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Synthesis of Pladienolide B and Its 7-Epimer with Insights into the Role of the Allylic Acetate

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Diastereomeric macrolactones **41** and **48**, which are epimeric at C-7, were both prepared by a synthesis based on our previously developed route to the macrolactone core of pladienolide B. Both compounds contain all the functionality of the macrolactone core plus the vinyl iodide unit in the side chain. The key step to construct the *seco* acid for the macrolactonization was a Horner–Wadsworth–Emmons (HWE) reaction to produce acyclic enone **17**. The required keto phosphonate for the HWE reaction was originally obtained from (*R*)-(–)-linalool. The derived macrolactone underwent a reduction of the enone function to give 7-*epi*-alcohol **20**, and its acetylation, either under Mitsunobu or classical acylation conditions, produced allylic acetate **40**. This represents a rare case in which a Mitsunobu reaction occurred with retention of configuration. The complete side chain that contains all the functionality was attached by a Stille cross-coupling reaction to lead to 7-*epi*-pladienolide B (**42**). To obtain pladienolide B (**1**), the reduction of acyclic enone **17** under chelation-controlled conditions [$Zn(BH_4)_2$, Et_2O] gave allylic alcohol **43** with the correct configuration at C-7 with regard to the natural product. Conversion of this allylic alcohol to *seco* acid **46** followed by a Shiina macrolactonization afforded vinyl iodide **48**. Its Stille coupling with vinylstannane **39** provided pladienolide B (**1**). Preliminary testing for cytotoxicity against the L929 cell line showed 7-*epi*-pladienolide B (**42**) to be completely inactive, which is in contrast to pladienolide B (**1**) that displayed an IC_{50} (half maximal inhibitory concentration) value of 7.5 nM. These results point to the importance of the correct configuration of the OAc functional group at C-7 of pladienolide B.

Introduction

In recent years a range of bacterial fermentation products were discovered that show a different antitumor spectrum from existing cytotoxic drugs. Subsequent biochemical studies, which include pull-down experiments in combination with photoaffinity labeling showed that these natural products bind to components of the spliceosome.[1,2] A rather complex molecular machinery, the spliceosome is responsible for the correct removal of introns from mRNA precursors in eukaryotic cells. Prominent natural products in this regard are pladienolides **1** and **2**,[3] the related macrolide FD-895[4] (**4**), and the pyran derivatives FR901464[5] (**5**), spliceostatin A[1a] (**6**), and thailanstatin A[6] (**7**, see Figure 1). By now, it seems that these natural products, which have an epoxide-containing region and an allylic acetate group in common, represent promising lead structures for synthesis programs that are directed at finding new antitumor drugs.[7,8]

Pladienolide B was one of seven related macrolides that were described in 2004 by scientists from the Eisai Co.[3] The most active of these compounds were pladienolides B and D with IC_{50} (half maximal inhibitory concentration) values of 0.86 nM for **1** and 5.9 nM for **2** (WiDr cell line). However, their stereostructures only became known in 2007[9] and were also supported by the first total synthesis of pladienolides B and D.[10] The analogue E7107 (**3**), which was already reported in the 2007 paper,[10] made it to clinical trials.[2c] Key structural elements of pladienolide B include a 12-membered macrolactone ring that features five stereocenters. One is a secondary acetate group that is allylic to a *trans* double bond. Vicinal to the OAc group at C-7 is a tertiary alcohol at C-6. From C-11, a rather complex side chain that contains a conjugated diene, a *trans* epoxide, and three additional stereocenters extends into space. After the first total synthesis of pladienolide B by Kotake et al.,[10] further successful syntheses were published by Ghosh[11] and Chandrasekhar.[12] In addition, a synthesis of the macrolactone devoid of the side chain[13] and a separate synthesis of the side chain were reported.[14] Even though the related macrolide FD-895 (**4**) had been known since 1994,[4] the Burkart group was only recently able to delineate its stereochemistry through a total synthesis.[15] Interestingly, they were able to find two stereoisomers of **4** (i.e., 16-*epi*, 17-*epi*) that were more active than FD-895 itself and had an IC_{50} value of 24 nM against HCT-116 tumor cells.

