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Diastereoseletive Transannular Oxa-Conjugate Addition Generates the 2,6-*cis*-Disubstituted Tetrahydropyran of Neopeltolide

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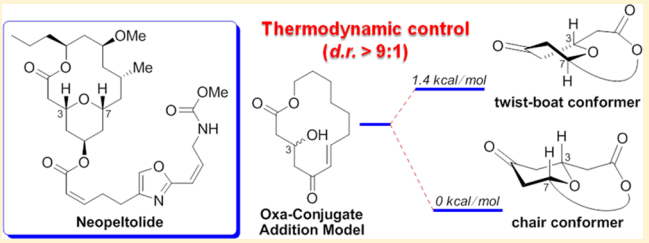
Supporting Information

ABSTRACT: Transannular 2,6-disubstituted pyrans, like the one found in the cytotoxic marine natural product neopeltolide, are a key functional group in many polyketides. While oxa-conjugate additions have been shown to provide direct and rapid access to tetrahydropyrans in acyclic neopeltolide intermediates, a transannular strategy for construction of this ring system in a macrocyclic core has not been investigated. In this study, we demonstrate that a transannular oxa-conjugate addition strategy is a viable approach to the construction of the bicyclic core of neopeltolide. We show that transannular addition occurs readily with an α,β-unsaturated ketone as the Michael acceptor and does not occur when an α,β-unsaturated ester is the Michael acceptor. Our data indicates that oxa-conjugate addition is reversible and that the stereochemical outcome can be under thermodynamic control. Using computational chemistry, we show that the lowest energy diastereomer is the desired *cis*-pyran found in neopeltolide, and we experimentally demonstrate that the *trans* and *cis* diastereomers are interconvertible under reaction conditions with the *cis*-pyran product predominating. This oxa-conjugate addition strategy should provide a viable route to accessing the fully elaborated macrocyclic core of neopeltolide.



INTRODUCTION

2,6-Disubstituted pyrans are a common ring system found in polyketides, which add significant conformational rigidity to these natural products and can play a role in controlling the bioactive conformation of the molecule. While pyrans with varying oxidation states are observed in polyketides, a common and important motif is the tetrahydropyran (THP), as seen in the natural products neopeltolide[1] (**1**, Figure 1), leucascandrolide[2] (**2**), bryostatin[3] (**3**), and dactylolide[4] (**4**). In line with our efforts to develop bioinspired transannular oxa-conjugate addition strategies for the total synthesis and chemo-enzymatic syntheses of this class of natural products,[5] we present two strategies for accessing the neopeltolide macrocyclic core via a transannular oxa-conjugate addition.

Neopeltolide is a 14-membered macrolide natural product that was isolated from a deep-water sponge of the family Neopeltidae, collected off the northern coast of Jamaica by Wright and co-workers in 2007.[1] They established the planar structure and relative configuration of **1** through extensive NMR spectroscopic data. Subsequent reassignment of the relative stereochemistry and determination of the absolute configuration were independently reported by Panek[6] and Scheidt[7] through total syntheses. The key structural elements of **1** include a 14-membered macrocyclic backbone containing a 2,6-*cis*-tetrahydropyran ring with an oxazole-bearing side chain attached to the THP.

Initial biological evaluation revealed that neopeltolide exhibits potent cytotoxic activities against several cell lines

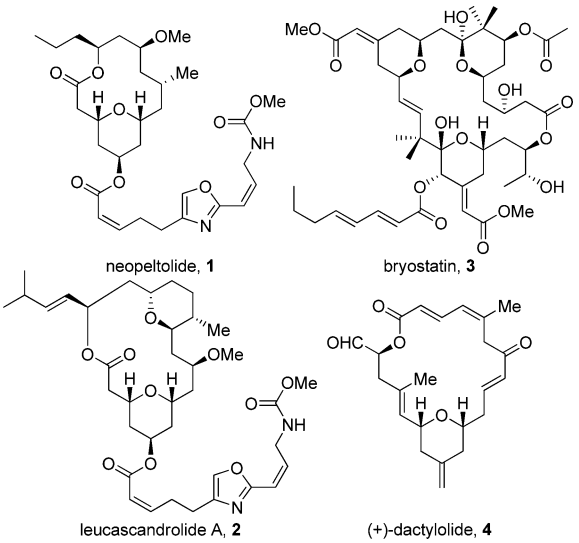


Figure 1. Selected polyketide natural products that possess a 2,6-disubstituted THP motif.

with nanomolar IC_{50} values.[1] Kozmin and co-workers reported that neopeltolide targets cytochrome bc_1 complex and may inhibit mitochondrial ATP synthesis.[8] Because of its promising

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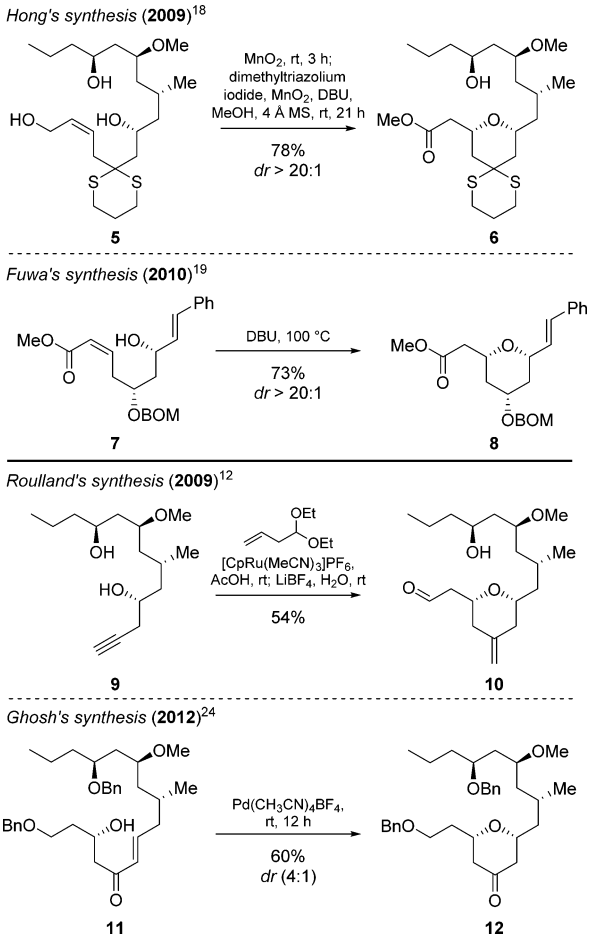
biological activity and appealing architecture, several total syntheses,[6,7,9−14] formal total syntheses,[15−25] and analog syntheses[8,26−33] have been reported. In this paper, we report the synthesis of a neopeltolide model that exploits an acid-catalyzed transannular oxa-conjugate addition for the construction of the 2,6-*cis*-disubstituted tetrahydropyran ring.

While Michael additions using carbon or nitrogen nucleophiles are common and typically facile, Michael additions with oxygen nucleophiles are more challenging.[34,35] These oxa-conjugate additions are typically under thermodynamic control and are enthalpically unfavorable. In addition, the hard oxygen nucleophile is mismatched with the softer electrophilic β-carbon of the α,β-unsaturated carbonyl.

However, since oxa-conjugate additions provide direct and rapid access to THPs, this strategy has been applied to the construction of neopeltolide (Scheme 1). Both Hong in 2009[18]

Scheme 1. Literature Examples of Oxa-Conjugated Ester and Aldehyde/Ketone Michael Addition Strategies Used To Access the 2,6-Disubstituted THP Ring of Neopeltolide



and Fuwa in 2010[19] used addition of a ζ-hydroxy into a linear α,β-unsaturated ester to generate the *cis*-THP found in neopeltolide (**6** and **8**, Scheme 1). Roulland (2009)[12] and Ghosh (2012)[24] both developed mild oxa-conjugate addition routes to the neopeltolide THP core. These two strategies relied on addition to α,β-unsaturated aldehydes and ketones respectively (**10** and **12**, Scheme 1). The lowest unoccupied molecular orbital (LUMO) energies for these electrophiles is significantly lower in energy as compared to the corresponding α,β-unsaturated esters, facilitating the addition reaction.

