1, 139.6, 134.8, 131.5, 130.9, 125.3, 125.1, 110.5, 89.6, 77.0, 73.1, 66.7, 66.1, 53.9, 52.9, 43.7, 41.9, 36.2, 35.7, 34.2, 32.7, 30.7, 29.6, 29.2, 27.2, 26.1, 18.1, 18.1; HRMS (ESI) m/z 547.2906 [calcd for $C_{30}H_{43}O_9$ (M + H) 547.2907]. Lactol-β: FTIR (thin film/NaCl) 3200 (br), 2928 (s), 2855 (s), 1723 (s), 1699 (s), 1695 (s), 1642 (s), 1435 (s), 1357 (m), 1280 (m), 967 (m), 924 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43−5.38 (m, 4H), 3.96 (s, 4H), 3.81 (s, 3H), 3.78 (s, 3H), 3.56 (d, J = 2.5 Hz, 1H), 3.52 (s, 1H), 3.13 (d, J = 3.2 Hz, 1H), 2.1−1.75 (m, 9H), 1.7−1.55 (m, 8H), 1.42−1.20 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 165.5, 165.1, 139.8, 133.3, 131.5, 131.0, 125.1, 125.1, 110.3, 89.9, 74.4, 66.5, 65.8, 53.8, 52.8, 52.8, 45.8, 40.8, 35.9, 39.9, 34.3, 32.6, 29.6, 29.1, 29.1, 27.1, 26.2, 18.1; HRMS (ESI) m/z 547.2913 [calcd for $C_{30}H_{43}O_9$ (M + H) 547.2907].

Silyl Ethers 38α/38β. To a solution of lactols-α/β (2.1 g, 4.04 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added Et_3N (676 μL, 4.84 mmol, 1.2 equiv) and TMSCl (651 μL, 4.84 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 5h, at which point additional Et_3N (169 μL, 1.24 mmol, 0.3 equiv) and TMSCl (163 μL, 1.21 mmol, 0.3 equiv) were added. The reaction mixture was stirred at 0 °C for an additional hour and then diluted sequentially with CH_2Cl_2 (20 mL), water (5 mL), and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (5−50% EtOAc/hexanes eluent) furnished TMS-acetal **38α** (131 mg, 5.3% yield, eluting first), TMS-acetal **38β** (1012 mg, 40.5% yield, eluting second), and lactols-α/β (650 mg, 29.5% yield, eluting third) as clear oils. **38α**: FTIR (thin film/NaCl) 2954 (s), 2929 (s), 2855 (s), 1736 (s), 1725 (s), 1643 (m), 1436 (m), 1355 (m), 1276 (s), 1250 (s), 1208 (s), 1188 (s), 1145 (m), 1083 (s), 1045 (m), 847 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48−5.35 (m, 4H), 4.00−3.89 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.54 (dd, J = 12.1, 2.3 Hz, 1H), 3.47 (d, J = 2.5 Hz, 1H), 3.0 (d, J = 3.4 Hz, 1H), 2.15−1.70 (m, 8H), 1.66−1.52 (m, 10H), 1.41−1.19 (m, 8H). 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 165.9, 165.4, 140.4, 132.6, 131.5, 130.9, 125.0, 110.5, 91.7, 73.4, 66.3, 65.3, 55.3, 52.7, 52.5, 48.7, 41.4, 35.6, 35.0, 34.8, 32.6, 29.6, 29.1, 28.3, 27.1, 26.4, 18.1, 1.44; HRMS (ESI) m/z 619.3298 [calcd for $C_{33}H_{51}O_9Si$ (M + H) 619.3302]. **38β**: FTIR (thin film/NaCl) 2954 (s), 2928 (s), 2855 (m), 1755 (s), 1725 (s), 1640 (w), 1436 (m), 1361 (w), 1277 (s), 1249 (s), 1185 (m), 1154 (w) 1082 (m), 1046 (s), 966 (m), 875 (m), 848 (s), 758 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46−5.37 (m, 4H), 4.07−4.00 (m, 2H), 3.95−3.86 (m, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.46 (d, J = 1.5 Hz, 1H), 3.19 (d, J = 2.7 Hz, 1H), 2.12−1.92 (m, 8H), 1.71−1.55 (m, 10H), 1.34−1.20 (m, 8H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 165.6, 165.4, 140.2, 134.1, 131.5, 130.9, 125.2, 125.0, 110.7, 91.4, 72.9, 66.6, 66.2, 54.9, 52.7, 52.6, 45.4, 44.0, 35.8, 35.5, 34.6, 32.7, 31.1, 29.6, 29.2, 27.2, 26.9, 26.0, 18.0, 1.5; HRMS (ESI) m/z 619.3306 [calcd for $C_{33}H_{51}O_9Si$ (M + H) 619.3302].

Preparation of Tertiary Amine 40: Enolate 39. To a solution of diisopropylamine (537 μL, 4.08 mmol, 2.5 equiv) in THF (5 mL) at −78 °C was added n-BuLi (1.6 M in hexane: 2.4 mL, 3.84 mmol, 2.4 equiv) dopwise over 5 min. The resultant mixture was stirred at −20 °C for 5 min, and then cooled to −78 °C. To this mixture was added methyl-3-(dimethylamino)propionate (515 μL, 3.6 mmol, 2.2 equiv) in THF (2 mL) dropwise over 5 min. The reaction mixture was stirred at −78 °C for 30 min, 0 °C for 15 min, and rt for 15 min, and then cooled to −78 °C.

