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Total Synthesis

A Short and Efficient Approach for the Total Synthesis of (*S*)-Zearalenone and (*R*)-De-*O*-methyllasiodiplodin by Using Stille and RCM Protocols

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Abstract: A concise, flexible, and linear approach has been devised for the total synthesis of the resorcinylic acid lactones (*S*)-zearalenone (**2**) and (*R*)-de-*O*-methyllasiodiplodin (**4**) by using a Stille cross-coupling strategy. The other key steps of the synthesis include a ring-closing metathesis (RCM), a chemoselective reduction of an α,β-unsaturated ketone, and a transesterification reaction.

Introduction

A large number of resorcinylic acid lactones[1] with varying bioactivities have been isolated from different fungal and plant sources, and, hence, they have become prominent synthetic targets for organic chemists worldwide. The first discovered resorcinylic acid lactone was radicicol[2] (**1**), which binds to Hsp90 and alters its function. Hsp90 proteins play an important role in the regulation of the cell cycle, cell growth, cell survival, apoptosis, angiogenesis, and oncogenesis. Both zearalenone (**2**) and lasiodiplodin (**3**) are structurally related resorcinylic acid lactones (RALs), which were isolated from the two different fungal sources *Gibberella zeae* (*Fusarium graminearum*)[3] and *Lasiodiplodia theobromae*,[4] respectively. These RALs are known to have a wide range of biological activities such as antibiotic, estrogenic, uterotropic, antibacterial, antileukemic, antimicrobial, and antitumor effects along with being a prostaglandin synthesis inhibitor.[5,6]

Both **2** and **4** (Figure 1) contain a macrolide core that has an even-numbered ring (for **2**, a 14-membered ring and for **4**, a 12-membered ring). They belong to a same class of compounds as the orsellinic acid (i.e., 2,4-dihydroxy-6-methylbenzoic acid) family of natural products, and both contain one stereogenic center with a methyl carbinol moiety. The relative and absolute stereochemistry of both macrolides have been determined by total synthesis[7] as well as X-ray crystallography.[6a]

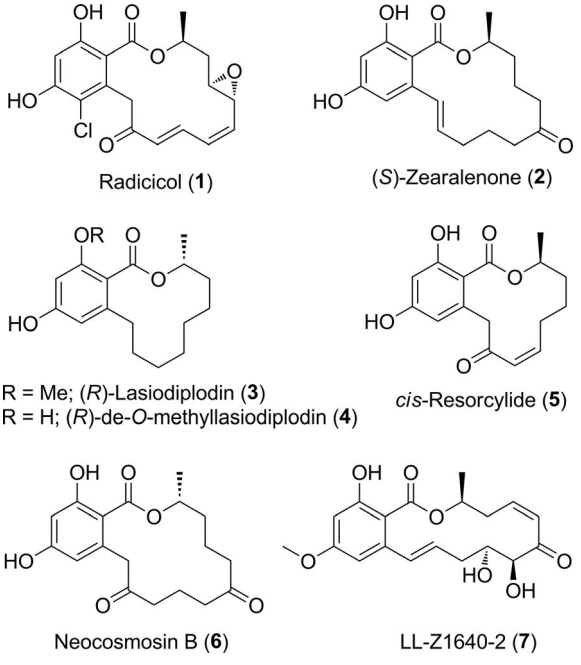

Figure 1. Structures of some naturally occurring RALs.

Inspired by their inherent biological activity, several groups have been involved in the development of synthetic routes for both macrolides.[7–9] However, employing a Stille coupling[10] to construct the styryl C-1′–C-2′ *trans*-olefin (Scheme 1) found in both **9** and **14** has not yet been reported. We propose that a Stille coupling might be a successful tool to construct the styryl olefin of both RALs. Because of their fascinating structural features, we became interested in the development of a concise synthetic strategy for **2** and **4**, which would also be effective for the total syntheses of other RALs. Following our interests in the total syntheses of bioactive RALs, we herein report a concise

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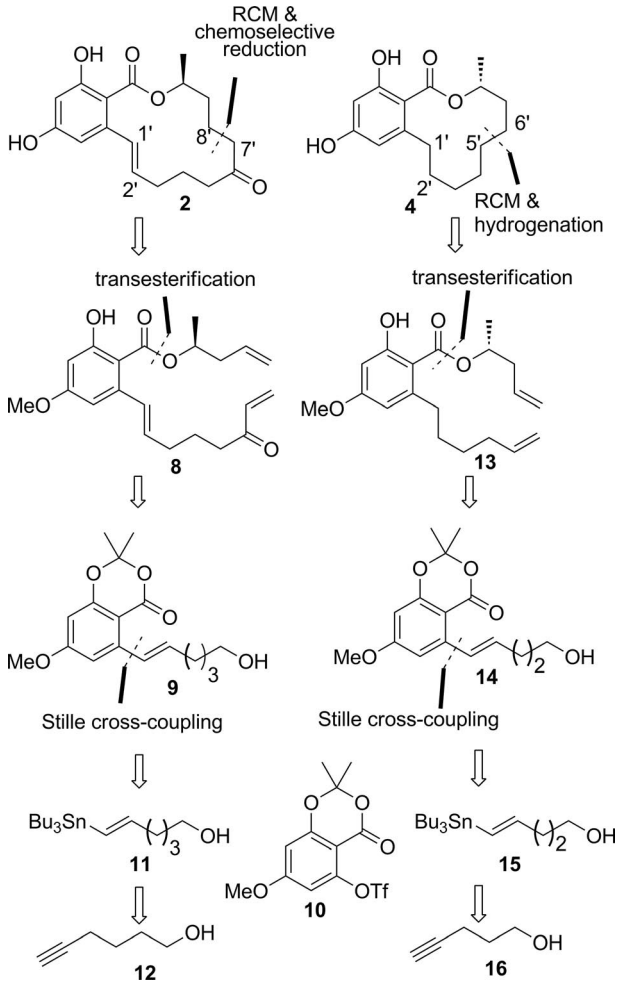
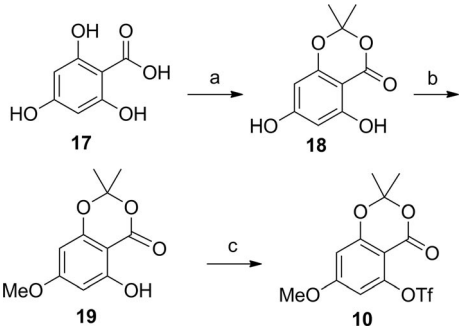
approach to the total synthesis of (*S*)-zearalenone (**2**) and (*R*)-de-*O*-methyllasiodiplodin (**4**) by employing Stille and ring-closing metathesis reactions as the key steps.



Scheme 1. Retrosynthetic analysis of **2** and **4** (TfO = trifluoromethanesulfonate).