While both the ester and aldehyde/ketone strategies provide strong precedent for use of oxa-conjugate addition in the construction of the *cis*-THP from neopeltolide, they also highlight some of the challenges associated with this strategy. For example, Fuwa's system required moderately high temperatures for THP formation, and low diastereoselectivity was observed under the mild conditions employed by Ghosh. In this study, we investigate the effect of preorganizing the nucleophilic alcohol and the electrophilic α,β-unsaturated carbonyl for oxa-conjugate addition by constraining it in a 14-membered macrocycle. Like Hong's[18] use of the Thorpe−Ingold effect,[36] this preorganization is expected to lower the reaction energy barrier, thereby enabling milder reaction conditions. The macrocycle is also expected to exacerbate the energetic differences between the *cis*- and *trans*-THP, resulting in increased diastereoselectivity. Herein we validate this approach by demonstrating transannular addition to an α,β-unsaturated ketone is effective in accessing the neopeltolide macrocyclic core in both high yield and high diastereoselectivity.

RESULTS AND DISCUSSION

Two conjugated model substrates were designed to address the impact of the macrocycle on oxa-conjugate addition approaches to the neopeltolide core (**13**, Figure 2). In the first model

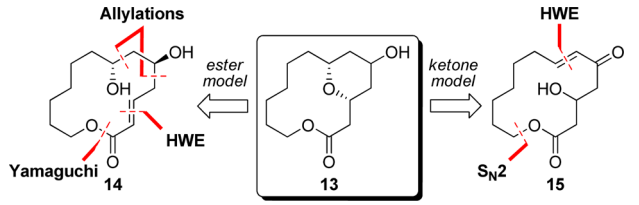


Figure 2. Unsaturated ester and ketone model systems for accessing the macrocyclic core of neopeltolide via transannular oxa-conjugate addition.

system, THP formation relies on the addition of a ζ-hydroxy group into an α,β-unsaturated ester (**14**). Ester **14** was envisioned to be readily accessible through sequential allylations with the macrocyclic core being synthesized by a Yamaguchi macrolactonization. In the second system THP formation relies on the addition of a β'-hydroxy into an α,β-unsaturated ketone (**15**). Ketone **15** was deigned to be accessed through a convergent route relying on a Horner−Wadsworth−Emmons olefination and an S_N2 lactonization.

***α,β*-Unsaturated Ester System.** Synthesis of the α,β-unsaturated ester system began by addition of allylmagnesium bromide to the known aldehyde **16**[37] (Scheme 2) to afford the corresponding homoallylic alcohol. The alcohol was protected with a *tert*-butyldimethylsilyl (TBS) group to yield the silyl ether, **17**, in 64% yield over two steps. The olefin was dihydroxylated and the diol was oxidatively cleaved to provide its aldehyde, which was used in a second nondiastereoselective allylation and subsequent TBS protection. Conversion of olefin **18** to its corresponding aldehyde allowed for a Horner−Wadsworth−Emmons (HWE)[38] coupling with triethylphosphonoacetate to give the desired *trans*-α,β-unsaturated ethyl ester **19** in 57% yield. Removal of the PMB ether and saponification of the ethyl ester yielded the *seco*-acid, which

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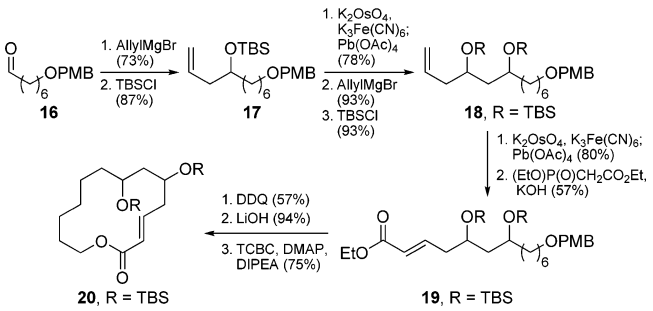
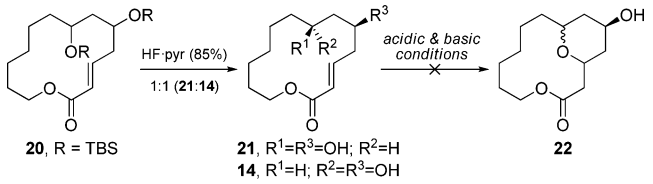
Scheme 2. Synthesis of the α,β-Unsaturated Ester Model System of Neopeltolide



cleanly underwent Yamaguchi macrolactonization[39] to provide macrolactone **20** in 75% yield as an inseparable mixture of *syn* and *anti* diastereomers.

With macrolactone **20** in hand, desilylation was accomplished by treatment with HF to provide a 1:1 ratio of separable *syn*- (**14**) and *anti*-diols (**21**, Scheme 3) in high yield. The Rychnovsky acetal-based appraoch[40] was used to establish the relative stereochemistry of the diols in each diastereomer.[41]

Scheme 3. Transannular Oxa-Michael Addition Fails for Ester-Conjugated Model System of Neopeltolide



A stock solution of 0.1 M DBU in C_6D_6 was prepared and used as the reaction solvent for both diastereomers **21** and **14**. Contrary to the successful use of DBU in the oxa-conjugate additions observed for both linear and transannular systems by Fuwa[13] and Shishido,[42,43] respectively, **21** and **14** were unreactive at room temperature and completely consumed at reflux without observable formation of the desired THP product. Elimination, leading toward formation of sorbate containing compounds, predominated. Screening of a variety of alternative basic and acidic reaction conditions similarly failed to find conditions that accessed the THP from **14** and **21**.

α,β-Unsaturated Ketone System. We hypothesized that the ability to access the THP system from either of diastereomers **14** and **21** was limited by the high energy of the α,β-unsaturated ester LUMO. Because α,β-unsaturated ketones possess markedly lower energy LUMOs as compared to their α,β-unsaturated esters homologues,[44] we redesigned the model system to incorporate this functional group as the Michael acceptor, **15**.

A key precedent for our ketone model system (**15**) was Rizzacasa and co-workers' study of apicularen A.[45,46] In their total synthesis of apicularen A, which possesses a *trans* dihydropyrone, they rely on a reversible acid-catalyzed transannular addition of a β′-hydroxy into an α,β-unsaturated ketone **23** (Figure 3). Their studies showed that they could access the kinetic *cis*-pyran **24**[45] and that, via E1cB elimination/oxa-conjugate addition mechanisms, they were able to equilibrate the products to the thermodynamically favored *trans* diastereomer **25** with a good diastereomeric ratio (>10:1).[46]

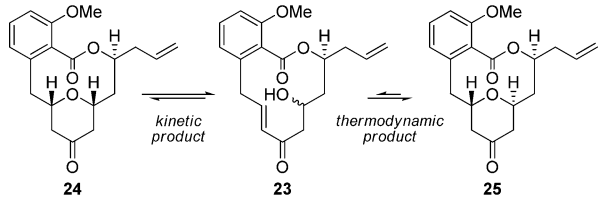
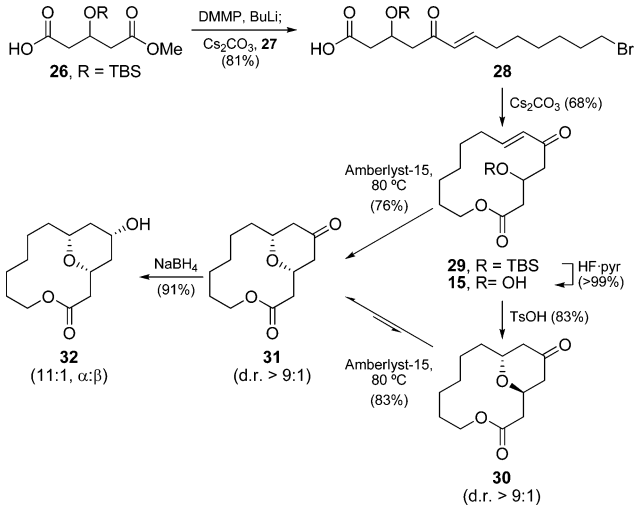