Tertiary Amine 40. A solution of TMS-ether ketone **38β** (1.01 g, 1.63 mmol, 1.0 equiv) in THF (10 mL) was added dropwise to enolate **39** over 10 min. The temperature was maintained at −78 °C for 1 h, at which time it was treated with EtOAc (5 mL) and saturated NH_4Cl (3 mL) and then warmed to rt. The layers of the biphasic mixture were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (5−10% MeOH/CH_2Cl_2 eluent) furnished **40** (1.31 g, 93.5% yield) as a clear oil. FTIR (thin film/NaCl) 3467 (br), 2951 (s), 2928 (s), 2856 (m), 2772 (w), 1721 (s), 1644 (m), 1436 (m), 1347 (w), 1274 (s), 1249 (s), 1195 (m), 1169 (m), 1087 (m), 1071 (m), 1046 (m), 966 (w), 921 (w), 867 (w), 845 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44−5.36 (m, 4H), 4.90 (dd, J = 10.6, 5.2 Hz, 1H), 4.00−3.90 (m, 4H), 3.76 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H). 3.22 (dd, J = 13.0, 8.3 Hz, 1H), 3.01 (d, J = 1.7 Hz, 1H), 2.79−2.69 (m, 2H), 2.67 (d, J = 2.5 Hz, 1H), 2.29−2.20 (m, 2H), 2.20 (s, 6H), 2.10−1.90 (m, 4H), 1.69−1.49 (m, 10H), 1.33−1.18 (m, 8H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 166.5, 166.5, 139.7, 136.7, 131.8, 131.5, 124.8, 124.6, 111.5, 99.7, 80.7, 73.8, 66.1, 65.0, 60.1, 52.2, 52.2, 51.8, 50.7, 50.2, 49.1, 46.4, 37.1, 36.3, 34.9, 34.7, 32.7, 29.7, 29.5, 28.6, 27.4, 26.6, 18.1, 2.0; HRMS (ESI) m/z 750.4252 [calcd for $C_{39}H_{63}NO_{11}Si$ (M + H) 750.4249].

Preparation of Lactone 37β: Unsaturated Ester. Before beginning the reaction, a column of basic alumina was prepared: h = 3 cm, d = 4.5 cm, packed with CH_2Cl_2 (it is critical that the pad of alumina be short and thick). To a solution of tertiary amine **40** (767 mg, 1.02 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added a solution of m-CPBA (275 mg, 1.53 mmol, 1.5 equiv) in CH_2Cl_2

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(5 mL) dropwise over 5 min. The reaction was stirred at −78 °C for 9 min, at which time basic alumina was added (1.5 g). The reaction mixture quickly moved to the prepared alumina column, and the reaction mixture was filtered through basic alumina using CH_2Cl_2/MeOH (10:1) with careful monitoring by TLC. The collected fractions contained both the desired ester (**37β**) and the noneliminated *N*-oxide intermediate (baseline spot on TLC). Upon rotary evaporation, the polar spot is converted to the desired compound (i.e., the baseline spot disappears in the TLC). Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished the unsaturated ester (664 mg, 92.1% yield) as a clear oil. FTIR (thin film/NaCl) 3435 (br), 2953 (s), 2927 (s), 2855 (m), 1716 (s), 1644 (w), 1437 (m), 1321 (m), 1276 (s), 1249 (s), 1181 (m), 1100 (m), 1056 (m), 965 (m), 923 (m), 864 (m), 846 (m), 811 (w), 760 (w), 734 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.68 (s, 1H), 5.56 (s, 1H), 5.50−5.45 (m, 2H), 5.41−5.37 (m, 2H) 4.87 (dd, J = 10.8, 5.4 Hz, 1H), 4.00−3.90 (m, 4H), 3.77 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.35 (d, J = 1.7 Hz, 1H), 2.63 (d, J = 2.6 Hz, 1H), 229 (m, 1H), 2.20−1.90 (m, 5H), 1.80−1.58 (m, 10H), 1.35−1.21 (m, 8H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.7, 165.7, 143.9, 143.5, 132.8, 131.7, 131.3, 124.9, 124.9, 120.0, 111.4, 99.2, 82.2, 74.5, 66.3, 65.3, 52.6, 52.2, 52.0, 50.6, 46.0, 38.1 36.1, 34.9, 34.8, 32.7, 29.7, 29.5, 28.3, 27.5, 26.8, 18.2, 18.2, 1.61; HRMS (ESI) m/z 705.3654 [calcd for $C_{37}H_{57}O_{11}Si$ (M + H) 705.3670].

Lactone 37β. To a solution of unsaturated ester (1.52 g, 2.15 mmol, 1.0 equiv) in THF (21.5 mL) was added AcOH (616 μL, 10.75 mmol, 5 equiv) and TBAF (1.0 M in THF: 4.3 mL, 4.3 mmol, 2 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min, allowed to warm to rt, and stirred at rt for 2.5 h. At that time, an additional equivalent of TBAF was added (2.15 mL, 2.15 mmol, 1 equiv), and stirring continued for 45 min, when a fourth equivalent of TBAF was added (2.15 mL, 2.15 mmol, 1 equiv). After an additional 15 min, water was added (50 mL) and the reaction was diluted with EtOAc (50 mL). The resultant biphasic mixture was separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (25−33% EtOAc/hexanes eluent) furnished **34** (1.26 g, 98% yield) as a clear oil. **37β**: FTIR (thin film/NaCl) 3420 (br), 2927 (s), 2855 (m), 1781 (s), 1733 (s), 1718 (s), 1457 (m), 1436 (m), 1280 (s), 1148 (m), 1088 (s), 1010 (m), 966 (m), 919 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 1H), 5.98 (s, 1H) 5.5−5.35 (m, 4H), 4.57 (dd, J = 11.5, 3.7 Hz, 1H), 4.40 (s, 1H), 4.15−3.85 (m, 4H), 3.24 (s, 3H), 3.21 (s, 3H), 3.28 (d, J = 1.7 Hz, 1H), 2.96 (d, J = 2.6, 1H), 2.2−1.55 (m, 16H), 1.35−1.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 165.7, 165.2, 140.8, 138.9, 136.9, 131.5, 130.8, 127.5, 125.4, 125.0, 111.0, 104.2, 76.7, 76.6, 66.5, 66.3, 52.8, 52.7, 48.3, 46.0, 37.7, 36.0, 35.8, 33.9, 32.7, 29.6, 29.6, 29.3, 27.4, 25.9, 18.1; HRMS (ESI) m/z 601.2999 [calcd for $C_{33}H_{45}O_{10}$ (M + H) 601.2996].