Results and Discussion

The retrosynthetic analysis of **2** and **4** is illustrated in Scheme 2. A close assessment of the structures of (*S*)-zearalenone (**2**) and (*R*)-de-*O*-methyllasodiplodin (**4**) reveals that precursors to both of them contain similar styryl moieties that can be easily installed by a Stille cross-coupling reactions of *trans*-stannanes **11** and **15**, which are directly synthesized from commercially available 5-hexyn-1-ol (**12**) and 4-pentyn-1-ol (**16**), respectively. At a later stage, ring-closing metathesis (RCM) precursors **8** and **13** could be obtained by a transesterification[11] with the required chiral homoallylic alcohols to convert the lactone into the ester moiety and free phenolic residue that is associated with both targets. The C-7′–C-8′ bond of **2** and the C-5′–C-6′ bond of **4** could be established through a ring-closing metathesis followed by a chemoselective reduction through a 1,4-hydride addition to obtain **2** and a catalytic hydrogenation to give **4**.

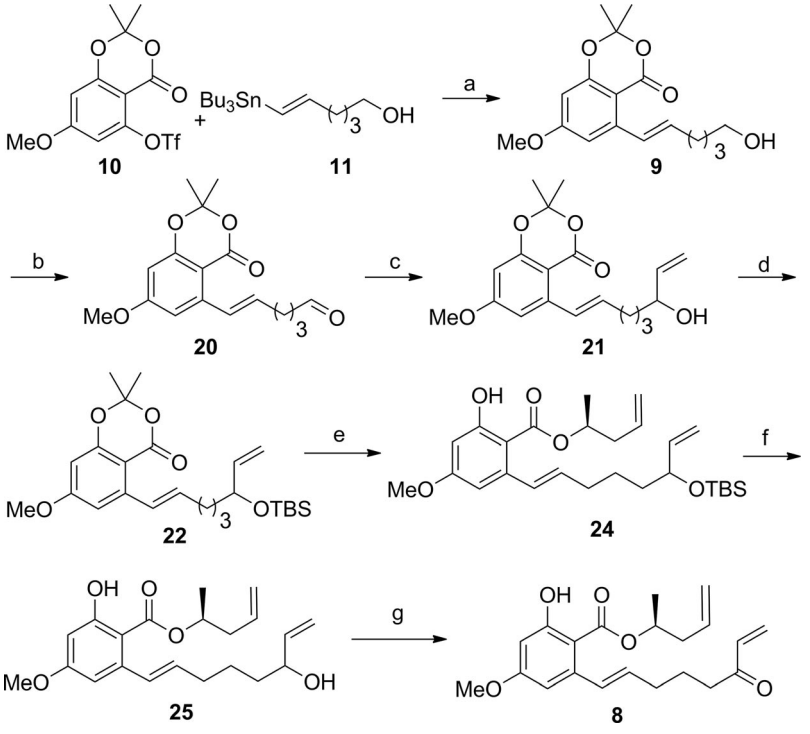


Scheme 2. Reagents and conditions: (a) acetone, trifluoroacetic acid (TFA), trifluoroacetic anhydride (TFAA), room temp., 20 h, 76 %; (b) MeOH, diisopropyl azodicarboxylate (DIAD), PPh_3, tetrahydrofuran (THF), 0 °C to room temp., 4 h, 81 %; (c) Tf_2O, pyridine (Py), 0 °C, 2 h, 96 %.

The common building block **10** was synthesized according to a literature procedure.[12] First, commercially available 2,4,6-trihydroxybenzoic acid (**17**, Scheme 2) was converted into lactone **18** in 76 % yield by using acetone and a mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA). Compound **18** was then subjected to Mitsunobu conditions by using methanol and a combination of Ph_3P and diisopropyl azodicarboxylate (DIAD), which resulted in the regioselective *O*-methylation of the non-hydrogen bonded phenolic residue to obtain compound **19** in 81 % yield. The conversion of **19** into corresponding triflate **10** was readily achieved in 96 % yield under standard conditions.

With the required starting materials in hand, we attempted the total synthesis of (*S*)-zearalenone. Accordingly, stannane **11** was prepared from commercially available 5-hexyn-1-ol (**12**). After screening a number of reports in the literature, we found the Menche protocol[13] was the most suitable to produce the required *trans*-vinyl stannane **11** in high yield with excellent selectivity. The Stille cross-coupling reaction of triflate **10** and stannane **11** was examined as a method to construct the C-1′–C-2′ styryl double bond of **2** (Scheme 3). Among various Stille conditions[14] (see Table 1), we found the best results involved the treatment of **10** with $Pd_2(dba)_3{\cdot}CHCl_3$ (dba = dibenzylideneacetone, 1 mol-%), 0.08 equiv. of the tri(2-furyl)phosphine ligand, 3 equiv. of LiCl, and 1.1 equiv. of stannane **11** in *N*-methyl-2-pyrrolidone (NMP) at 60 °C to provide the *trans*-olefin in 88 % yield (Table 1, Entry 6).

After the successful optimization of the Stille reaction (Table 1, Entry 6), compound **9** was oxidized by treatment with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl/[bis(acetoxy)iodo]-benzene (TEMPO/BAIB)[15] to give the corresponding aldehyde **20** in good yield. Other oxidizing conditions [e.g., pyridinium chlorochromate (PCC), Dess–Martin periodinane (DMP), and Swern conditions] afforded aldehyde **20** in poor yield. The Grignard reaction of aldehyde **20**[16] with vinylmagnesium bromide at low temperature furnished allyl alcohol **21** in 90 % yield (based on recovery of starting material). It is noteworthy that the vinyl Grignard reagent only underwent a reaction with the aldehyde and did not affect the lactone ring. The secondary hydroxy group of **21** was subsequently protected as its silyl ether under standard conditions to obtain compound **22** in 95 % yield.



Scheme 3. Reagents and conditions: (a) $Pd_2(dba)_3$·$CHCl_3$, LiCl, tri(2-furyl)phosphine, NMP, 60 °C, 3 h, 88 %; (b) TEMPO/BAIB, CH_2Cl_2, 0 °C to room temp., 2 h, 90 %; (c) vinylmagnesium bromide (3.0 M), THF, –78 °C, 2 h, 90 %; (d) TBSOTf (TBS = *tert*-butyldimethylsilyl), *N*,*N*-diisopropylethylamine (DIPEA), CH_2Cl_2, 0 °C to room temp., 30 min, 95 %; (e) (*S*)-4-penten-2-ol (**23**), NaH, THF, 0 °C to room temp., 4 h, 75 %; (f) HF·Py, THF, room temp., 12 h, 95 %; (g) DMP, 0 °C to room temp., 2 h, 92 %.

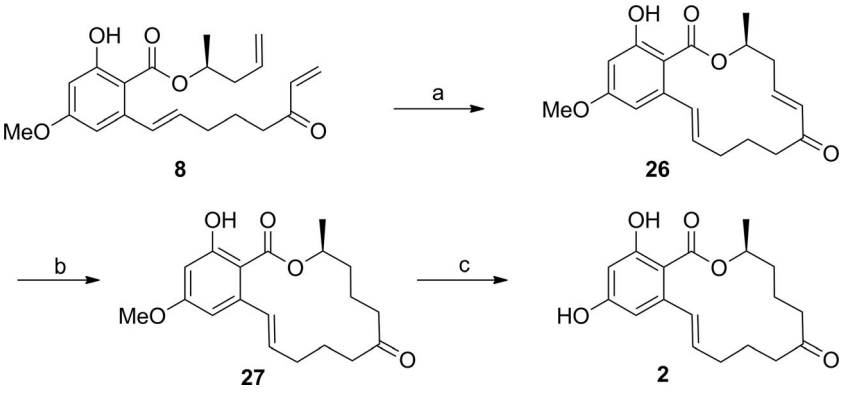
Table 1. Optimization of Stille cross-coupling between triflate **10** and stannane **11**.