Figure 3. Rizzacasa and co-workers' study of apicularen A demonstrates the success of a reversible acid-catalyzed transannular addition of a β′-hydroxy into an α,β-unsaturated ketone.[45,46]

Based on this precedent, we undertook the synthesis of model system **15** to access the THP of neopeltolide (Scheme 4). The synthesis began with the HWE-coupling of the

Scheme 4. Synthesis of the α,β-Unsaturated Ketone System of Neopeltolide Model



phosphonate, generated from addition of dimethyl methylphosphonate to the acid **26**,[47] and 7-bromoheptanal (**27**), to yield the bromo acid **28** in good yield. Base-mediated S_N2 macrolactonization generated macrocyclic enone **29**, which was desilylated with HF to yield the oxa-conjugate addition precursor **15**.

Oxa-conjugate addition precursor **15** failed to produce THP containing products under a wide variety of typical base-mediated conditions for oxa-conjugate addition, including DBU[13] and KOtBu,[48−50] at room temperature and elevated temperatures (up to 110 °C). Treatment with *p*-toluenesulfonic acid at room temperature however rapidly (<15 min) led to formation of the THP containing macrocycle **30** with high diastereoselectivity (d.r. > 9:1). Extensive 1D and 2D NMR analysis (HSQC, COSY, NOESY, Figure S1) confirmed that the major product was the 2,6-*trans*-THP.

A computational approach was used to evaluate the relative energies of the *cis* and *trans* diastereomers to determine if reversible oxa-conjugate addition under thermodynamic control could access the desired *cis* product. The structures of **30** and **31** were subjected to an initial PM6[51] optimization prior to a B3LYP/6-31++G** energy minimization.[52−54] Potential energies of the energy-minimized structures were computed. A vibrational analysis was performed and resulted in no imaginary frequencies, indicating the geometries of each compound occupy a local minimum. The *trans*-THP (**30**) was found to be in a twist boat conformation and was approximately 1.4 kcal/

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mol higher in energy that the *cis*-THP (**31**), which was predicted to adopt a chair conformation.

Based on these computational results, we identified reaction conditions that led to thermodynamic control for the transannular oxa-conjugate addition. **15** was converted in high diastereoselectivity (>9:1 d.r.) to the thermodynamic product **31** by treatment with Amberlyst-15 (80 °C, 4 h). The observed *cis*-to-*trans* product ratio of 90:10 is in good agreement with the computationally predicted equilibrium ratio at 80 °C of 87.5:12.5 *cis*-to-*trans*. To confirm that formation of the *cis* product is occurring from the kinetic *trans* product, the *trans*-THP **30** was subjected to identical Amberlyst-15 conditions and the *cis* product was isolated in comparable yield with identical diastereoselectivity (>9:1 d.r.).

Under thermodynamic conditions, THP ring opening of **30** and **32** is expected to occur through elimination of the C3−*O* bond and C7−*O* bond as is seen for thermodynamically controlled oxa-conjugate additions of linear enantiopure *β*-hydroxy enones[54] and the transannular oxa-conjugate addition based synthesis of apicularen.[46] For linear enantiopure *β*-hydroxy enones, this dual elimination pathway is problematic as it leads to loss of stereochemical integrity.[55] However, in the context of transannular oxa-conjugate addition approaches, it enables remote stereochemical control of both stereogenic centers as was shown in the synthesis of **25** from **23**, where the configuration of the lactone stereocenter was sufficient to control both THP stereogeneic centers.[46] This remote stereocontrol may ultimately prove useful in the synthesis of neopeltolide by an oxa-conjugate addition approach.

Selective reduction of the ketone **31** was accomplished with $NaBH_4$ into key alcohol **32** (11:1, *α*:*β*). Under Mitsunobu conditions,[56] Scheidt[7] and others[8,9,11−14,26,29−31,33] have established that this configuration at C5 allows coupling with a suitable oxazole-bearing neopeltolide side chain.

CONCLUSIONS

In this study, we have demonstrated that a transannular oxa-conjugate addition strategy is a viable approach to the construction of the macrocyclic core of neopeltolide. We have shown that addition of an intramolecular alcohol to an *α*,*β*-unsaturated ketone embedded in a 14-membered macrolactone is superior to the strategy where the corresponding *α*,*β*-unsaturated ester acts as the Michael acceptor. Our experimental and computational data indicate that the addition is reversible and can be performed under kinetic control to access the *trans*-THP product or thermodynamic control to access the *cis*-THP. This oxa-conjugate addition strategy should provide a viable route to accessing the fully elaborated macrocyclic core of neopeltolide. Finally due to the strategic position of the functional groups required for oxa-conjugate addition, engineered polyketide synthase pathways can be designed to produce these oxa-conjugate addition substrates, opening the door to *in vivo*[57] or *in vitro*[58] chemoenzymatic production of THP precursors that can be chemically converted into THP containing compounds.[5]

EXPERIMENTAL SECTION

7-(*O*-*p*-Methoxybenzyloxy)heptanal (16). To an oven-dried round-bottom flask under N_2 containing a Teflon stir bar were added SO_3-pyridine (12.2 g, 76.6 mmol, 2.0 equiv), methylene chloride (75 mL), and DMSO (27.0 mL, 383 mmol, 10 equiv). The resulting suspension was cooled to 0 °C in an ice bath. To the vigorously stirred suspension was added triethylamine (27 mL, 192 mmol, 5 equiv) followed by stirring at 0 °C for 30 min. Known PMB alcohol[37] (9.67 g, 38.3 mmol, 1.0 equiv) was dissolved in methylene chloride (65 mL) in a separate flask and added to the vigorously stirred solution of the activated DMSO complex at 0 °C via cannula. An additional portion of methylene chloride (10 mL) was used to transfer via cannula any remaining starting material. The reaction was allowed to warm to rt and stirred for an additional 6 h. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) followed by the addition of distilled water (50 mL). The organic layer was washed with a second portion of 1:1 v/v saturated aqueous NH_4Cl/distilled water (100 mL total volume) followed by saturated aqueous NH_4Cl (100 mL). The organic layer was washed with brine (100 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography (silica gel, 20% ethyl acetate in hexanes) to obtain 7.19 g of a colorless oil (28.7 mmol, 75% yield). R_f = 0.50 (silica gel, 40% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.73 (t, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.40 (td, *J* = 7.5, 1.8 Hz, 2H), 1.66−1.52 (m, 4H), 1.42−1.27 (m, 4H) ppm. NMR spectra consistent with those previously reported within literature.[37]

4-Hydroxy-10-(*O*-*p*-methoxybenzyloxy)dec-1-ene (S1). To an oven-dried round-bottom flask under N_2 charged with a Teflon stir bar and PMB aldehyde **16** (7.19 g, 28.7 mmol, 1 equiv) was added THF (250 mL). The resulting solution was cooled to 0 °C in an ice bath, and allylmagnesium bromide, 1.0 M in THF (30 mL, 30 mmol, 1.05 equiv), was added dropwise over 5 min. The reaction was stirred at 0 °C for 10 min. The reaction was quenched with saturated aqueous NH_4Cl (150 mL), and the organic layer was removed. The aqueous phase was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (60 g) with a 20% ethyl acetate in hexanes solvent system to obtain 6.10 g of colorless oil (20.9 mmol, 73% yield). R_f = 0.45 (silica gel, 40% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.86−5.72 (m, 1H), 5.11−5.04 (m, 2H), 4.38 (s, 2H), 3.73 (s, 3H), 3.56 (br s, 1H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.27−2.18 (m, 1H), 2.18−2.04 (m, 2H), 1.57 (p, *J* = 7.0 Hz, 2H), 1.40−1.26 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.0, 135.0, 130.7, 129.2, 117.6, 113.7, 72.4, 70.6, 55.2, 41.9, 36.7, 29.6, 29.4, 26.1, 25.6 ppm. HRMS (ESI+ TOF) *m*/*z*: calculated for $C_{18}H_{28}O_3K$ [(M + K)$^+$] 331.1675, observed 331.1666 (Δ = 0.9 mmu).