Alternate Preparation of Lactone 37β: LTMP. To a cooled (−10 °C) solution of 2,2,6,6-tetramethylpiperidine (115 μL, 0.68 mmol, 4.0 equiv) in THF (1.5 mL) was added *n*-BuLi (1.6 M in hexane: 360 μL, 0.58 mmol, 3.4 equiv). This solution was stirred at −10 °C for 30 min, at which time it was cooled to −40 °C.

To a mixture of **36αβ** (100 mg, 0.17 mmol, 1.0 equiv) and Eschenmoser's salt (189 mg, 1.02 mmol, 6.0 equiv) was added THF (2.5 mL), and this was cooled to −40 °C. The solution of LTMP was transferred to the second flask via cannula. This mixture was allowed to warm to rt over 1.5 h, and then let stir overnight (~16 h) at ambient temperature. It was then quenched with water (3 mL), diluted with EtOAc (10 mL), and separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (30% EtOAc/hexanes eluent) furnished **37β** (15 mg, 15% yield) as a clear oil.

Bromoacetal 41. To a solution of tertiary alcohol **37β** (1.52 g, 2.53 mmol, 1.0 equiv) in CH_2Cl_2 (12.6 mL, 0.2M) was added *N*,*N*-dimethylaniline (1.61 mL, 12.65 mmol, 5 equiv) and the dibromoacetal (1.7 mL, 12.65 mmol, 5.0 equiv) at rt. The reaction mixture was stirred at rt for 24 h, at which time it was treated with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (10−33% EtOAc/hexanes eluent) furnished **41** (1.79 g, 94% yield) as a clear oil. FTIR (thin film/NaCl) 2928 (m), 2825 (m), 1781 (s), 1721(s), 1652 (w), 1646 (w), 1436 (m), 1364 (w), 1282 (s), 1193 (w), 1148 (m), 1092 (s), 1071 (s), 1010 (m), 967 (m), 921 (w), 821 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 0.5H), 6.48 (s, 0.5H), 6.05 (s, 0.5H), 5.84 (s, 0.5H), 5.47−5.37 (m, 4H), 4.81 (dd, J = 7.3, 3.4 Hz, 0.5H), 4.73 (dd, J = 4.4, 2.8 Hz, 0.5H), 4.66 (dd, J = 12.1, 3.7 Hz, 0.5H), 4.53 (dd, J = 12.3, 4.1 Hz, 0.5H), 4.13−3.91 (m, 4H), 3.77 (dd, J = 11.3, 4.5 Hz, 0.5H), 3.74 (s, 1.5H), 3.738 (s, 1.5H), 3.71 (s, 1.5H), 3.70 (s, 1.5H), 3.59 (dd, J = 11.3, 2.8 Hz, 0.5H), 3.57 (d, J = 2.1 Hz, 0.5H), 3.55−3.31 (m, 3.5H), 2.94 (d, J = 2.8 Hz, 0.5H), 2.91 (d, J = 2.7 Hz, 0.5H), 2.26 (m, 1H), 2.1−1.58 (m, 16H), 1.36−1.10 (m, 9H), 1.22 (t, J = 7 Hz, 1.5H), 1.07 (t, J = 7.0 Hz, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 166.4, 165.9, 165.8, 165.2, 165.0, 139.2, 139.2, 136.7, 135.7, 135.2, 131.6, 131.5, 131.1, 130.9, 130.1, 126.9, 125.3, 125.2, 125.0, 125.0, 111.0, 110.9, 104.9, 104.2, 97.5, 97.8, 81.7, 80.9, 66.8, 66.7, 66.6, 61.3, 61.2, 52.7, 52.7, 52.7, 52.7, 48.6, 47.6, 46.8, 46.7, 38.2, 37.9, 35.9, 35.8, 35.4, 35.2, 35.0, 34.5, 32.7, 32.7, 32.5, 31.8, 29.7, 29.6, 29.3, 29.2, 27.3, 27.3, 26.1, 26.0, 18.1, 18.1, 15.3, 15.1; HRMS (ESI) m/z 751.2687 [calcd for $C_{37}H_{52}O_{11}Br$ (M + H) 751.2693].