A substantial amount of work with regard to the structure–activity relationship (SAR) of the somewhat simpler

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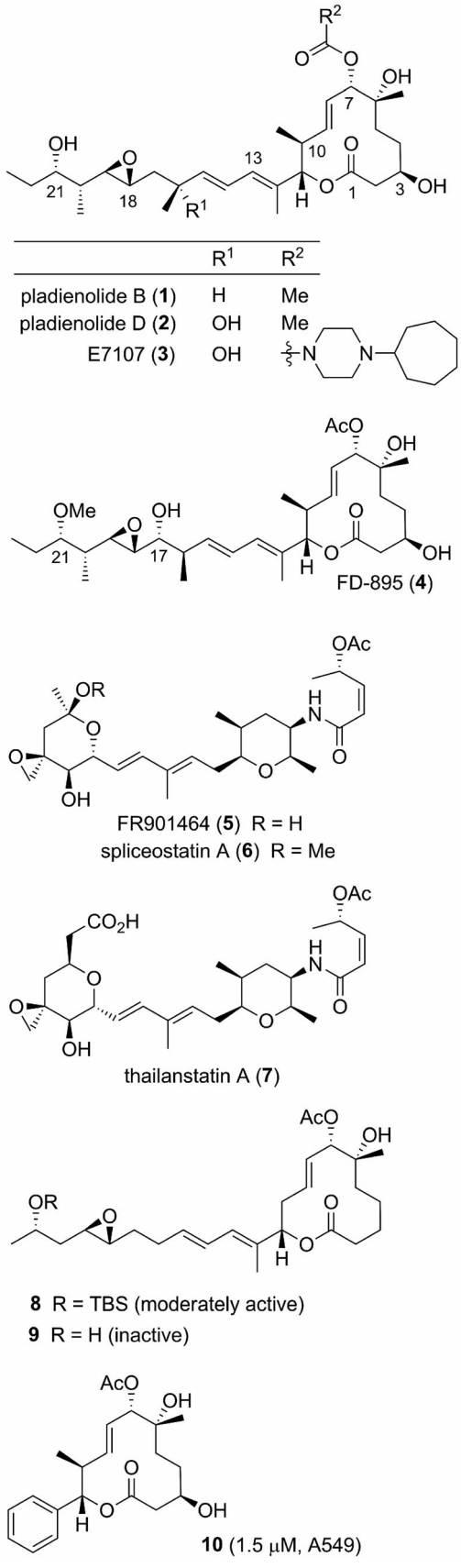


Figure 1. Structures of spliceosome inhibitors (TBS = *tert*-butyldimethylsilyl).