4-(*O*-*tert*-Butyldimethylsilyloxy)-10-(*O*-*p*-methoxybenzyloxy)-dec-1-ene (17). To an oven-dried round-bottom flask under a N_2 atmosphere containing a Teflon stir bar and hydroxyalkene **S1** (6.1 g, 20.9 mmol, 1 equiv) were added *N*,*N*-dimethylformamide (50 mL) and imidazole (2.13 g, 31.4 mmol, 1.5 equiv), followed by *tert*-butyldimethylsilyl chloride (3.46 g, 22.9 mmol, 1.1 equiv). The resulting solution was stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the organics were extracted with ethyl acetate (3 × 150 mL). The combined organic layers were then washed with 1:1 v/v saturated aqueous NaCl/distilled water (2 × 100 mL) followed by brine (200 mL). The organic layer was then dried with $MgSO_4$ and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography on silica gel (50 g) with a stepwise ethyl acetate in a hexanes gradient (200 mL 10%; 200 mL 20%) to obtain 7.4 g of a colorless oil (18.2 mmol, 87% yield). R_f = 0.45 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.79 (ddt, *J* = 16.8, 10.6, 7.2 Hz, 1H), 5.03−4.98 (m, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.65 (p, *J* = 5.6 Hz, 1H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.23−2.12 (m, 2H), 1.61−1.54 (m, 2H), 1.43−1.19 (m, 8H), 0.86 (s, 9H), 0.022 (s, 3H), 0.017 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.1, 135.5, 130.8, 129.2, 116.5, 113.8, 72.5, 72.0, 70.2, 55.3, 41.9, 36.8, 29.7, 29.6, 26.2, 25.9, 25.3, 18.2, −4.4, −4.5 ppm. HRMS (EI) *m*/*z*: calculated for $C_{24}H_{42}O_3Si$ [M] 406.2903, observed 406.2885 (Δ = 1.8 mmu).

4-Hydroxy-6-(*O*-*tert*-Butyldimethylsilyloxy)-12-(*O*-*p*-methoxy-benzyloxy)dodec-1-ene (S2). To an oven-dried round-bottom flask under N_2 containing alkene **17** (0.1477 g, 0.363 mmol, 1

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equiv) was added a Teflon stir bar followed by methylene chloride (3 mL), *tert*-butanol (1.5 mL), distilled water (1.5 mL), potassium ferricyanate (0.359 g, 1.09 mmol, 3 equiv), and potassium carbonate (0.150 g, 1.09 mmol, 3 equiv). A solution of potassium osmate dihydrate (0.02 g, 0.54 mmol, 0.015 equiv) was prepared in 15% w/w NaOH (1.07 mL) and added to the vigorously stirred biphasic solution of alkene **17**, and then the reaction was sealed with a glass stopper and allowed to stir overnight at rt. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organics were extracted with methylene chloride (3 × 10 mL). The combined organic layers were then washed with brine (20 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The crude diol was dissolved in methylene chloride (8 mL) and partitioned into two equal (4 mL) portions under N_2. A Teflon stir bar was added to the flask and then cooled to 0 °C in an ice bath. A portion of lead(IV) acetate (0.579 g, 0.13 mmol, 1.2 equiv) was added, and the resulting brown suspension was stirred at 0 °C for 30 min. The white solids were filtered on a plug of Celite (0.5 g) and then washed with methylene chloride (2 × 1 mL). The organic layers were pooled and concentrated *in vacuo* to give a black oil. The residue was purified by flash chromatography on silica gel (10 g) with a 30% ethyl acetate in hexanes solvent system to obtain 0.0584 g of a colorless oil (0.143 mmol, 78% yield). R_f = 0.69 (silica gel, 30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, J = 2.4 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.40 (s, 2H), 4.15 (t, J = 5.9 Hz, 1H), 3.78 (s, 3H), 3.41 (t, J = 6.6 Hz, 2H), 2.49−2.47 (m, 2H), 1.60−1.53 (m, 2H), 1.53−1.46 (m, 2H), 1.38−1.25 (m, 6H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 159.1, 130.7, 129.1, 113.7, 72.4, 70.0, 68.1, 55.0, 50.8, 37.7, 29.7, 29.4, 26.2, 25.8, 17.9, −4.4, −4.7 ppm. To an oven-dried round-bottom flask under N_2 charged with a Teflon stir bar and the obtained aldehyde (58.4 mg, 0.143 mmol, 1 equiv) was added THF (2 mL). The resulting solution was cooled to 0 °C in an ice bath, and allylmagnesium bromide, 1.0 M in THF (0.176 mL, 0.176 mmol, 1.2 equiv), was added dropwise. The reaction was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was removed. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography on silica gel (7 g) with a 20% ethyl acetate in hexanes solvent system to obtain 60.0 mg of a colorless oil (0.133 mmol, 93% yield). R_f = 0.26 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.87−5.69 (m, 1H), 5.1−4.97 (m, 2H), 4.36 (s, 3H), 3.94−3.72 (m, 2H), 3.70 (s, 3H), 3.37 (t, J = 6.7 Hz, 2H), 2.21−2.12 (m, 2H), 1.58−1.41 (m, 6H), 1.35−1.19 (m, 6H), 0.86 (d, J = 1.7 Hz, 9H), 0.06−0.03 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 135.02, 134.97, 130.7, 129.1, 117.3, 117.2, 113.7, 72.7, 72.5, 71.4, 70.0, 69.9, 67.6, 55.1, 42.5, 42.2, 41.2, 37.8, 36.4, 29.7, 29.7, 29.6, 26.22, 26.19, 25.9, 25.6, 24.6, 17.96, 17.94, −4.0, −4.5, −4.6, −4.7 ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{26}H_{46}O_4SiK$ $[(M + K)^+]$ 489.2802, observed 489.2754 (Δ = 4.8 mmu).