Acetals 42 and 43. To a solution of bromoacetal **41** (144 mg, 0.19 mmol, 1.0 equiv) and Bu_3SnH (80 μL, 0.29 mmol, 1.5 equiv) in benzene (6 mL, 0.03 M) was added AIBN (8 mg, 0.048 mmol, 0.25 equiv) at rt, and the reaction was heated to reflux. After 2.5 h, no reaction was observed, so an additional 0.25 equiv of AIBN (8 mg, 0.048 mmol, 0.25 equiv) was added. After 30 min more at reflux, still no reaction was observed, so additional portions of Bu_3SnH (80 μL, 0.29 mmol, 1.5 equiv) and AIBN (8 mg, 0.048 mmol, 0.25 equiv) were added. After 2 h more at reflux, the solvent was removed in vacuo, and the reaction was purified via silica gel chromatography (0−20% EtOAc/hexanes eluent) to furnish **43** (29 mg, 22% yield, eluting first) and **42** (65 mg, 50% yield, eluting second) as clear oils. **42**: FTIR (thin film/NaCl) 2928 (s), 2856 (m), 1789 (s), 1732 (s), 1436 (m), 1371 (m), 1257 (m), 1232 (s), 1148 (s), 1096 (m), 1041 (s), 995 (m), 733 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.42−5.27 (m, 5H), 4.18−3.77 (m, 6H), 3.70−3.59 (m, 7H), 3.49−3.37 (m, 2H), 3.31−3.24 (m, 1H), 3.16 (m, 3H), 3.04 (d, J = 14.2 Hz, 1H), 2.88 (d, J = 3 Hz, 1H), 2.69 (dd, J = 5.7, 14 Hz, 1H), 2.59−2.48 (m, 3H), 2.28 (d, J = 14.7 Hz, 1H), 2.25−1.38 (m, 19H), 1.29−1.05 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 176.1, 174.2, 170.8, 170.8, 131.3, 131.1, 125.0, 124.9, 124.9, 124.8, 110.5, 110.5, 109.3, 107.1, 106.5, 97.6, 97.4, 75.5, 74.4, 66.5, 66.2, 66.1, 65.4, 64.1, 62.7, 59.1, 54.9, 53.4, 53.4, 52.9, 52.3, 52.2, 44.0, 43.7, 43.3, 43.5, 41.6, 41.5, 41.5, 39.6, 39.4, 35.2, 34.6, 34.1, 34.0, 33.9, 32.5, 32.4, 32.3, 30.8, 29.5, 29.5, 29.2, 29.2, 27.7, 27.6, 26.0, 25.8, 17.9, 15.1, 14.9; HRMS (ESI) m/z 673.3588 [calcd for $C_{37}H_{53}O_{11}$ (M + H) 673.3588]. **43**: FTIR (thin film/NaCl) 2927 (s), 2857 (m), 1784 (s), 1749 (s), 1438 (m), 1300 (m), 1267 (m), 1215 (s), 1144 (s), 1045 (m), 1002 (s), 854 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.47−5.38 (m, 4H), 4.92 (s, 1H), 4.14−3.94 (m, 5H), 3.75 (dd, (J = 9.5, 7.1 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.56 (d, J = 2.5, 1H), 3.48 (dd, J = 9.5, 7.1, 1H), 3.11 (d, J = 4.9, 1H), 2.50 (m, 1H), 2.25−1.95 (m, 1H), 2.05−1.89 (m, 6H), 1.83−1.44 (m, 18H), 1.38−1.13 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 170.8, 170.3, 131.8, 131.5, 125.0, 124.9, 110.5, 107.7, 96.8, 74.4, 73.6, 66.3, 65.4, 63.4, 55.7, 52.5, 52.4, 47.7, 44.0, 43.3, 42.5, 38.5, 34.3, 33.8, 33.5, 32.8, 31.4, 29.8, 29.7, 29.4, 28.1, 26.2, 26.1, 18.1, 15.2, 14.2; HRMS (ESI) m/z 673.3583 [calcd for $C_{37}H_{53}O_{11}$ (M + H) 673.3588].

Alternate Preparation of 42 Using SmI_2: Preparation of 0.1 M SmI_2 in THF. Samarium metal (2.6 g, 17.3 mmol, 1.75 equiv) was placed in a flame-dried 250 mL flask and lightly flame-dried under vacuum. THF (100 mL) was then added, and the mixture was lightly degassed by three repetitive cycles of vacuum (1−2 s), and nitrogen refilling. 1,2-Diiodoethane (2.8g, 9.95 mmol, 1.0 equiv) was added in one portion, and the degassing sequence was repeated. The time required for initiation of the reaction was variable, but always fastest

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when freshly prepared samarium filings were employed. Within 30 min of the addition of diiodoethane, the reaction mixture should begin to turn a blue-green color. Eventually, the color will change to a deep Prussian blue, which is characteristic of THF solutions of SmI_2. After 3 h of stirring, the reagent was deemed to be of a good quality, and stirring was halted, allowing the excess samarium metal to settle to the bottom. When using this reagent (i.e., transferring by syringe), care was taken to try to take only the supernatant.

To a solution of SmI_2 in THF (80.5 mL, 8.05 mmol, 3.4 equiv) was added a solution of bromoacetal **41** (1.79 g, 2.37 mmol, 1.0 equiv) in THF (5 + 3 + 3 mL = 11 mL). The reaction mixture was stirred at rt for 10 min, treated with saturated aqueous NH_4Cl (20 mL), 1.0 N HCl (5 mL), and EtOAc (20 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (20−33% EtOAc/hexanes eluent) furnished **42** (2.83 g, 96.9% yield) as a pale yellow oil.

Isotwistane 44. To a solution of SmI_2 in THF (5 mL, 0.5 mmol, 5.0 equiv) was added a solution of tertiary alcohol **37*β*** (60 mg, 0.1 mmol, 1.0 equiv) in THF (0.5 + 0.3 mL = 0.8 mL). The reaction mixture was stirred at rt for 10 min, treated with saturated aqueous NH_4Cl (2 mL), 1.0 N HCl (0.5 mL), and EtOAc (5 mL), and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (20−33% EtOAc/hexanes eluent) furnished **44** (50.5 mg, 84% yield) as a colorless oil. FTIR (thin film/NaCl) 3431 (br), 2927 (m), 2855 (w), 1787 (s), 1731 (s), 1436 (m), 1366 (w), 1285 (m), 1213 (s), 1151 (m), 1100 (m), 1071 (m), 968 (m), 927 (w), 736 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.49−5.38 (m, 4H), 4.29 (dd, J = 12.1, 3.4 Hz, 1H), 4.07−3.89 (m, 4H), 3.78 (s, 3H), 3.68 (s, 3H), 3.63 (s, 1H), 3.54 (s, 1H), 3.03 (dd, J = 10.7, 3.0 Hz, 1H), 2.78−2.69 (m, 2H), 2.66 (d, J = 2.6 Hz, 1H), 2.51 (d, J = 1.6 Hz, 1H), 2.39−1.92 (m, 4H), 1.84−1.72 (m, 4H), 1.67−1.49 (m, 10H), 1.36−1.19 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 174.8, 170.9, 131.5, 130.9, 125.4, 125.1, 110.8, 107.7, 85.8, 76.5, 66.7, 66.3, 53.3, 53.1, 52.5, 51.1, 50.1, 44.8, 40.5, 39.5, 35.7, 35.3, 33.9, 33.1, 32.7, 31.4, 29.7, 29.4, 27.9, 26.0, 18.1; HRMS (ESI) m/z 625.2991 [calcd for $C_{33}H_{46}O_{10}Na$ (M + Na) 625.2989].