Entry	Pd catalyst	Ligand/additive	Solvent	Temperature [°C]	Time [h]	Yield of **9** [%][a,b]
1	$Pd(PPh_3)_4$	–	NMP	100	12	trace
2	$Pd(PPh_3)Cl_2$	CuI	toluene	110	12	–
3	$Pd(PPh_3)_2Cl_2$	PPh_3, LiCl	DMF[c]	60	8	50
4	$Pd_2(dba)_3$·$CHCl_3$	$AsPh_3$, CuI, LiCl	DMF	80	12	60
5	$Pd_2(dba)_3$·$CHCl_3$	tri(2-furyl)phosphine	DMF	60	6	75
6	$Pd_2(dba)_3$·$CHCl_3$	tri(2-furyl)phosphine	NMP	60	3	88

[a] Only the (*E*) isomer was observed by ^1H NMR spectroscopy. [b] Yield was calculated after purification of product by column chromatography. [c] DMF = *N*,*N*-dimethylformamide.

Next, we performed the pivotal base-catalyzed lactone ring-opening/transesterification reaction (under De Brabander's conditions)[11] by using commercially available (*S*)-4-penten-2-ol (**23**) and non-nucleophilic bases such as sodium hexamethyldisilazide (NaHMDS), LiHMDS, and KHMDS. Among them, NaH afforded satisfactory results to furnish **24** in a reasonable yield (75 %). Next, removal of the silyl ether protecting group by using HF·Py in THF afforded compound **25** without any side reaction because of the presence of different olefins. Allylic alcohol **25** was subsequently oxidized to the corresponding vinyl ketone by using DMP[17] to obtain the required RCM precursor **8** (Scheme 3). As expected, the macrocyclic core of **2** was obtained as a single diastereomer in a satisfactory yield (75 %) with *trans* selectivity by an RCM reaction using Grubbs II catalyst.[18] A chemoselective hydride-mediated reduction of enone **26** to give **27** was achieved at low temperature by a 1,4-addition of copper(I) hydride, which was generated in situ from CuBr/sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al).[19] We made several attempts to cleave the *O*-methyl ether of **27**. Of these, AlI_3/tetra-*n*-butylammonium iodide (TBAI)[20] was the most effective reagent and furnished (*S*)-zearalenone (**2**) in a short time as a white crystalline solid in 82 % yield (Scheme 4).

After successfully synthesizing (*S*)-zearalenone (**2**), we decided to examine the generality of our strategy by carrying out the total synthesis of (*R*)-de-*O*-methyllasiodiplodin (**4**). In 1990, the first asymmetric total synthesis of **4** was achieved in 18 steps and 0.8 % overall yield.[9a] A comparatively shorter route was published in 1996 by Alois Fürstner and co-workers, which involved a more complicated Kolbe–Schmitt reaction.[9b] Although Guo and co-workers reported the total synthesis of **4** in nine steps and 28.3 % overall yield, they found the final de-

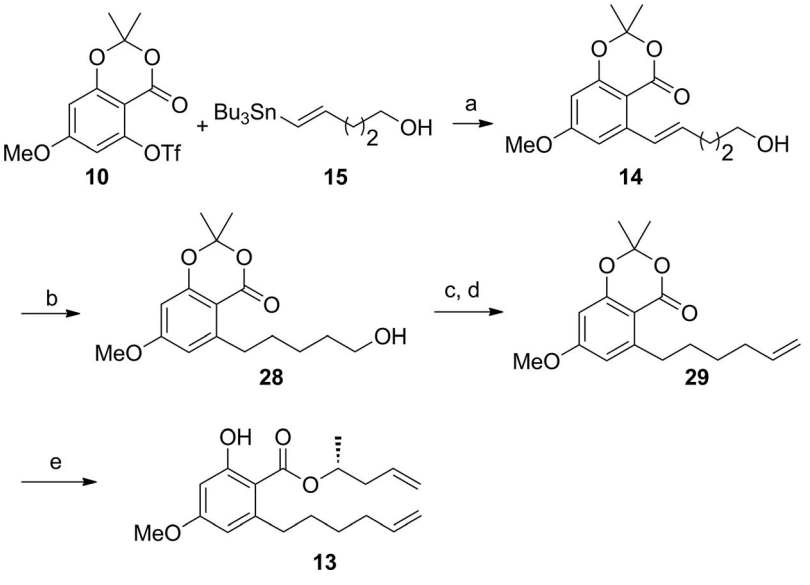


Scheme 4. Reagents and conditions: (a) Grubbs II, CH_2Cl_2, reflux, 4 h, 75 %; (b) CuBr/Red-Al, THF, –78 °C to –20 °C, 1 h, 70 %; (c) AlI_3, TBAI, benzene, 10 °C, 30 min, 82 %.

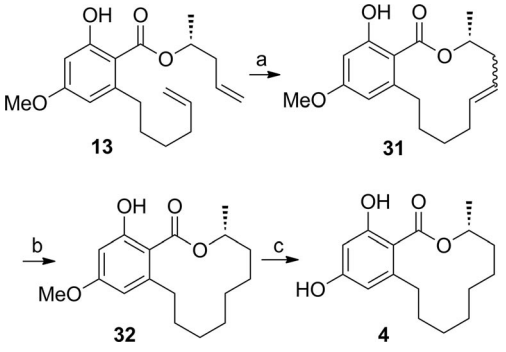
methylation step to be relatively low yielding (57 %).[9c] In spite of these results, we herein report the synthesis of **4** from triflate **10** in seven steps and an overall yield of 34.1 %.

Under similar conditions to those described earlier (Table 1, Entry 6), the synthesis of **4** began from a Stille cross-coupling between aromatic triflate **10** and *trans*-vinyl stannane **15**, which was derived from 4-pentyn-1-ol (**16**), to furnish compound **14** in 85 % yield (Scheme 5). For the remainder of the synthesis of **4**, we followed a similar reaction sequence to that employed for **2** such as an oxidation reaction by using TEMPO/BAIB, a Wittig homologation, a transesterification, and an RCM reaction by using Grubbs II catalyst. However, the RCM step was relatively low yielding (40 %), probably a result of a competing RCM reaction between the terminal olefin and the relatively more reactive styryl olefin.[21] Therefore, we decided to reduce the styryl double bond of compound **14** prior to the oxidation step. Hence, the olefin was reduced under transfer hydrogenation conditions with $NiCl_2{\cdot}6H_2O/NaBH_4$[22] to give **28** in 95 % yield. The subsequent oxidation by using TEMPO/BAIB[15] followed by a one-carbon Wittig homologation furnished compound **29** in good yield. Under similar reaction conditions to those described earlier (Scheme 3), **29** was then subjected to a sodium hydride mediated transesterification[11] reaction with commercially available (*R*)-4-penten-2-ol (**30**) to give compound **13**. The ring-closing metathesis of **13** with Grubbs II catalyst[18] afforded macrocycle **31** in a comparatively high yield (80 %) with selectivity for the (*E*) isomer (*E*/*Z*, 4:1). Finally, compound **31** was subjected to a catalytic hydrogenation by using Pd/C to furnish saturated product **32**, the demethylation of which by using AlI_3/TBAI[19] afforded (*R*)-de-*O*-methyllasiodiplodin (**4**) as a white solid in 85 % yield (Scheme 6).