4,6-(Di-*O*-*tert*-butyldimethylsilyloxy)-12-(*O*-*p*-methoxybenzyl-oxy)dodec-1-ene (18). To an oven-dried round-bottom flask under a N_2 atmosphere containing a Teflon stir bar and hydroxyalkene **S2** (0.4055 g, 0.90 mmol, 1 equiv) were added *N*,*N*-dimethylformamide (1 mL), imidazole (0.122 g, 1.8 mmol, 2 equiv), and *N*,*N*-dimethylpyridine (11 mg, 0.09 mmol, 0.1 equiv), followed by *tert*-butyldimethylsilyl chloride (0.203 g, 1.35 mmol, 1.5 equiv). The resulting solution was stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organics were extracted with ethyl acetate (3 × 10 mL). The combined organic layers were then washed with 1:1 v/v saturated aqueous NaCl/distilled water (2 × 10 mL) followed by brine (10 mL). The organic layer was then dried with $MgSO_4$ and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography on silica gel (15 g) with a stepwise ethyl acetate in hexanes gradient (200 mL 5%; 200 mL 20%) to obtain 0.4747 g of colorless oil (0.84 mmol, 93% yield). R_f = 0.44 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.90−5.79 (m, 1H), 5.09−5.03 (m, 2H), 4.43 (s, 2H), 3.89−3.75 (m, 2H), 3.78 (s, 3H), 3.44 (t, J = 6.8 Hz, 2H), 2.34−2.15 (m, 2H), 1.69−1.54 (m, 4H), 1.50−1.30 (m, 8H), 0.93−0.92 (m, 18H), 0.10−0.08 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 135.04, 134.98, 130.8, 129.2, 116.93, 116.92, 113.7, 72.6, 70.1, 69.8, 69.5, 69.2, 55.1, 45.0, 44.6, 42.6, 42.0, 37.9, 37.3, 31.7, 29.8, 29.7, 26.34, 26.32, 26.01, 25.99, 25.98, 25.96, 25.1, 25.0, 22.7, 18.13, 18.11, 18.09, 14.2, −3.81, −3.89, −4.07, −4.22, −4.24, −4.34, −4.46 ppm. HRMS (EI) m/z: calculated for $C_{32}H_{60}O_4Si_2Na$ $[(M + Na)^+]$ 587.3928, observed 587.3946 (Δ = 1.8 mmu).

Ethyl (*E*)-5,7-(Di-*O*-*tert*-butyldimethylsilyloxy)-2,3-ene-13-(*O*-*p*-methoxybenzyloxy)tridecanoate (19). To an oven-dried round-bottom flask under N_2 containing alkene **18** (2.022 g, 3.58 mmol, 1 equiv) was added a Teflon stir bar, followed by *tert*-butanol (20 mL), deionized water (20 mL), potassium ferricyanate (3.52 g, 10.7 mmol, 3 equiv), and potassium carbonate (1.48 g, 10.7 mmol, 3 equiv). A solution of potassium osmate dihydrate (0.02 g, 0.054 mmol, 0.015 equiv) was prepared in 15% w/w NaOH (1.07 mL) and added to the vigorously stirred biphasic solution of alkene **18**, and then the reaction was sealed with a glass stopper and stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the organics were extracted with methylene chloride (3 × 75 mL). The combined organic layers were then washed with brine (200 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The crude diol was dissolved in methylene chloride (50 mL), and a Teflon stir bar was added to the flask, followed by cooling to 0 °C in an ice bath. A portion of lead(IV) acetate (1.67 g, 3.76 mmol, 1.05 equiv) was added, and the resulting brown suspension was stirred at 0 °C for 30 min. The white solids were filtered on a plug of Celite (1 g) and then washed with two portions of methylene chloride (10 mL). The organic layers were pooled and concentrated *in vacuo* to give a black oil. The residue was purified by flash chromatography on silica gel (50 g) with a 30% ethyl acetate in hexanes solvent system to obtain 1.634 g of a colorless oil (2.88 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (dt, J = 3.10, 1.9 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.41 (s, 2H), 4.34−4.20 (m, 1H), 3.78 (s, 3H), 3.74−3.64 (m, 1H), 3.41 (t, J = 6.6 Hz, 2H), 2.62−2.42 (m, 2H), 1.79−1.67 (m, 1H), 1.64−1.53 (m, 3H), 1.50−1.35 (m, 2H), 1.35−1.23 (m, 4H), 0.87−0.83 (m, 18H), 0.07−0.01 (m, 12H) ppm. To an oven-dried round-bottom flask under N_2 containing the obtained aldehyde (0.809 g, 1.4 mmol, 1 equiv) were added a Teflon stir bar, THF (10 mL), and triethylphosphonoacetate (0.31 mL, 1.5 mmol, 1.1 equiv). Freshly powdered KOH (0.16 g, 2.8 mmol, 2 equiv) was added in one portion to the vigorously stirred solution. The resulting suspension was stirred at rt for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organics were extracted with ethyl acetate (3 × 20 mL). The combined organic layers were then washed with brine (2 × 50 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography on silica gel (20 g) with a stepwise gradient of ethyl acetate in hexanes (200 mL 2%; 100 mL 5%; 100 mL 100% ethyl acetate) to obtain 0.4976 g of a colorless oil (0.798 mmol, 57% yield). R_f = 0.30 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.93 (dt, J = 15.6, 7.8 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.81 (ddt, J = 15.7, 5.3, 1.3 Hz, 1H), 4.41 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.91−3.84 (m, 2H), 3.78 (s, 3H), 3.73−3.65 (m, 1H), 3.41 (t, J = 6.6 Hz, 2H), 2.43−2.21 (m, 2H), 1.66−1.48 (m, 4H), 1.46−1.35 (m, 2H), 1.34−1.31 (m, 2H), 1.29−1.22 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 0.87−0.85 (m, 18H), 0.02−0.01 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.3, 159.1, 145.8, 144.8, 140.9, 130.8, 130.4, 129.2, 123.4, 119.6, 113.7, 72.5, 71.7, 70.1, 69.4, 68.6, 68.0, 60.2, 60.1, 55.2, 44.9, 40.9, 40.1, 37.4, 37.1, 29.74, 29.72, 29.6, 26.24, 26.20, 25.90, 25.86, 25.84, 25.6, 25.3, 25.0, 18.09, 18.04, 18.02, 14.31, 14.27, −4.2, −4.4, −4.5 ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{35}H_{64}O_6Si_2Na$ $[(M + Na)^+]$ 659.4139, observed 659.4101 (Δ = 3.8 mmu).

Ethyl 5,7-(Di-*O*-*tert*-butyldimethylsilyloxy)-13-hydroxy-(*E*)-2,3-enetridecanoate (S3). To an oven-dried round-bottom flask under an Ar atmosphere containing a Teflon stir bar and PMB ether

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19 (0.331 g, 0.53 mmol, 1 equiv) was added 9:1 v/v methylene chloride/deionized water (10 mL) and cooled to 0 °C in an ice bath. The septum was removed, and DDQ (0.1498 g, 0.66 mmol, 1.2 equiv) was added. The resulting dark green suspension was sealed with a glass stopper and then allowed to warm to rt. After 15 min, the green color had dissipated yielding a white precipitate and was stirred for an additional 30 min at rt. The resulting solids were filtered off through a plug of Celite (0.5 g), and the solids were washed with methylene chloride (3 × 10 mL). The organics were pooled and washed with 1:1 v/v thiosulfate/saturated $NaHCO_3$ (10 mL). The organics were removed, and the resulting aqueous layer was washed with methylene chloride (3 × 10 mL). The organic layers were combined and washed with brine (20 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give an orange oil. The residue was purified by flash chromatography on silica gel (10 g) with a 15% ethyl acetate in a hexanes solvent system to obtain 0.1563 g of a colorless oil (0.302 mmol, 57% yield). R_f = 0.40 (silica gel, 30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (dt, J = 15.7, 7.2 Hz, 1H), 5.81 (ddt, J = 15.7, 4.8, 1.2 Hz, 1H), 3.95−3.83 (m, 1H), 3.74−3.65 (m, 1H), 3.62 (dt, J = 1.2, 6.6 Hz, 2H), 2.48−2.26 (m, 2H), 1.72−1.48 (m, 4H), 1.46−1.36 (m, 2H), 1.36−1.25 (m, 6H), 1.86−1.85 (m, 18H), 0.05−0.00 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.06, 170.96, 148.51, 148.47, 122.93, 122.85, 70.0, 69.3, 69.1, 68.4, 63.0, 45.3, 44.6, 41.0, 40.1, 37.8, 37.4, 32.65, 32.59, 29.62, 29.55, 25.91, 25.88, 25.83, 25.7, 24.9, 18.1, 18.03, 18.01, −3.9, −4.15, −4.18, −4.2, −4.3, −4.4, −4.50, −4.53 ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{27}H_{56}O_5Si_2Na$ $[(M + Na)^+]$ 539.3564, observed 539.3566 (Δ = 0.2 mmu).