Bromoacetal 45. To a solution of SmI_2 in THF (5 mL, 0.5 mmol, 5.0 equiv) at −78 °C was added a solution of bromoacetal **42** (75 mg, 0.1 mmol, 1.0 equiv) in THF (0.5 + 0.3 mL = 0.8 mL). The reaction mixture was stirred at −78 °C for 30 min, treated with saturated aqueous NH_4Cl (2 mL), 1.0 N HCl (0.5 mL), and EtOAc (2 mL), and warmed to rt, at which point the phases were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished **45** (28 mg, 37% yield) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 5.48−5.35 (m, 4H), 5.20 (t, J = 4.5 Hz, 1H), 4.26 (dd, J = 12.2, 3.4 Hz, 1H), 4.16−3.91 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H), 3.68−3.57 (m, 5H), 3.50 (s, 1H), 2.78−2.64 (m, 3H), 2.15−1.45 (m, 22H), 1.34−1.29 (m, 12H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 174.8, 170.8, 131.5, 130.9, 125.4, 125.1, 110.9, 108.8, 98.8, 90.0, 77.8, 76.5, 66.9, 66.7, 61.9, 54.5, 53.1, 52.5, 50.3, 46.7, 44.5, 41.4, 39.7, 36.1, 35.2, 34.9, 33.2, 32.7, 32.4, 31.8, 29.9, 29.7, 29.3, 29.2, 27.8, 26.1, 18.1, 15.4; HRMS (ESI) m/z 753.2851 [calcd for $C_{37}H_{54}O_{11}Br$ (M + H) 753.2849].

Bis-dithiolane 46. To a cooled (0 °C) solution of ethyl acetal **42** (157 mg, 0.233 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) was added ethanedithiol (195 μL, 2.33 mmol, 10 equiv) and then $BF_3{\cdot}OEt_2$ (148 μL, 1.17 mmol, 5.0 equiv). After stirring 30 min at 0 °C, saturated aqueous $NaHCO_3$ (3 mL) was added, and the reaction was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification via silica gel chromatography (20−40% EtOAc/hexanes eluent) furnished **46** (127 mg, 72% yield) as a white foam. FTIR (thin film/NaCl) 3242 (br), 2926 (s), 2853 (m), 1775 (s), 1730 (s), 1434 (m), 1366 (w), 1275 (m), 1231 (m), 1168 (m), 1091 (m), 1067 (m), 992 (m), 911 (w) 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.51−5.38 (m, 4H), 5.01 (dd, J = 8.8, 4.1 Hz, 1H), 4.63 (dd, J = 9.4, 3.0 Hz, 1H), 4.01 (s, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.33−3.20 (m, 8H), 3.00 (d, J = 14.2 Hz, 1H), 2.58−2.49 (m, 4H), 2.36−2.23 (m, 3H), 2.16−2.07 (m, 1H), 1.95−1.74 (m, 7H). 1.64−1.57 (m, 7H), 1.35−1.18 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.9, 170.9, 131.5, 130.7, 125.7, 125.1, 106.8, 85.8, 80.4, 78.2, 74.1, 53.3, 53.3, 53.2, 52.5, 49.3, 49.2, 44.3, 44.1, 42.7, 40.9, 40.5, 40.4, 39.8, 38.8, 38.6, 38.5, 35.4, 33.5, 32.8, 32.7, 29.9, 29.7, 29.5, 29.3, 27.8, 18.2, 18.1; HRMS (ESI) m/z 753.2633 [calcd for $C_{37}H_{53}O_8S_4$ (M + H) 753.2623].

Bis-dithiane 47. To a cooled (−10 °C) solution of ethyl acetal **42** (360 mg, 0.53 mmol, 1.0 equiv) in CH_2Cl_2 (5.4 mL) was added propanedithiol (540 μL, 5.38 mmol, 10.1 equiv) and then $BF_3{\cdot}OEt_2$ (148 μL, 1.17 mmol, 2.2 equiv). The reaction mixture was allowed to warm to rt, and after 2 h, was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) The reaction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes eluent) furnished **47** (296 mg, 71% yield) as a white foam. FTIR (thin film/NaCl) 3488 (br), 2925 (s), 2854 (m), 2257 (w), 1779 (s), 1731 (s), 1435 (m), 1375 (w), 1276 (m), 1231 (s), 1160 (m), 1147 (m), 1087 (m), 994 (m), 967 (m), 910 (m) 732 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46−5.31 (m, 4H), 4.79 (dd, J = 12.1, 3.1 Hz, 1H), 4.48 (dd, J = 8.3, 6.7 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.62 (s, 1H), 3.51 (s, 1H), 3.40−3.28(m, 2H), 3.00 (d, J = 14.2 Hz, 1H), 2.91−2.77 (m, 4H), 2.63−2.49 (m, 7H), 2.30−2.25 (m, 2H), 2.14−1.74 (m, 12H), 1.65−1.29 (m, 8H), 1.33−1.18 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 174.8, 170.8, 131.4, 130.3, 126.0, 125.1, 106.4, 86.0, 84.2, 53.8, 53.2, 53.2, 52.8, 52.5, 49.0, 45.1, 44.4, 42.1, 40.9, 39.5, 39.2, 38.0, 35.2, 33.7, 32.6, 32.3, 29.7, 29.3, 29.2, 28.7, 27.8, 27.7, 27.5, 25.5, 25.0, 18.1; HRMS (ESI) m/z 781.2936 [calcd for $C_{39}H_{57}O_8S_4$ (M + H) 781.2936].