The physical characteristics and spectroscopic data of both synthetic products **2** and **4** were consistent with those reported in the literature (see Supporting Information).[8,9c]



Scheme 5. Reagents and conditions: (a) $Pd_2(dba)_3{\cdot}CHCl_3$, LiCl, tri(2-furyl)phosphine, NMP, 60 °C, 3 h, 85 %; (b) $NiCl_2{\cdot}6H_2O$, MeOH, 0 °C, 20 min, 95 %; (c) TEMPO/BAIB, CH_2Cl_2, 0 °C to room temp., 2 h, (d) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C to room temp., 4 h, 80 % over two steps; (e) (*R*)-4-penten-2-ol (**30**), NaH, THF, 0 °C to room temp., 5 h, 82 %.



Scheme 6. Reagents and conditions: (a) Grubbs II, CH_2Cl_2, reflux, 6 h, 80 %, *E*/*Z*, 4:1; (b) H_2, 10 % Pd/C, EtOAc, room temp., 3 h, 90 %; (c) AlI_3, TBAI, benzene, 10 °C, 30 min, 85 %.

Conclusions

In summary, a concise, efficient, and linear synthesis of the two resorcinylic acid lactones (*S*)-zearalenone (**2**) and (*R*)-de-*O*-methyllasiodiplodin (**4**) has been accomplished in 10 steps (in 19.1 % overall yield) and 7 steps (34.1 % overall yield), respectively. The present synthesis involves Stille, transesterification, chemoselective reduction, and ring-closing metathesis reactions. Our strategy is a viable route to synthesize analogues of **2** and **4** as well as other RALs.

Experimental Section

General Methods: All reactions that required anhydrous conditions were conducted in a flame-dried glass apparatus under nitrogen. THF was freshly distilled from sodium/benzophenone ketyl prior to use. *N*-methyl-2-pyrrolidone and CH_2Cl_2 were freshly distilled from CaH_2, and benzene was dried azeotropically by using a Dean–Stark apparatus. Anhydrous methanol was obtained by distillation from magnesium alkoxide and stored under nitrogen over activated molecular sieves (4 Å). Reactions were monitored by TLC analysis using silica plates with fluorescent indicator (254 nm). Unless otherwise mentioned, all column chromatography was done with 60–120 mesh silica gel. All commercially available reagents were purchased and typically used as supplied. The ^1H and ^{13}C NMR spectroscopic data were recorded in Fourier transform mode at the field strength specified (300, 400, or 500 MHz for ^1H NMR and 75, 100, or 125 MHz for ^{13}C NMR). Chemical shifts (δ) are reported in ppm and referenced to residual $CHCl_3$ (δ = 7.26 ppm) for ^1H NMR and $CDCl_3$ (δ = 77.16 ppm) for ^{13}C NMR. Data are reported as follows: chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), quintet (quint), m (multiplet), br. (broad), app (apparent), ABq (AB quartet)], coupling constant, number of protons, assignment. Ratios of diastereomers (*dr*) were obtained from ^1H NMR (400 MHz) spectra, which were obtained with a signal/noise ratio of >200:1. Infrared spectra were recorded with an FTIR instrument, and the values are reported as the frequency of absorption (cm^{-1}). Melting points were recorded with a melting point instrument. Optical rotations were measured with a polarimeter that was equipped with a sodium lamp (589 nm, D line) and a 2 dm, 2 mL quartz sample cell. The values are reported as $[\alpha]_D$ (concentration in g 100 mL^{-1} solvent). For high resolution mass spectra, the ion mass/charge (*m*/*z*) ratios are reported as values in atomic mass units.

(*E*)-5-(6-Hydroxyhex-1-en-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (9): Triflate **10** (5 g, 14 mmol) was dissolved in degassed *N*-methyl-2-pyrrolidone (30 mL), and the resulting solution was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (144.9 mg, 0.14 mmol), tri(2-furyl)phosphine (259 mg, 1.12 mmol), and anhydrous LiCl (1.68 g, 42 mmol). The solution was stirred at room temperature for 10 min. A solution of stannane **11** (6 g, 15.4 mmol) in NMP (30 mL) was added dropwise, and the mixture was stirred at 60 °C for 3 h. Upon completion, the reaction mixture was diluted with a saturated KF solution (50 mL), and the resulting mixture was extracted with EtOAc (2 × 100 mL). The organic extract was dried with Na_2SO_4 and concentrated. Purification of the residue by column chromatography (EtOAc/PE, 40:60) afforded compound **9** (3.77 g, 88 %) as a colorless liquid; R_f = 0.2 (EtOAc/PE, 40:60). IR (neat): $\tilde{\nu}_{max}$ = 3424, 2936, 1724, 1606, 1280, 1159, 1204, 1064, 962 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.56–1.72 (m, 4 H), 1.70 (s, 6 H), 2.29–2.34 (m, 2 H), 3.68 (t, *J* = 6.2 Hz, 2 H), 3.85 (s, 3 H), 6.18 (dt, *J* = 6.8, 15.7 Hz, 1 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.73 (d, *J* = 2.4 Hz, 1 H), 7.42 (d, *J* = 15.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 25.6, 32.0, 32.5, 55.5, 62.7, 100.0, 103.6, 104.9, 108.1, 128.6, 134.7, 144.2, 158.6, 160.3, 164.7 ppm. HRMS (ESI): calcd. for $C_{17}H_{23}O_5$ $[M + H]^+$ 307.15400; found 307.15331.

(*E*)-6-(7-Methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxin-5-yl)hex-5-enal (20): To a stirred solution of alcohol **9** (4 g, 13.0 mmol) in CH_2Cl_2 (40 mL) were added sequentially [bis(acetoxy)iodo]benzene (5.06 g, 15.7 mmol) and TEMPO (409 mg, 2.6 mmol). After stirring at room temperature for 2 h, a saturated aqueous solution of $Na_2S_2O_3$ (20 mL) and diethyl ether (100 mL) were added. The isolated organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) followed by H_2O (10 mL). The combined aqueous phases were extracted with diethyl ether (2 × 50 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (EtOAc/PE, 25:75) to provide aldehyde **20** (3.58 g, 90 %) as a yellow liquid; R_f = 0.3 (EtOAc/PE, 30:70). Aldehyde **20** was immediately used in the Grignard reaction.