(*E*)-6,8-Bis(*tert*-butyldimethylsilyloxy)oxacyclotetradec-3-en-2-one (20). To an oven-dried round-bottom flask under an N_2 atmosphere containing a Teflon stir bar and ethyl ester **S3** (0.126 g, 0.24 mmol, 1 equiv) were added 95% ethanol (3 mL) and 1.0 M LiOH (0.5 mL, 0.5 mmol, 2.1 equiv). The resulting solution was stirred at rt overnight. The reaction was quenched with the addition of water (10 mL), and 1.0 M HCl was added dropwise until the aqueous phase was acidic indicated by pH paper. Ethyl acetate was added, the organics were removed, and the aqueous phase was washed with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a clear oil. The residue was purified by flash chromatography on silica gel (6 g) with a 30% ethyl acetate in hexanes solvent system to obtain 0.1106 g of a colorless oil (0.226 mmol, 94% yield). R_f = 0.42 (silica gel, 50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dt, J = 15.6, 7.7 Hz, 1H), 5.83 (d, J = 15.5 Hz, 1H), 3.93−3.85 (m, 1H), 3.75−3.67 (m, 1H), 3.62 (t, J = 6.6 Hz, 2H), 2.47−2.26 (m, 2H), 1.61−1.47 (m, 4H), 1.46−1.36 (m, 2H), 1.36−1.24 (m, 6H), 0.86 (s, 9H), 0.85 (s, 9H), 0.05−0.03 (m, 12H) ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{25}H_{52}O_5Si_2Na$ $[(M + Na)^+]$ 511.3251, observed 511.3254 (Δ = 0.3 mmu). To an oven-dried round-bottom flask under N_2 containing a Teflon stir bar and azeotropically dried (3 × 5 mL PhH) obtained hydroxy acid (0.1003 g, 0.205 mmol, 1 equiv) were added freshly distilled PhH (20 mL), diisopropylethylamine (0.36 mL, 2.07 mmol, 10 equiv), and 2,4,6-trichlorobenzoylyl chloride (0.32 mL, 2.07 mmol, 10 equiv). The resulting mixture was stirred at rt overnight. Powdered DMAP (0.375 g, 3.075 mmol, 15 equiv) was added, and the resulting suspension was stirred at rt for 2 h. The reaction was quenched with deionized water (50 mL) and was acidified by dropwise addition of 1 M HCl until pH = 2. The organics were extracted with ethyl acetate (20 mL), and the aqueous phase was washed with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (50 mL), washed with brine (50 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a white solid. The residue was purified by flash chromatography on silica gel (9 g) with a 5% ethyl acetate in hexanes solvent system to obtain 72.8 mg of a colorless oil (0.15 mmol, 75% yield). R_f = 0.77 (silica gel, 40% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01−6.83 (m, 1H), 5.85−5.80 (m, 1H), 4.50−4.34 (m, 1H), 4.09−4.01 (m, 1H), 3.96−3.79 (m, 1H), 3.74−3.66 (m, 1H), 2.60−2.35 (m, 2H), 1.79−1.58 (m, 4H), 1.54−1.17 (m, 8H), 0.86 (d, J = 7.4 Hz, 9H), 0.86 (d, J = 7.4 Hz, 9H), 0.05−0.01 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.8, 145.8, 145.6, 124.5, 123.4, 69.7, 68.6, 68.4, 68.3, 65.5, 64.2, 48.4, 42.7, 42.5, 39.3, 36.8, 34.5, 29.0, 27.8, 26.9, 26.5, 26.3, 25.9, 25.79, 25.78, 24.6, 24.0, 23.5, 18.1, 18.03, 18.00, 17.98, −4.0, −4.1, −4.55, −4.61, −4.70, −4.73, −4.77, −4.8 ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{25}H_{50}O_4Si_2Na$ $[(M + Na)^+]$ 493.3145, observed 493.3111 (Δ = 3.4 mmu).

(*E*)-6,8-Dihydroxyoxacyclotetradec-3-en-2-one (14 and 21). To a polypropylene Eppendorf tube charged with diTBS lactone **20** (27.8 mg, 59 μmol, 1 equiv) was added acetonitrile (600 μL) followed by 48% HF (41 μL, 1.2 mmol, 20 equiv) and the resulting solution was vortexed and allowed to sit at rt overnight with occasional vortexing. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (2 mL), and the organics were removed with ethyl acetate (2 mL). The aqueous layer was washed with saturated aqueous $NaHCO_3$ (3 × 2 mL). The organic layers were pooled, washed with brine (5 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give a pale yellow oil. The diastereomers were separated with preparative TLC using a 90% v/v ethyl acetate in hexanes solvent system to give a 1:1 mixture of diastereomers; 6.8 mg of the *anti* and 5.3 mg of the *syn* (50 mmol, 85% yield).

Syn (14). R_f = 0.22 (silica gel, 90% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (dt, J = 15.8, 7.8 Hz, 1H), 5.88 (dt, J = 15.7, 1.3 Hz, 1H), 4.30 (ddd, J = 11.1, 7.5, 3.7 Hz. 1H), 4.19 (ddd, J = 11.1, 7.0, 3.7 Hz, 1H), 4.07−3.99 (m, 1H), 3.71−3.62 (m, 1H), 2.68 (dddd, J = 13.3, 7.9, 4.4, 1.3 Hz, 1H), 2.35 (dtd, J = 13.3, 8.1, 1.3 Hz, 1H), 2.05 (br s, 1H), 1.85 (ddd, J = 14.3, 7.8, 2.6 Hz, 1H), 1.79−1.54 (m, 4H), 1.52−1.42 (m, 3H), 1.40−1.24 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 144.4, 124.9, 69.4, 69.2, 65.0, 43.3, 40.0, 36.6, 27.9, 26.9, 26.5, 24.4 ppm. HRMS (ESI+ TOF) m/z: calculated for $C_{13}H_{22}O_4Na$ $[(M + Na)^+]$ 265.1416, observed 265.1423 (Δ = 0.7 mmu).

Anti (21). R_f = 0.35 (silica gel, 90% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (ddd, J = 15.7, 9.4, 6.4 Hz, 1H), 5.89 (d, J = 15.7 Hz, 1H), 4.32−4.24 (m. 1H), 4.21−4.11 (m, 1H), 4.09−3.98 (m, 1H), 3.09 (br s, 1H), 2.70−2.61 (m, 1H), 2.45 (dt, J = 13.4, 9.2, Hz, 1H), 2.18 (br s, 1H), 1.75−1.69 (m, 2H), 1.68−1.18 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 144.8, 124.6, 68.83, 68.80, 65.2, 39.2, 38.5, 36.5, 28.2, 26.93, 26.87, 24.7 ppm. HRMS (ESI + TOF) m/z: calculated for $C_{13}H_{22}O_4Na$ $[(M + Na)^+]$ 265.1416, observed 265.1418 (Δ = 0.2 mmu).