Lactol 48. To a solution of lactone **47** (143 mg, 0.20 mmol, 1.0 equiv) in THF (3 mL) at −50 °C was added DIBAL (1.0 M in hexanes: 1 mL, 1 mmol, 5.0 equiv). The reaction was allowed to slowly warm to −25 °C. After 45 min, the reaction was quenched with a 10% aqueous solution of Rochelle's salt (3 mL) and allowed to stir overnight. After ∼16 h, EtOAc (10 mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organics were washed with brine and dried over Na_2SO_4, and the solvent was removed in vacuo. Purification by silica gel chromatography (20−40% EtOAc/hexanes eluent) gave lactol **48** (122 mg, 86% yield) as a white foam. FTIR (thin film/NaCl) 3494 (br), 2525 (s), 2855 (m), 1730 (s), 1437 (m), 1231 (s), 1082 (s), 1004 (m), 968 (m), 910 (w), 732 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46−5.29 (m, 4H), 5.23 (s, 1H), 4.92 (dd J = 11.6, 3.0 Hz, 1H), 4.17 (dd J = 8.6, 5.8 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 3.33−3.16 (m, 4H), 2.96−2.77 (m, 5H), 2.68−2.38 (m, 4H), 2.24 (m, 1H), 2.13−1.75 (m, 13H), 1.72−1.48 (m, 10H), 1.31−1.14 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.0 131.5, 130.6, 125.7, 124.9, 108.1, 102.1, 88.2, 79.9, 55.1, 54.8, 52.9, 52.0, 51.6, 49.4, 45.7, 44.2, 40.3, 39.8, 39.6, 38.4, 37.2, 35.4, 34.2, 32.6, 32.4, 31.0, 30.7, 29.6, 29.2, 27.8, 27.7, 27.5, 27.1, 25.6, 25.1, 18.1; HRMS (ESI) m/z 805.2923 [calcd for $C_{39}H_{58}O_8S_4Na$ (M + Na) 805.2912].

Acetal 49. To a solution of lactol **48** (107 mg, 0.137 mmol, 1.0 equiv) in MeOH (2 mL) was added *p*-TsOH (30 mg, 0.159 mmol, 1.16 equiv). The mixture was heated to reflux overnight, cooled to rt, quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography furnished methyl acetal **49** (80 mg, 73% yield) as a white foam. FTIR (thin film/NaCl) 3540 (br), 2926 (s), 2854 (s), 1729 (s), 1434 (m), 1230 (m), 1165 (w), 1094 (s), 998 (w), 967 (m), 911 (m), 733 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46−5.33 (m, 4H), 4.91 (dd, J = 12.2, 3.5 Hz, 1H), 4.71 (s, 1H), 4.09 (dd, J = 10.2, 4.3 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.33 (s, 3H), 3.23−3.16 (m, 3H), 2.94 (ddd, J = 13.9, 11.8, 2.5 Hz, 1H), 2.86−2.77 (m, 4H), 2.66−2.59 (m, 2H), 2.55 (d, J = 2.5 Hz,

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1H), 2.48−2.42 (m, 3H), 2.35 (d, J = 15.0, 1H), 2.29−2.22 (m, 1H), 2.14−2.09 (m, 2H), 2.02−1.75 (m, 9H), 1.74−1.53 (m, 10H), 1.32−1.17 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 172.1, 131.5, 130.8, 125.6, 127.0, 108.5, 107.6, 88.1, 79.5, 55.5, 55.1, 54.5, 52.9, 52.0, 51.5, 49.5, 45.9, 44.5, 40.5, 40.1, 39.3, 38.2, 37.2, 35.5, 34.3, 32.6, 32.6, 32.5, 31.2, 30.6, 29.7, 29.3, 27.9, 27.8, 27.1, 25.7, 25.1, 18.1, 18.1; HRMS (ESI) m/z 819.3059 [calcd for $C_{40}H_{60}O_8S_4Na$ (M + Na) 819.3069].

Xanthate 50. To a mixture of KH (31.3 mg, 0.783 mmol, 5.4 equiv) in THF (2 mL) at 0 °C was added a solution of acetal **49** (115 mg, 0.144 mmol, 1.0 equiv) in THF (1 mL + 1 mL + 0.5 mL). The reaction mixture was allowed to react at rt for 15 min, and then cooled to 0 °C. After stirring at 0 °C for 15 min, CS_2 (80 μL, 1.33 mmol, 9.2 equiv) was added, and the reaction was warmed to rt. After stirring at rt for 15 min, the reaction was cooled to 0 °C and stirred for 15 min, at which time CH_3I (90 μL, 1.44 mmol, 10 equiv) was added. The reaction was stirred at rt for 2 h, at which point MeOH (1 mL) and a saturated aqueous solution of NH_4Cl (1 mL) were added. The mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (1.25% EtOAc/benzene eluent) furnished xanthate **50** (70.8 mg, 55% yield) as a clear oil. FTIR (thin film/NaCl) 2960 (s), 2925 (s), 2854 (m), 1733 (s), 1455 (m), 1435 (m), 1374 (w), 1261 (s), 1208 (s), 1102 (s), 1017 (s), 967 (m), 940 (w), 910 (m), 865 (w), 799 (s), 734 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47−5.33 (m, 4H), 4.15 (d, J = 2.6 Hz, 1H), 4.67 (s, 1H), 4.46 (dd, J = 11.4, 3.7 Hz, 1H), 4.06 (dd, J = 9.1, 5.3 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.61−3.46 (m, 2H), 3.32 (s, 3H), 3.20 (s, 1H), 2.92 (ddd, J = 14.0, 11.9, 2.5 Hz, 1H), 2.85−2.74 (m, 5H), 2.63−2.50 (m, 12H), 2.19 (ddd, J = 12.5, 12.3, 4.5 Hz, 1H), 2.16−1.96 (m, 4H), 1.96−1.78 (m, 7H), 1.76−1.57 (m, 10H), 1.48 (dt, J = 12.7, 3.7 Hz, 1H), 1.31−1.14 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 176.1, 172.2, 131.6, 131.0, 125.6, 125.0, 108.6, 108.5, 102.7, 83.1, 58.0, 55.1, 54.9, 53.2, 52.1, 48.4, 48.1, 44.7, 44.5, 41.3, 40.0, 39.2, 39.0, 38.8, 35.5, 34.4, 33.1, 32.7, 31.4, 30.9, 29.7, 29.4, 28.0, 27.8, 27.6, 27.2, 25.7, 25.5, 20.4, 18.2, 18.1; HRMS (ESI) m/z 909.2686 [calcd for $C_{42}H_{62}O_8S_6Na$ (M + Na) 909.2667].