(*E*)-5-(6-Hydroxyocta-1,7-dien-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (21): To a stirred solution of **20** (3.5 g, 11.5 mmol) in THF (30 mL) was added dropwise vinylmagnesium bromide (3.0 M solution in THF, 7.7 mL, 23.0 mmol) at –78 °C. The reaction mixture was stirred at same temperature for 2 h and then quenched with an aqueous saturated solution of NH_4Cl (20 mL). The organic layer was separated, and the aqueous portion was extracted with EtOAc (50 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (20 mL) and then dried with Na_2SO_4. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (EtOAc/PE, 25:75) to afford pure (±)-**21** (3.09 g, 90 %) and recovered compound **20** (350 mg); R_f = 0.2 (EtOAc/PE, 30:70). IR (neat): $\tilde{\nu}_{max}$ = 3426, 2932, 2854, 1725, 1605, 1571, 1277, 1159, 1036, 915 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.59–1.69 (m, 4 H), 1.70 (s, 6 H), 2.27–2.35 (m, 2 H), 3.85 (s, 3 H), 4.12–4.18 (m, 1 H), 5.11 (dt, *J* = 1.5, 10.3 Hz, 1 H), 5.24 (dt, *J* = 1.5, 17.2 Hz, 1 H), 5.85–5.93 (m, 1 H), 6.18 (dt, *J* = 6.8, 15.7 Hz, 1 H), 6.33 (d, *J* = 2.7 Hz, 1 H), 6.73 (d, *J* = 2.7 Hz, 1 H), 7.42 (d, *J* = 15.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 25.6, 32.7, 36.3, 55.5, 72.9, 100.0, 103.6, 104.9, 108.1, 114.6, 128.6, 134.7, 141.1, 144.2, 158.6, 160.2, 164.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{24}O_5Na$ $[M + Na]^+$ 355.15160; found 355.15083.

(*E*)-5-{6-[(*tert*-Butyldimethylsilyl)oxy]octa-1,7-dien-1-yl}-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (22): Anhydrous DIPEA (3.1 mL, 18 mmol) was added at 0 °C to a solution of allylic alcohol **21** (2 g, 6.02 mmol) in dry dichloromethane (DCM, 20 mL) at 0 °C, and the mixture was stirred at 0 °C under N_2. After

15 min, TBSOTf (1.7 mL, 7.22 mmol) was added dropwise, and the mixture was stirred at room temp. for 30 min, whereupon TLC analysis indicated complete consumption of starting material. The reaction was then quenched with H_2O (10 mL), and the mixture was extracted with DCM (2 × 20 mL). The organic extracts were combined and washed with brine (50 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (EtOAc/PE, 7:93) to give **22** (2.55 g, 95 %) as a yellow liquid; R_f = 0.5 (EtOAc/PE = 20:80). IR (neat): $\tilde{\nu}_{max}$ = 2931, 2855, 1730, 1605, 1573, 1275, 1159, 1035, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 1.49–1.57 (m, 4 H), 1.69 (s, 6 H), 2.25–2.30 (m, 2 H), 3.84 (s, 3 H), 4.10–4.14 (m, 1 H), 5.02 (ddd, *J* = 1.2, 1.6, 10.3 Hz, 1 H), 5.14 (dt, *J* = 3.0, 17.1 Hz, 1 H), 5.80 (ddd, *J* = 6.1, 10.3, 17.1 Hz, 1 H), 6.32 (d, *J* = 2.6 Hz, 1 H), 6.74 (d, *J* = 2.6 Hz, 1 H), 7.43 (d, *J* = 15.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.4, 18.2, 24.7, 25.6, 25.8, 33.0, 37.5, 55.5, 73.6, 100.0, 103.7, 104.8, 108.0, 113.5, 128.3, 135.1, 141.7, 144.2, 158.6, 160.1, 164.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{38}O_5NaSi$ $[M + Na]^+$ 469.23807; found 469.23736.

(*S*)-Pent-4-en-2-yl 2-{(*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]octa-1,7-dien-1-yl}-6-hydroxy-4-methoxybenzoate (24): Sodium hydride (60 % dispersion in mineral oil, 358 mg, 8.96 mmol) was slowly added to a magnetically stirred solution of homoallylic alcohol **23** (481 mg, 5.6 mmol) in dry THF (8 mL) at 0 °C under nitrogen. The mixture was stirred at room temperature for 1 h and then cooled again to 0 °C. Acetonide **22** (500 mg, 1.12 mmol) in THF (5 mL) was slowly added to the mixture, which was then allowed to stir at room temperature for 4 h. Upon completion of the reaction, the solution was treated with a saturated aqueous solution of $NaHCO_3$ (10 mL) and ethyl acetate (20 mL). The separated organic phase was washed with brine (1 × 10 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (EtOAc/PE, 5:95) to give compound **24** (398 mg, 75 %) as a yellow oil; R_f = 0.5 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = +21.41 (*c* = 0.24, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2929, 2855, 1647, 1256, 1159, 1032, 835, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03, (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 1.36 (d, *J* = 6.3 Hz, 3 H), 1.51–1.58 (m, 4 H), 2.15–2.23 (m, 2 H), 2.37–2.52 (m, 2 H), 3.81 (s, 3 H), 4.01–4.14 (m, 1 H), 5.03 (dt, *J* = 1.3, 10.4 Hz, 1 H), 5.09–5.14 (m, 2 H), 5.25 (dd, *J* = 6.2, 12.3 Hz, 1 H), 5.74–5.91 (m, 3 H), 6.37 (d, *J* = 2.7 Hz, 1 H), 6.4 (d, *J* = 2.7 Hz, 1 H), 6.95 (d, *J* = 15.5 Hz, 1 H), 11.76 (d, *J* = 0.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.8, –4.4, 18.2, 19.6, 24.8, 25.8, 33.1, 37.7, 40.2, 55.3, 71.8, 73.7, 99.6, 104.0, 108.1, 113.6, 118.1, 131.4, 132.3, 133.3, 141.6, 143.7, 163.8, 164.9, 170.8 ppm. HRMS (ESI): calcd. for $C_{27}H_{42}O_5NaSi$ $[M + Na]^+$ 497.26937; found 497.26865.

(*S*)-Pent-4-en-2-yl 2-Hydroxy-6-[(*E*)-6-hydroxyocta-1,7-dien-1-yl]-4-methoxybenzoate (25): In a 10 mL round-bottom plastic tube, a stirred solution of **24** (300 mg, 0.632 mmol) in dry THF (5 mL) was cooled to 0 °C, and a solution of HF•Py (0.2 mL) in THF (0.7 mL) was added. The reaction was stirred at room temperature for 12 h and then quenched at 0 °C by pouring it into a solution of saturated aqueous $NaHCO_3$ (10 mL). The product was extracted into ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with a saturated aqueous solution of $CuSO_4$ (10 mL) and water (10 mL) and then dried with $MgSO_4$. After concentration of the organic extracts, the crude product was purified by column chromatography (EtOAc/PE, 30:70) to afford **25** (216 mg, 95 %) as a colorless liquid; R_f = 0.2 (EtOAc/PE, 30:70). $[\alpha]_D^{25}$ = +32.06 (*c* = 0.44, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3077, 2931, 2856, 1647, 1574, 1255, 1159, 1115, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.2 Hz, 3 H), 1.51–1.64 (m, 4 H), 2.20–2.26 (m, 2 H), 2.39–2.52 (m, 2 H), 3.81 (s, 3 H), 4.12–4.16 (m, 1 H), 4.38 (dd, *J* = 7.1, 14.3 Hz, 1 H), 5.1–5.14 (m, 2 H), 5.15–5.17 (m, 1 H), 5.21–5.28 (m, 2 H), 5.78–5.93 (m, 3 H), 6.37 (d, *J* = 2.7 Hz, 1 H), 6.4 (d, *J* = 2.7 Hz, 1 H), 6.97 (d, *J* = 15.4 Hz, 1 H), 11.74 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 25.0, 32.8, 36.5, 40.2, 55.3, 71.8, 73.1, 99.6, 108.1, 114.7, 118.1, 131.5, 132.0, 133.0, 141.1, 143.5, 163.8, 164.9, 170.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{29}O_5$ $[M + H]^+$ 361.20095; found 361.20105.