3-(*tert*-Butyldimethylsilyloxy)-5-methoxy-5-oxopentanoic acid (26). R_f = 0.20 (silica gel, 20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.65 (br s, 1H), 4.53 (p, J = 6.0 Hz, 1H), 3.66 (s, 3H), 2.65−2.53 (m, 4H), 0.83 (s, 9H), 0.06 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 171.3, 66.1, 51.7, 42.1, 41.9, 25.6, 17.9, −5.0 ppm. NMR spectra were consistent with those previously reported within literature data.[59]

7-Bromoheptanal (27). To a round-bottom flask charged with 7-bromo-1-alkene (400 mg, 2.09 mmol, 1.0 equiv) in *tert*-butanol/deionized water (1:1, 20 mL) were added potassium ferricyanide (2.07 g, 6.27 mmol, 3.0 equiv) and potassium carbonate (867 mg, 6.27 mmol, 3.0 equiv). A solution of potassium osmate dihydrate (15 mg, 0.04 mmol, 2 mol %) was prepared in 15% w/w NaOH (0.5 mL) and added to the vigorously stirred biphasic solution of bromoalkene, sealed with a glass stopper and stirred at rt overnight. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and the organics were extracted with methylene chloride (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield a clear oil. The crude diol in methylene chloride (8.5 mL) was added a portion of lead tetraacetate (1.1 g, 2.50 mmol, 1.2 equiv) and left to stir at rt for 60 min under an Ar atmosphere. The reaction mixture was concentrated to 20% volume *in vacuo* and added directly to a pre-equilibrated column (silica gel, 10% ethyl acetate in hexanes) for isolation of 288.3 mg of **27** (1.5 mmol, 72%) as clear, colorless oil. R_f = 0.36 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, J = 1.7 Hz, 1H), 3.39 (t, J = 6.7 Hz, 2H), 2.43 (dt, J = 1.7, 7.2 Hz, 2H), 1.89−1.80 (m, 2H), 1.63 (p, J = 7.5 Hz, 2H), 1.50−1.28 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 43.7, 33.7, 32.4, 28.2, 27.8, 21.8 ppm.

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NMR spectra were consistent with those previously reported within literature.[60]

(*E*)-13-Bromo-3-(*tert*-butyldimethylsilyloxy)-5-oxotridec-6-enoic Acid (28). A stirring solution of dimethyl methylphosphonate (750 μL, 6.70 mmol, 3.7 equiv) in dry THF (8 mL) was cooled to −78 °C under an inert atmosphere. To this solution 2.5 M *n*BuLi (2.5 mL, 6.25 mmol, 3.5 equiv) was added dropwise to effect a yellow color, followed by stirring for 2 h. Addition of acid **26** (500 mg, 1.81 mmol, 1.0 equiv) in THF (4 mL) via cannula yielded a clear, orange solution. The solution was brought to rt, and product formation was observed via TLC (silica gel, 5% MeOH in methylene chloride), where the product was bright red under visualization with *p*-anisaldehyde stain. Upon completion, the reaction was quenched with 1.0 M HCl solution (3 × 3 mL), diluted in ethyl acetate (3 × 20 mL), and separated. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to afford 645.6 mg of crude phosphonate as a pale yellow oil, which was spectroscopically pure enough for use in the following step. R_f = 0.24 (silica gel, 5% MeOH in methylene chloride; *p*-anisaldehyde stain); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 (p, *J* = 5.8 Hz, 1H), 3.78 (d, *J* = 11.3 Hz, 3H), 3.77 (d, *J* = 11.3 Hz, 3H), 3.11 (d, *J* = 22.7 Hz, 2H), 2.89 (d, *J* = 6.1 Hz, 2H), 2.58 (dd, *J* = 5.9, 15.4 Hz, 1H), 2.49 (dd, *J* = 5.5, 15.4 Hz, 1H), 0.84 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H) ppm; ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.6 ppm. HRMS (EI) *m*/*z*: calculated for $C_{10}H_{20}O_7PSi$ [M − *t*-Bu] 311.0716, observed 311.0705 (Δ = 1.1 mmu). A solution of the obtained phosphonate (230 mg, 0.62 mmol, 1.2 equiv) in isopropanol (4 mL, dried over 4 Å MS) was cooled to 0 °C. Cesium carbonate (390 mg, 1.2 mmol, 1.9 equiv) was added in one portion, and the mixture was stirred at 0 °C for 2 h. To the reaction mixture a solution of bromoaldehyde **27** (99 mg, 0.51 mmol, 1.0 equiv) in isopropanol (1 mL, dried over 4 Å MS, 0.1 M overall reaction mixture) was added dropwise. The reaction mixture was warmed to 30 °C and stirred overnight. The reaction was diluted with ethyl acetate (10 mL) and quenched by the addition of 1.0 M HCl solution (4 mL). The mixture was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification via column chromatography (20% ethyl acetate/hexanes) yielded 179.9 mg of **28** (0.413 mmol, 81%) as a clear, colorless oil. R_f = 0.29 (silica gel, 20% Ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (br s, 1H), 6.81 (dt, *J* = 15.9, 6.9 Hz, 1H), 6.08 (dt, *J* = 15.9, 1.5 Hz, 1H), 4.59 (p, *J* = 5.9 Hz, 1H), 3.38 (t, *J* = 6.7 Hz, 2H), 2.84 (dd, *J* = 15.9, 6.4 Hz, 1H), 2.72 (dd, *J* = 15.9, 6.0 Hz, 1H), 2.60 (dd, *J* = 15.1, 5.5 Hz, 1H), 2.49 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.24−2.17 (m, 2H), 1.89−1.78 (m, 2H), 1.51−1.29 (m, 8H), 0.82 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 176.5, 148.3, 131.0, 66.0, 46.9, 42.3, 33.7, 32.5, 32.3, 28.3, 27.8, 27.7, 25.7, 17.9, −4.8, −5.0 ppm. HRMS (EI) *m*/*z*: calculated for $C_{15}H_{26}BrO_4Si$ [(M − *t*-Bu)] 377.0784, observed 377.0789 (Δ = 0.5 mmu).

(*E*)-4-(*tert*-Butyldimethylsilyloxy)oxacyclotetradec-7-ene-2,6-dione (29). To a flask charged with bromoacid **28** (120 mg, 0.28 mmol, 1.0 equiv) in anhydrous DMF (28 mL, 0.01 M) was added cesium carbonate (162.1 mg, 0.50 mmol, 1.8 equiv) under an Ar atmosphere at 0 °C. The reaction was left to warm to room temperature as it was stirred overnight. The reaction mixture was then diluted with ethyl acetate (40 mL) and washed with brine. The aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were washed with water (3 × 40 mL) and brine, dried ($MgSO_4$), filtered, and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford 66.3 mg of macrolactone **29** (0.19 mmol, 68%) as a clear, pale yellow oil. R_f = 0.54 (silica gel, 10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80 (ddd, *J* = 16.0, 8.1, 6.6 Hz, 1H), 6.05 (dt, *J* = 16.0, 1.4 Hz, 1H), 4.54 (ddt, *J* = 8.2, 4.3, 6.0 Hz, 1H), 4.15 (ddd, *J* = 11.1, 7.3, 3.1 Hz, 1H), 4.08−4.01 (m, 1H), 3.00 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.70 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.52 (dd, *J* = 14.7, 4.3 Hz, 1H), 2.47 (dd, *J* = 14.7, 6.1 Hz, 1H), 2.39−2.21 (m, 2H), 1.65−1.54 (m, 4H), 1.48−1.39 (m, 4H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 170.4, 149.5, 131.8, 67.3, 64.7, 47.0, 42.5, 32.2, 27.4, 27.2, 25.8, 25.7, 25.5, 18.0, −4.8, −4.8 ppm. HRMS (EI) *m*/*z*: calculated for $C_{15}H_{25}O_4Si$ [(M − *t*-Bu)] 297.1522, observed 297.1518 (Δ = 0.4 mmu).