Preparation of Fragmentation Product 51: Preparation of 0.1 M SmI_2 in THF. Samarium metal (2.6 g, 17.3 mmol, 1.75 equiv) was placed in a flame-dried 250 mL flask and lightly flame-dried under vacuum. THF (100 mL) was then added, and the mixture was lightly degassed by three repetitive cycles of vacuum (1−2 s), and nitrogen refilling. 1,2-Diiodoethane (2.8 g, 9.95 mmol, 1.0 equiv) was added in one portion, and the degassing sequence was repeated. The time required for initiation of the reaction was variable, but always fastest when freshly prepared samarium filings were employed. Within 30 min of the addition of diiodoethane, the reaction mixture should begin to turn a blue-green color. Eventually, the color will change to a deep Prussian blue, which is characteristic of THF solutions of SmI_2. After 3 h of stirring, the reagent was deemed to be of a good quality and stirring was halted, allowing the excess samarium metal to settle to the bottom. When using this reagent (i.e., transferring by syringe), care was taken to try to take only the supernatant.

Fragmentation Product 51. To a solution of freshly prepared SmI_2 in THF (25 mL, 2.5 mmol, 31 equiv) was added HMPA (6.1 mL, 35 mmol, 439 equiv). To this purple solution was added a solution of xanthate **50** (70.8 mg, 0.08 mmol, 1.0 equiv) in THF (4.4 mL) via syringe pump over 1 h. After the complete addition of **50**, the reaction was stirred for an additional 15 min, and then treated with a saturated aqueous solution of NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water (10 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (2.5% EtOAc/benzene eluent) furnished fragmentation product **51** (30.2 mg, 50% yield) as a clear oil. FTIR (thin film/NaCl) 2926 (s), 2853 (m), 2255 (w), 1731 (s), 1435 (m), 1368 (w), 1330 (w), 1275 (m), 1241 (s), 1193 (s), 1135 (w), 1100 (s), 1039 (m), 971 (s), 910 (m), 805 (w), 733 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (br, 1H), 5.48−5.35 (m, 4H), 4.96 (s, 1H), 4.20 (dd, J = 10.5, 4.0 Hz, 1H), 3.77 (dd, J = 11.5, 2.0 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.49 (m, 1H), 3.31 (s, 3H), 2.99−2.72 (m, 10H), 2.62 (dd, J = 7.9 2.0 Hz, 1H), 2.43 (dd, J = 14.7, 10.6 Hz, 1H), 2.39 (s, 1H), 2.22−2.16 (m, 1H), 2.11−1.84 (m, 14H), 1.78−1.75 (m, 1H), 1.66−1.59 (m, 7H), 1.42−1.24 (m, 12H), 1.07 (d, J = 13.4, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 172.7, 142.8, 131.6, 131.3, 126.3, 125.3, 125.1, 107.1, 104.5, 74.9, 56.5, 54.9, 54.3, 52.4, 51.9, 46.6, 45.2, 43.8, 41.6, 41.3, 39.9, 39.1, 38.3, 36.9, 36.2, 34.9, 32.7, 30.9, 30.3, 29.9, 29.6, 29.6, 29.3, 28.6, 27.7, 26.2, 25.8, 25.5, 22.9, 18.2, 18.1; HRMS (ESI) m/z 803.3122 [calcd for $C_{40}H_{60}O_7S_4Na$ (M + Na) 803.3120].

α-Bromoester 52. To a solution of **51** (22 mg, 0.028 mmol, 1 equiv) and CBr_4 (90 mg, 0.272 mmol, 9.7 equiv) in THF (3 mL) at −78 °C was added KHMDS (0.5 M in toluene: 600 μL, 0.3 mmol, 10.7 equiv). The mixture was allowed to stir for 50 min at −78 °C, at which point it was quenched by the addition of MeOH (0.5 mL) and saturated aqueous NH_4Cl (1 mL). The mixture was warmed to rt, and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (0−5% EtOAc/benzene eluent) gave α-bromoester **52** (22 mg, 90% yield) as a clear oil. FTIR (thin film/NaCl) 2928 (s), 2854 (m), 1751 (m), 1733 (s), 1436 (m), 1259 (m), 1151 (m), 1104 (s), 1054 (m), 967 (s), 911 (m), 803 (w), 733 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (br, 1H), 5.47−5.336 (m, 4H), 4.99 (s, 1H), 4.19 (dd, J = 10.9, 3.7 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, J = 11.6, 2.3 Hz, 1H), 3.71 (s, 3H), 3.50 (d, J = 13 Hz, 1H), 3.33 (s, 3H), 2.98 (ddd, J = 14.1, 11.3, 2.4 Hz, 1H), 2.91−2.73 (m, 9H), 2.39 (dd, J = 15.2, 11.0 Hz, 1H), 2.20−1.85 (m, 15H), 1.73 (m, 1H), 1.66−1.30 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 141.0, 131.6, 131.1, 127.7, 125.3, 125.1, 106.6, 103.7, 77.8, 74.9, 64.0, 56.9, 56.4, 56.0, 55.1, 54.8, 52.9, 52.0, 44.0, 43.5, 41.7, 38.0, 37.1, 36.8, 35.7, 34.5, 32.7, 30.9, 30.2, 29.7, 29.3, 28.5, 27.7, 26.2, 26.1, 25.7, 25.4, 18.2, 18.12; HRMS (ESI) m/z 859.2403 [calcd for $C_{40}H_{60}BrO_7S_4$ (M + H) 859.2405].