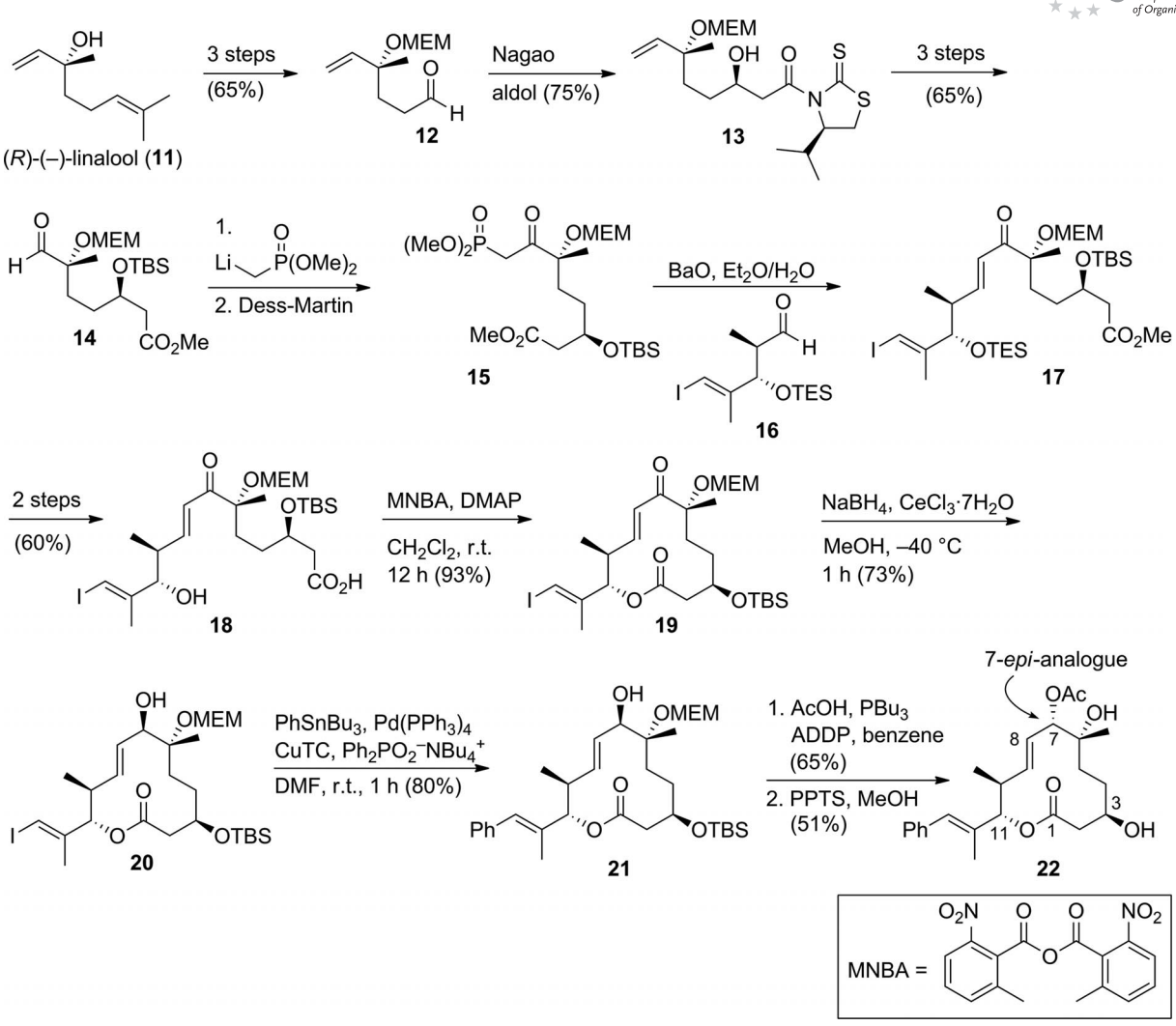
spliceosome inhibitor FR901464 was carried out by Webb.[16] In essence, they put forward the hypothesis that the presence of both the allylic acetate and the epoxide as well as their correct distances is important for biological activity. With pladienolide B, the SAR data available so far are less conclusive. For the core macrolactone, no activity data have been reported,[13] however, a recent study by Webb described data for the simplified analogues **8** and **9**, both of which contain the epoxide and allylic acetate.[17] Although analogue **9** surprisingly was inactive, the corresponding silyl ether **8** showed moderate activity (IC_{50} between 10 and 20 μM against various cell lines). During the course of a total synthesis, the Chandrasekhar group also prepared a range of side-chain truncated analogues.[12] Reasonable activity was reported for phenyl derivative **10**. However, it is not clear how reliable these values are, as they only reported moderate activity for **1** (IC_{50} = 1.4 μM, A549 cells).