(*S*,*E*)-Pent-4-en-2-yl 2-Hydroxy-4-methoxy-6-(6-oxoocta-1,7-dien-1-yl)benzoate (8): A solution of the alcohol **25** (100 mg, 0.277 mmol) in CH_2Cl_2 (8 mL) under argon was cooled to 0 °C, and then Dess–Martin periodinane (176 mg, 0.415 mmol) was added. The resulting solution was stirred at room temperature for 2 h. The mixture was filtered through Celite, and the filter cake was thoroughly washed with DCM (2 × 10 mL). The filtrate was washed with water (5 mL) and brine (5 mL) and then dried with Na_2SO_4. The DCM was evaporated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc/PE, 10:90) to give enone **8** (91.2 mg, 92 %) as a colorless liquid; R_f = 0.5 (EtOAc/PE, 20:80). $[\alpha]_D^{25}$ = +19.18 (*c* = 0.44, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2929, 1646, 1608, 1573, 1257, 1159, 964, 770 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.3 Hz, 3 H), 1.79–1.87 (m, 2 H), 2.24 (ddd, *J* = 1.3, 7.9, 14.6 Hz, 2 H), 2.39–2.53 (m, 2 H), 2.66 (t, *J* = 7.3 Hz, 2 H), 3.82 (s, 3 H), 5.09–5.13 (m, 1 H), 5.16 (dd, *J* = 1.4, 3.1 Hz, 1 H), 5.26 (dd, *J* = 6.2, 12.3 Hz, 1 H), 5.76–5.90 (m, 3 H), 6.23 (dd, *J* = 1.2, 17.6 Hz, 1 H), 6.37 (dd, *J* = 10.5, 17.6 Hz, 1 H), 6.38 (d, *J* = 2.5 Hz, 1 H), 6.43 (d, *J* = 2.5 Hz, 1 H), 6.99 (d, *J* = 15.5 Hz, 1 H), 11.71 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 23.4, 32.3, 38.9, 40.2, 55.3, 71.8, 99.7, 104.0, 108.1, 118.2, 128.0, 131.3, 132.0, 133.3, 136.5, 143.3, 163.8, 164.9, 170.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{27}O_5$ $[M + H]^+$ 359.18530; found 359.18533.

(*S*,5*E*,11*E*)-16-Hydroxy-14-methoxy-3-methyl-3,4,9,10-tetrahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (26): A stirred solution of diene **8** (70 mg, 0.195 mmol) in CH_2Cl_2 (50 mL) was purged with argon, and Grubbs II catalyst (14.8 mg, 0.017 mmol) was added. The reaction mixture was then heated at reflux for 4 h under argon. After this time, the reaction was cooled and diluted with EtOAc (20 mL), and the resulting mixture was washed with H_2O (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography (EtOAc/PE, 12:88) to furnish unsaturated macrocycle **26** (48.5 mg, 75 %) as a white solid; R_f = 0.2 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = –138.2 (*c* = 0.03, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3420, 2925, 2853, 1658, 1610, 1256, 1205, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.5 Hz, 3 H), 1.78–1.89 (m, 1 H), 2.01–2.15 (m, 2 H), 2.28 (ddd, *J* = 3.5, 6.9, 13.2 Hz, 1 H), 2.31–2.42 (m, 2 H), 2.81–2.93 (m, 2 H), 3.83 (s, 3 H), 5.55–5.63 (m, 1 H), 5.83 (ddd, *J* = 4.6, 9.1, 15.4 Hz, 1 H), 6.17 (d, *J* = 16.1 Hz, 1 H), 6.41 (d, *J* = 2.5 Hz, 1 H), 6.49 (d, *J* = 2.5 Hz, 1 H), 6.94 (d, *J* = 15.4 Hz, 1 H), 7.02 (ddd, *J* = 6.2, 8.5, 16.2 Hz, 1 H), 11.51 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 25.9, 31.2, 34.6, 36.4, 55.4, 70.0, 99.9, 104.0, 108.4, 132.5, 133.1, 136.4, 142.7, 143.4, 164.1, 164.9, 170.2, 203.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.15400; found 331.15441.

(*S*,*E*)-16-Hydroxy-14-methoxy-3-methyl-3,4,5,6,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (27): A solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene (Vitride or Red-Al, 70 % solution, 0.11 mL, 0.36 mmol) was added dropwise to a suspension of cuprous bromide (38 mg, 0.27 mmol) in dry THF (2 mL) at 0 to –5 °C under argon. The resulting brown-black suspension was stirred at 0 °C for 0.5 h and then cooled to –78 °C. To this mixture at –78 °C was added by syringe a solution of **26** (30 mg, 0.090 mmol) in THF (3 mL). After 10 min, the solution

was stirred at –20 °C for 1 h and then quenched by the addition of water (3 mL). The resulting mixture was poured into a saturated aqueous ammonium chloride solution (10 mL). Ether (20 mL) was added, and the blue (copper) aqueous solution was separated. The ether layer was washed with water (2 × 3 mL), concentrated and purified by column chromatography (EtOAc/PE, 10:90) to afford compound **27** (20.9 mg, 70 %) as a white solid; R_f = 0.2 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = –160.8 (*c* = 0.1, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3451, 2924, 2852, 1646, 1607, 1257, 1211, 1160, 770 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.1 Hz, 3 H), 1.45–1.82 (m, 6 H), 2.10–2.24 (m, 3 H), 2.32–2.42 (m, 1 H), 2.60 (ddd, *J* = 3.2, 5.8, 12.3 Hz, 1 H), 2.85 (ddd, *J* = 1.9, 12.0, 18.6 Hz, 1 H), 3.82 (s, 3 H), 4,97–5.04 (m, 1 H), 5.68 (ddd, *J* = 3.5, 10.5, 15.1 Hz, 1 H), 6.40 (d, *J* = 2.6 Hz, 1 H), 6.46 (d, *J* = 2.6 Hz, 1 H), 7.02 (dd, *J* = 1.8, 15.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 22.3, 30.9, 34.7, 36.6, 42.9, 55.4, 73.3, 77.2, 99.9, 103.5, 108.2, 132.3, 143.3, 164.0, 165.6, 211.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{25}O_5$ $[M + H]^+$ 333.16965; found 333.16910.