Aldehyde 53. A solution of α-bromoester **52** (22 mg, 0.025 mmol, 1.0 equiv) in pyridine (2 mL, 24.22 mmol, 989 equiv) in a sealed vial was heated to 115 °C for 5h. The mixture was then cooled to rt, the solvent was removed *in vacuo*, and the residue was dissolved in EtOAc (10 mL) and washed with aqueous $NaHCO_3$ (1 mL) and brine (1 mL). The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification by preparative TLC (5% EtOAc/hexanes eluent) gave aldehyde **53** (12 mg, 61% yield) as a yellow oil. FTIR (thin film/NaCl) 2925 (s), 2852 (m), 1772 (m), 1739 (s), 1717 (s), 1436 (m), 1261 (m), 1169 (m), 1077 (m), 1014 (m), 967 (s), 909 (m), 800 (w), 733 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 5.99 (s, 1H), 5.43−5.28 (m, 4H), 4.11 (dd, J = 11.8, 2.2 Hz, 1H), 3.89 (t, J = 7.1 Hz, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.24 (s, 1H, 3.00−2.90 (m, 2H), 2.76−2.42 (m, 10H), 2.30−1.70 (m, 20H), 1.60−1.20 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 172.5, 170.5, 136.7, 134.6, 131.7, 130.8, 128.8, 125.9, 125.4, 101.9, 80.7, 77.1, 76.9, 57.8, 55.4, 54.0, 53.1, 52.8, 48.2, 41.9, 40.8, 39.9, 37.3, 36.9, 35.5, 33.8, 32.9, 30.1, 29.8, 29.5, 28.6, 27.9, 27.3, 27.0, 25.3, 25.3, 18.4, 18.4; HRMS (ESI) m/z 765.2978 [calcd for $C_{39}H_{57}O_7S_4$ (M + H) 765.2987].

To a solution of α-bromoester **52** (30 mg, 0.035 mmol, 1.0 equiv) in CH_2Cl_2 (300 μL) was added MeOH (3 mL) and BTIB (120 mg, 0.28 mmol, 8 equiv). After 1 min, the mixture was treated with an aqueous solution of $NaHCO_3$ (1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting product, which was believed to be the bis-dimethyl acetal, was unstable to silica gel chromatography, and was, therefore, carried on directly. Thus, the product of the foregoing reaction was dissolved in acetone (3 mL), and to this was added Jones' reagent [prepared from 13.5 g of CrO_3, and 12.5 mL of H_2SO_4, diluted to 100 mL; 4 N, (150 μL, 0.6 mmol, 17 equiv)]. After stirring for 30 min, an additional portion of Jones' reagent was added (150 μL). After an additional 30 min, the reaction was quenched by the addition of isopropanol (100 μL), diluted with EtOAc (10 mL), and separated. The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with water (2 × 2 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography

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(25% EtOAc/hexanes +1% AcOH) furnished acid **54** (16 mg, 61% yield) as a colorless oil. FTIR (thin film/NaCl) 2926 (s), 2855 (m), 1734 (s), 1457 (m), 1436 (m), 1112 (m), 967 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.32−5.28 (m, 4H), 5.02 (s, 1H), 3.92 (dd, J = 10.9, 3.4 Hz, 1H), 3.67−3.59 (m, 4H), 3.21 (s, 3H), 2.76−2.45 (m, 10H), 2.14−1.16 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 169.3, 138.5, 130.2, 128.6, 127.1, 124.7, 123.9, 105.3, 103.1, 75.7, 75.4, 75.0, 61.2, 55.9, 54.0, 52.6, 51.7, 50.9, 42.4, 40.0, 37.0, 36.5, 35.4, 33.8, 33.7, 31.5, 28.7, 28.4, 28.0, 27.1, 25.0, 16.9, 16.9; HRMS (ESI) m/z 717.2243 [calcd for $C_{34}H_{47}O_{10}BrNa$ (M + Na) 717.2250].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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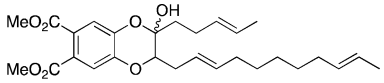
(17) The protecting group shuffle was required to avoid formation of a hemiacetal that would not engage in the aryl oxidation reaction.



(18) This approach has been previously employed in our efforts to prepare the carbocyclic core of the phomoidrides, and while successful, the isolated yield was low. See ref 5.

(19) Attempts at using the acetates **36α/β** in the subsequent aldol reaction failed, resulting in acetate cleavage.

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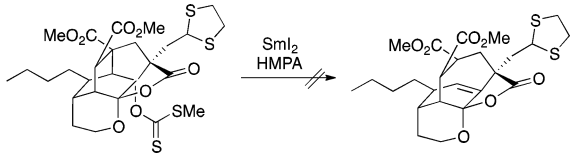
(21) (a) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.

(22) Alkyl bromides are relatively unreactive toward SmI2, being reduced only when heated or when HMPA is added as a cosolvent. In fact, it is reported that bromoacetal cyclizations with SmI_2 require HMPA to proceed at a reasonable rate. See: (a) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015. (b) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, *33*, 2007.

(23) (a) Inanaga, J.; Handa, Y.; Tabuchi, T.; Otsubo, K.; Yamaguchi, M.; Hanamoto, T. *Tetrahedron Lett.* **1991**, *32*, 6557. (b) Inanaga, J.; Sakai, S.; Handa, Y.; Yamaguchi, M.; Yokoyama, Y. *Chem. Lett.* **1991**, *20*, 2117. (c) Shinohara, I.; Okue, M.; Yamada, Y.; Nagaoka, H. *Tetrahedron Lett.* **2003**, *44*, 4649.

(24) It is possible that the initial cyclization is a radical event, in which case the resultant C(14) radical would be reduced to the enolate prior to the second cyclization.

(25) Fragmentation of a lactone-containing model substrate failed. Reduction of the lactone and protection as the mixed acetal was required for the fragmentation to be effective.



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