Our own group contributed to the research of pladienolide B through the synthesis of analogue **22** (see Scheme 1).[18] For this compound, actually now known as the 7-*epi*-derivative, no biological activity could be found. Because the stereochemistry at the allylic acetate moiety was not the natural one, we were unable to attribute the lack of activity to either the wrong configuration or the absence of the epoxide containing side chain. Therefore additional work was warranted to establish more meaningful SAR data.

Results and Discussion

In contrast to most of the routes that generate the macrocyclic core through a ring-closing metathesis, the strategy we developed relies on a classical macrolactonization reaction. The key steps of this route are summarized in Scheme 1.[18] The region from C-3 to C-7 originates from (*R*)-(–)-linalool (**11**). The double bonds serve as precursors for the aldehyde functions, which were extended by aldol reactions. Keto phosphonate **15** with aldehyde[18,19] **16** were combined and underwent a Horner–Wadsworth–Emmons reaction (HWE) to provide enone **17**. The derived hydroxy acid **18** was then cyclized by using the Shiina reagent to give macrocyclic enone **19**. Its reduction under Luche conditions led to allylic alcohol **20** as the major isomer, and the configuration at C-7 was unambiguously proven through a Mosher analysis.[20] Other conditions that were attempted for the reduction of enone **19** are summarized in Table S1 of the Supporting Information. In a model study, a Stille reaction was employed to couple a phenyl ring to the alkenyl iodide of the side chain of **20** to give styrene **21**. The introduction of the acetate group at C-7 was accomplished by a Mitsunobu reaction followed by a global deprotection to deliver analogue **22**.

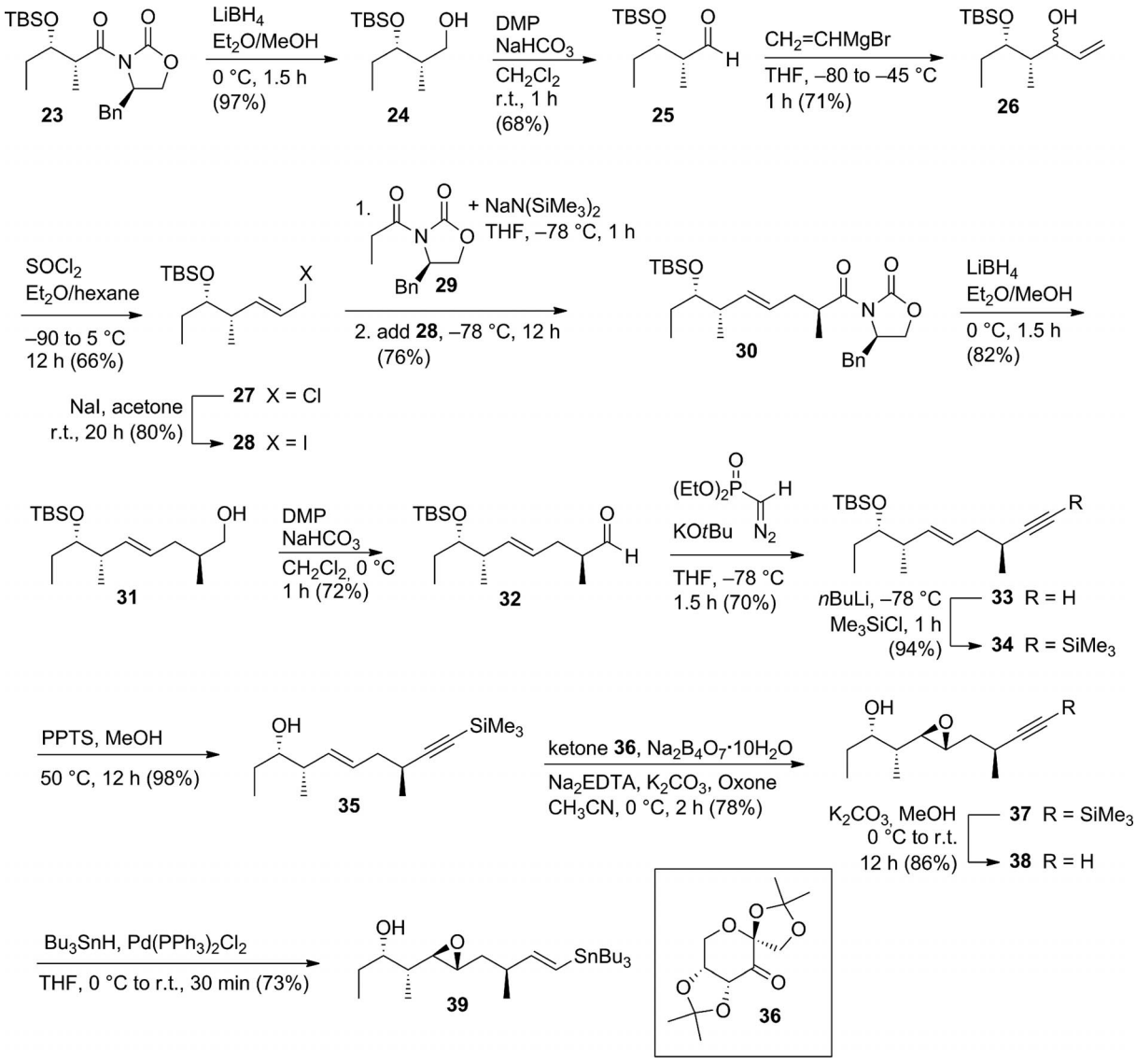
We then planned the synthesis of pladienolide B along these lines. The required side chain was prepared as shown in Scheme 2. Starting with the known TBS-protected aldol product[21] **23**, a redox sequence furnished aldehyde **25**. An