(*S*,*E*)-14,16-Dihydroxy-3-methyl-3,4,5,6,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (2): To a stirred solution of AlI_3 in benzene [prepared in situ from Al (48.6 mg, 2.25 mmol) and I_2 (320 mg, 1.26 mmol) in anhydrous benzene (3 mL) at 80 °C for 1 h] was added **27** (12 mg, 0.036 mmol) in anhydrous benzene (1 mL) at 10 °C. The reaction mixture was stirred for 30 min then quenched by the addition of solutions of aqueous NH_4Cl (2 mL) and aqueous $Na_2S_2O_5$ (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/PE, 30:70) to afford (*S*)-zearalenone (**2**, 9.3 mg, 82 %) as a white crystalline solid; R_f = 0.2 (EtOAc/PE, 30:70), m.p. 161–163 °C. $[\alpha]_D^{20}$ = –160.8 (*c* = 0.1, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3417, 2924, 2853, 1709, 1646, 1259, 1022, 803, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.1 Hz, 3 H), 1.45–1.81 (m, 6 H), 2.11–2.24 (m, 3 H), 2.33–2.440 (m, 1 H), 2.58–2.67 (m, 1 H), 2.85 (ddd, *J* = 2.6, 12.2, 18.6 Hz, 1 H), 3.68 (t, *J* = 6.4 Hz, 1 H), 4.96–5.03 (m, 1 H), 5.68 (ddd, *J* = 3.6, 10.5, 15.5 Hz, 1 H), 6.35 (d, *J* = 2.6 Hz, 1 H), 6.41 (d, *J* = 2.6 Hz, 1 H), 7.01 (dd, *J* = 1.8, 15.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8, 20.9, 22.2, 32.2, 34.7, 36.6, 42.9, 73.4, 102.4, 103.7, 108.4, 132.4, 133.1, 143.9, 160.6, 165.4, 171.3, 211.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{23}O_5$ $[M + H]^+$ 319.15400; found 319.15412.

(*E*)-5-(5-Hydroxypent-1-en-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (14): Triflate **10** (2 g, 5.6 mmol) was dissolved in degassed NMP (15 mL), and the resulting solution was treated with $Pd_2(dba)_3$·$CHCl_3$ (58 mg, 0.056 mmol), tri(2-furyl)phosphine (104 mg, 0.45 mmol), and anhydrous LiCl (705 mg, 16.8 mmol). The solution was stirred at room temperature for 10 min, and then a solution of stannane **15** (1.8 g, 6.17 mmol) in NMP (12 mL) was added dropwise. The resulting solution was stirred for 3 h and then diluted with a saturated KF solution (20 mL). The mixture was extracted with EtOAc (2 × 50 mL). The organic extract was dried with Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (EtOAc/PE, 40:60) afforded compound **14** (1.39 g, 85 %) as yellow oil; R_f = 0.3 (EtOAc/PE, 40:60). IR (neat): $\tilde{\nu}_{max}$ = 3426, 2996, 2939, 1724, 1605, 1279, 1160, 967, 856 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.70 (s, 6 H), 1.77 (AB quint, *J* = 6.4, 7.1 Hz, 2 H), 2.38 (ddd, *J* = 1.3, 7.1, 14.3 Hz, 2 H), 3.72 (t, *J* = 6.4 Hz, 2 H), 3.8 (s, 3 H), 6.16 (dt, *J* = 7.0, 15.7 Hz, 1 H), 6.33 (d, *J* = 2.6 Hz, 1 H), 6.7 (d, *J* = 2.6 Hz, 1 H), 7.40 (dd, *J* = 1.3, 15.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 29.3, 31.6, 55.5, 61.9, 100.0, 103.6, 104.9, 108.2, 128.9, 134.2, 144.1, 158.6, 160.3, 164.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{21}O_5$ $[M + H]^+$ 293.13835; found 293.13754.

5-(5-Hydroxypentyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (28): $NiCl_2$·$6H_2O$ (81 mg, 0.34 mmol) was added to a stirred solution of conjugated alkene **14** (1 g, 3.42 mmol) in MeOH (10 mL) at 0 °C. Then, $NaBH_4$ (259 mg, 6.84 mmol) was added portionwise. The reaction was stirred for 20 min and then quenched by the addition of a saturated solution of NH_4Cl (5 mL). The mixture was concentrated to obtain a residue, which was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (EtOAc/PE, 40:60) to provide the corresponding saturated compound **28** (955 mg, 95 %) as a clear oil; R_f = 0.4 (EtOAc/PE, 40:60). IR (neat): $\tilde{\nu}_{max}$ = 3427, 2933, 2857, 1728, 1612, 1279, 1160, 966, 855 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.43–1.50 (m, 2 H), 1.59–1.66 (m, 4 H), 1.69 (s, 6 H), 3.05 (app t, *J* = 7.8 Hz, 2 H), 3.65 (d, *J* = 6.5 Hz, 2 H), 3.83 (s, 3 H), 6.30 (d, *J* = 2.4 Hz, 1 H), 6.47 (d, *J* = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 21.1, 24.1, 24.7, 27.2, 30.8, 31.0, 33.6, 55.2, 75.0, 98.8, 105.1, 110.5, 148.5, 163.7, 165.6, 171.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}O_5$ $[M + H]^+$ 295.15400; found 295.15303.

5-(Hex-5-en-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (29): To a stirred solution of alcohol **28** (500 mg, 1.7 mmol) in CH_2Cl_2 (8 mL) were added sequentially [bis(acetoxy)iodo]benzene (657 mg, 2.04 mmol) and TEMPO (53 mg, 0.34 mmol). The resulting mixture was stirred at room temperature for 2 h, and then a saturated aqueous solution of $Na_2S_2O_3$ (5 mL) and diethyl ether (20 mL) were added. The isolated organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) followed by H_2O (5 mL). The combined aqueous layers were extracted with diethyl ether (2 × 20 mL), and the combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (EtOAc/PE, 30:70) to provide the corresponding aldehyde (471 mg) as a yellow liquid, which was immediately used in the next step. To the stirred solution of the $Ph_3P^+CH_3Br^-$ (1.74 g, 4.32 mmol) in anhydrous THF was added NaHMDS (3.6 mL, 3.6 mmol) dropwise at 0 °C. After 30 min, the previously prepared aldehyde (471 mg) was added at the same temperature, and the mixture was stirred at room temperature for 4 h. The reaction was quenched with cold water, and the resulting mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (EtOAc/PE, 10:90) gave pure compound **29** (394 mg, 80 % from **28**) as a colorless liquid; R_f = 0.5 (EtOAc/PE, 10:90). IR (neat): $\tilde{\nu}_{max}$ = 2928, 1729, 1611, 1577, 1277, 1059, 911 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45–1.52 (m, 2 H), 1.57–1.64 (m, 2 H), 1.69 (s, 6 H), 2.09 (dd, *J* = 7.1, 14.5 Hz, 2 H), 3.06 (app t, *J* = 7.7 Hz, 2 H), 3.83 (s, 3 H), 4.91–4.94 (m, 1 H), 5.00 (ddd, *J* = 1.5, 3.3, 17.2 Hz, 1 H), 5.77–5.86 (m, 1 H), 6.29 (d, *J* = 2.4 Hz, 1 H), 6.46 (d, *J* = 2.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.9, 28.1, 29.7, 32.9, 33.7, 54.8, 98.5, 104.0, 111.5, 113.6, 138.2, 149.3, 158.4, 159.3, 164.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{22}O_4Na$ $[M + Na]^+$ 313.14103; found 313.13998.