(*E*)-4-Hydroxyoxacyclotetradec-7-ene-2,6-dione (15). To a 1.5 mL polypropylene Eppendorf tube charged with macrolactone **29** (16 mg, 0.045 mmol, 1.0 equiv) were added acetonitrile (450 μL, 0.1 M) and pyridine (18 μL, 0.225 mmol, 5.0 equiv). The reaction mixture was vortexed to homogeneity, upon which 48% HF (82 μL, 0.450 mmol, 50 equiv) was added. The reaction mixture was again vortexed, then centrifuged, and left for 5 h. The reaction was quenched with water (2 × 1 mL) and diluted with ethyl acetate (2 × 2 mL). The aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to dryness *in vacuo*. The product was purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford 10.8 mg of **15** (0.045 mmol, > 99%) as a clear, colorless oil. R_f = 0.28 (silica gel, 40% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (dt, *J* = 16.0, 7.3 Hz, 1H), 6.07 (dt, *J* = 16.0, 1.4 Hz, 1H), 4.33−4.27 (m, 1H), 4.17 (t, *J* = 5.4 Hz, 2H), 3.73 (br s, 1H), 2.92 (d, *J* = 5.7 Hz, 2H), 2.62 (dd, *J* = 16.1, 3.6 Hz, 1H), 2.52 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.36 (dd, *J* = 7.1, 1.6 Hz, 1H), 2.32 (dd, *J* = 7.1, 1.4 Hz, 1H), 1.66−1.57 (m, 4H), 1.44−1.31 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 171.8, 151.9, 132.5, 66.7, 64.4, 41.6, 39.6, 32.6, 27.8, 27.7, 25.9, 25.6 ppm. HRMS (EI) *m*/*z*: calculated for $C_{13}H_{20}O_4$ [M] 240.1362, observed 240.1348 (Δ = 1.4 mmu).

***trans*-4,15-Dioxabicyclo[9.3.1]pentadecane-3,13-dione (30).** To a 5 mm NMR tube charged with **15** (3.5 mg, 14.57 μmol, 1.0 equiv) in $CDCl_3$ (0.5 mL) was added *p*-toluenesulfonic acid monohydrate (1.6 mg), of which most did not go into solution. Instantaneous conversion of material was realized via ^{1}H NMR and TLC (silica gel, 20% ethyl acetate in hexanes) monitoring, at which point the mixture was filtered, concentrated, and purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford 2.9 mg of **30** (12.09 μmol, 83%) as a clear, colorless oil. R_f = 0.19 (silica gel, 20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (ddt, *J* = 12.2, 6.3, 3.8 Hz, 1H), 4.47 (ddd, *J* = 11.2, 6.4, 2.4 Hz, 1H), 4.17 (dddd, *J* = 10.8, 8.7, 3.9, 1.9 Hz, 1H), 3.97 (ddd, *J* = 11.2, 9.4, 1.9 Hz, 1H), 2.71 (dd, *J* = 12.3, 1.4 Hz, 1H), 2.67 (ddd, *J* = 14.3, 6.2, 1.2 Hz, 1H), 2.42 (ddd, *J* = 14.1, 4.1, 1.7 Hz, 1H), 2.34 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.32−2.26 (m, 1H), 2.24 (ddd, *J* = 14.4, 4.3, 1.7 Hz, 1H), 1.92−1.82 (m, 1H), 1.73−1.43 (m, 5H), 1.43−1.26 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 170.4, 70.8, 69.9, 66.7, 48.2, 46.1, 39.6, 33.4, 26.8, 25.4, 25.1, 22.1 ppm. HRMS (EI) *m*/*z*: calculated for $C_{13}H_{18}O_3$ [M − H_2O] 222.1256, observed 222.1270 (Δ = 1.4 mmu).

***cis*-4,15-Dioxabicyclo[9.3.1]pentadecane-3,13-dione (31).** To a 5 mm NMR tube charged with **15** (4.7 mg, 19.56 μmol, 1.0 equiv) in $CDCl_3$ (0.5 mL) was added Amberlyst 15 hydrogen form (5 mg), followed by heating to 80 °C for 4 h. The reaction was monitored by ^{1}H NMR and TLC, and upon consumption of starting material the mixture was filtered, concentrated, and purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford 3.6 mg of **31** (14.87 μmol, 76%) as a clear, colorless oil. R_f = 0.25 (silica gel, 20% ethyl acetate in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (ddd, *J* = 11.0, 10.1, 2.9 Hz, 1H), 4.18 (ddd, *J* = 11.0, 4.7, 4.0 Hz, 1H), 3.95 (dddd, *J* = 11.5, 7.7, 6.4, 2.7 Hz, 1H), 3.58 (m, 1H), 2.51 (d, *J* = 7.7 Hz, 1H), 2.50 (d, *J* = 6.4 Hz, 1H), 2.41 (ddd, *J* = 14.4, 2.7, 1.6 Hz, 1H), 2.32 (ddd, *J* = 14.4, 3.1, 1.6 Hz, 1H), 2.36−2.18 (m, 2H), 1.93−1.78 (m, 1H), 1.77−1.27 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.1, 171.0, 77.2, 74.3, 64.4, 48.3, 47.1, 42.3, 33.6, 26.1, 25.2, 24.4, 24.2 ppm. HRMS (ESI+ TOF) *m*/*z*: calculated for $C_{13}H_{20}O_4Na$ [$(M + Na)^+$] 263.1259, observed 263.1276 (Δ = 1.7 mmu). Alternatively, to a 5 mm NMR tube charged with **30** (2.7 mg, 11.24 μmol, 1.0 equiv) in $CDCl_3$ (0.5 mL) was added Amberlyst 15 hydrogen form (5 mg) and heated to 80 °C for 4 h. The reaction was monitored by ^{1}H NMR, following key proton shifts in the range of δ 4.74−3.58 (H3, H7, H13A, H13B). Upon completion, the reaction mixture was filtered and purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford 2.2 mg of **31** (9.33 μmol, 83%) as a clear, colorless oil.

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***α-cis*-13-Hydroxy-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (32).** To a vial charged with *cis*-pyranone **31** (2.6 mg, 10.8 μmol, 1.0 equiv) in methanol (0.25 mL) at 0 °C was added $NaBH_4$ (1.2 mg, 32.5 μmol, 3.0 equiv) followed by stirring for 1 h. Upon completion, the reaction mixture was quenched with one drop of acetic acid and diluted with ethyl acetate and water. The layers were separated, and the aqueous later was re-extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford 2.2 mg of the α-product **32** (9.16 μmol, 84%) and 0.2 mg of the β-product (0.83 μmol, 7%) as clear, colorless oil. R_f = 0.38 (silica gel, 50% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (dt, *J* = 3.2, 11.0 Hz, 1H), 4.06 (dt, *J* = 11.0, 4.6 Hz, 1H), 3.81 (dddd, *J* = 11.0, 11.0, 4.6, 4.6 1H), 3.66 (m, 1H), 3.27 (m, 1H), 2.43−2.41 (m, 2H), 1.96 (ddt, *J* = 12.0, 4.7, 1.9 Hz, 1H), 1.88−1.76 (m, 2H), 1.74−1.66 (m, 1H), 1.61−1.32 (m, 6H), 1.31−1.14 (m, 4H) ppm, hydroxyl proton absent (H/D exchange); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 76.3, 73.4, 68.1, 63.9, 42.2, 41.7, 40.6, 33.2, 26.2, 25.5, 24.8, 23.7 ppm. HRMS (ESI+ TOF) *m/z*: calculated for $C_{13}H_{22}O_4Na$ [(M + Na)$^+$] 265.1410, observed 265.1408 (Δ = 0.2 mmu). NMR spectra were consistent with those previously reported within literature.[31]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02014.

^{1}H and ^{13}C NMR spectra of all new compounds, and NOESY, COSY, and HSQC for compounds **30**−**32** (PDF)

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Notes

The authors declare no competing financial interest.

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