(*R*)-Pent-4-en-2-yl 2-(Hex-5-en-1-yl)-6-hydroxy-4-methoxybenzoate (13): Sodium hydride (60 % dispersion in mineral oil, 165 mg, 4.13 mmol) was slowly added to a magnetically stirred solution of homoallylic alcohol **30** (223 mg, 2.6 mmol) in dry THF (5 mL) at 0 °C under nitrogen. The mixture was stirred for 1 h at room temperature and then cooled again to 0 °C. Acetonide **29** (151 mg, 0.520 mmol) in THF (3 mL) was added slowly to the mixture, which was then allowed to stir at room temperature for 5 h. Upon completion of the reaction, the solution was treated with a

saturated aqueous solution of $NaHCO_3$ (8 mL) and ethyl acetate (10 mL). The separated organic phase was washed with brine (1× 10 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (EtOAc/PE, 10:90) to give compound **13** (134.8 mg, 82 %) as a yellow oil; R_f = 0.5 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = –13.22 (*c* = 0.64, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3446, 2929, 2855, 1646, 1579, 1255, 1158, 1047, 931 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.3 Hz, 3 H), 1.41–1.50 (m, 2 H), 1.52–1.60 (m, 2 H), 2.08 (ddt, *J* = 7.2, 14.3, 1.2 Hz, 2 H), 2.38–2.55 (m, 2 H), 2.76–2.98 (m, 2 H), 3.80 (s, 3 H), 4.94 (d quin, *J* = 1.1. 10.1 Hz, 1 H), 5.00 (ddd, *J* = 1.6, 3.5, 17.1 Hz, 1 H), 5.09–5.14 (m, 2 H), 5.30 (ddd, *J* = 6.3, 12.6, 18.8 Hz, 1 H), 5.75–5.87 (m, 2 H), 6.27 (d, *J* = 2.7 Hz, 1 H), 6.33 (d, *J* = 2.7 Hz, 1 H), 11.9 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 29.1, 31.5, 33.8, 36.7, 40.2, 55.2, 71.6, 98.8, 104.9, 110.6, 114.5, 118.2, 133.2, 138.7, 147.6, 163.7, 165.6, 170.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}O_4$ for $[M + H]^+$ 319.19039; found 319.19019.

(*R*)-14-Hydroxy-12-methoxy-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (31): A stirred solution of diene **13** (50 mg, 0.157 mmol) in CH_2Cl_2 (40 mL) was purged with argon, and Grubbs II catalyst (1.3 mg, 0.001 mmol) was added. The reaction mixture was then heated at reflux for 6 h under argon. After this time, the mixture was cooled and then diluted with EtOAc (20 mL). The resulting solution was washed with H_2O (2 × 10 mL) and brine (10 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc/PE, 10:90) to furnish the unsaturated macrocycle **31** (36.4 mg, 80 %; separable diastereomeric mixture; *E*/*Z*, 4:1) as a yellow liquid; R_f = 0.4 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = +3.67 (*c* = 0.32, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2927, 2854, 1645, 1578, 1256, 1158, 1040, 834, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.1 Hz, 3 H), 1.47–1.62 (m, 6 H), 1.92–2.89 (m, 4 H), 3.79 (s, 3 H), 5.07–5.14 (m, 1 H), 5.37 (ddd, *J* = 4.7, 10.7, 16.1 Hz, 1 H), 5.52 (ddd, *J* = 5.8, 10.7, 16.1 Hz, 1 H), 6.28 (d, *J* = 2.7 Hz, 1 H), 6.32 (d, *J* = 2.7 Hz, 1 H), 12.1 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 27.7, 29.8, 35.5, 55.2, 72.6, 98.8, 104.5, 110.7, 125.6, 133.0, 148.6, 163.8, 165.8, 171.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{23}O_4$ $[M + H]^+$ 291.15909; found 291.15817.

(*R*)-14-Hydroxy-12-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (32): To a solution of olefin **31** (20 mg, 0.068 mmol) in of EtOAc (1.5 mL) was added a catalytic amount of 10 % Pd/C under an inert atmosphere. The reaction flask was purged with hydrogen and then closed under a positive pressure of hydrogen. The progress of the reaction was monitored by TLC analysis. Upon completion, the reaction mixture was filtered through a small pad of Celite, and the filtrate was concentrated under reduced pressure. Purification of the crude residue by silica gel column chromatography (EtOAc/PE, 10:90) to afforded saturated product **32** (17.9 mg, 90 %) as a colorless oil; R_f = 0.5 (EtOAc/PE, 10:90). $[\alpha]_D^{25}$ = +21.41 (*c* = 0.24, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2924, 2854, 1644, 1612, 1416, 1253, 1208, 1157, 1040, 813 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.2 Hz, 3 H), 1.39–1.69 (m, 10 H), 1.73–1.89 (m, 1 H), 1.88–1.99 (m, 1 H), 2.46–2.55 (m, 1 H), 3.30 (td, *J* = 4.2, 12.8 Hz, 2 H), 3.80 (s, 3 H), 6.29 (d, *J* = 2.7 Hz, 1 H), 6.33 (d, *J* = 2.7 Hz, 1 H), 11.99 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 21.1, 24.1, 24.7, 27.2, 30.8, 31.0, 33.6, 55.2, 75.0, 98.8, 105.1, 110.5, 148.5, 163.7, 165.6, 171.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{25}O_4$ $[M + H]^+$ 293.17474; found 293.17412.

(*R*)-12,14-Dihydroxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1*H*-benzo[*c*][1]oxacyclododecin-1-one (4): To a stirred solution of AlI_3 in benzene [prepared in situ from Al (54 mg, 2.0 mmol) and I_2 (362 mg, 1.42 mmol) in anhydrous benzene (3 mL) at 80 °C for 1 h] was added **32** (12 mg, 0.040 mmol) in anhydrous benzene (1 mL) at 10 °C. The reaction was stirred for 30 min then quenched by the addition of solutions of aqueous NH_4Cl (2 mL) and aqueous $Na_2S_2O_5$ (2 mL). The mixture was extracted with EtOAc (3 × 6 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/PE, 30:70) to afford **4** (9.4 mg, 85 %) as a white solid; R_f = 0.3 (EtOAc/PE, 30:70). $[\alpha]_D^{25}$ = +26.82 (*c* = 0.20, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 2924, 2854, 1640, 1460, 1260, 1096, 1019, 3358 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.2 Hz, 3 H), 1.39–1.71 (m, 10 H), 1.75–1.82 (m, 1 H), 1.88–1.97 (m, 1 H), 2.50 (td, *J* = 5.8, 11.6 Hz, 1 H), 3.50 (td, *J* = 3.9, 11.6 Hz, 2 H), 6.22 (d, *J* = 2.7 Hz, 1 H), 6.27 (d, *J* = 2.7 Hz, 1 H), 11.96 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 21.1, 24.0, 24.6, 27.2, 29.6, 30.7, 31.0, 33.5, 75.1, 101.3, 105.5, 110.7, 149.4, 160.0, 165.3, 171.8 ppm. HRMS (ESI): calcd. for $C_{16}H_{23}O_4$ $[M + H]^+$ 279.15909; found 279.15908.

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