Scheme 1. Summary of the synthesis of macrolactone **20** from (*R*)-(–)-linalool and aldehyde **16**. Cross-coupling reaction to give styrene derivative **21** and Mitsunobu reaction of the allylic alcohol of **21** to give the 7-*epi*-analogue **22** [MEM = β-methoxyethoxymethyl, TES = triethylsilyl, MNBA = 2-methyl-6-nitrobenzoic anhydride (Shiina reagent), DMAP = 4-(dimethylamino)pyridine, CuTC = copper(I) thiophene-2-carboxylate, DMF = *N*,*N*-dimethylformamide, ADDP = azodicarboxylic acid dipiperidide, PPTS = pyridinium *p*-toluenesulfonate].

extension of the side chain through a Grignard reaction of **25** with vinylmagnesium chloride was followed by chlorination of **26** with thionyl bromide to lead to primary chloride **27**. Prior to its use as an electrophile, the chloride was replaced with an iodide through a Finkelstein reaction. The addition of allylic iodide **28** to the sodium enolate of propionyloxazolidinone **29** furnished nonenoic acid derivative **30**. A second redox sequence starting from **30** produced aldehyde **32**. We then tried to convert aldehyde **32** into terminal alkyne **33**. Although this was possible with the Bestmann–Ohira reagent,[22] the reaction was accompanied by substantial epimerization at C-16, and the initial conversion of aldehyde **32** into the corresponding 1,1-dibromoalkene suffered from a low yield. The best results were obtained by using the Seyferth–Gilbert homologation.[23] Thus, the reaction of aldehyde **32** with the anion of diethyl (diazomethyl)-phosphonate[24] gave alkyne **33** in reasonable yield. We found it necessary to silylate the terminal acetylene to achieve reproducible results in the subsequent Shi epoxidation reaction. Furthermore, the silyl ether at C-21 was cleaved by an acid-catalyzed transetherification giving rise to enynol **35**. Gratifyingly, the Shi epoxidation,[25,26] of alkene **35** using Oxone as the oxygen source and ketone **36** as a chiral inducer gave epoxide **37**, essentially as a single isomer in good yield. After desilylation of the terminal alkyne, the palladium-catalyzed hydrostannylation of **38** furnished the key vinyl stannane **39**.

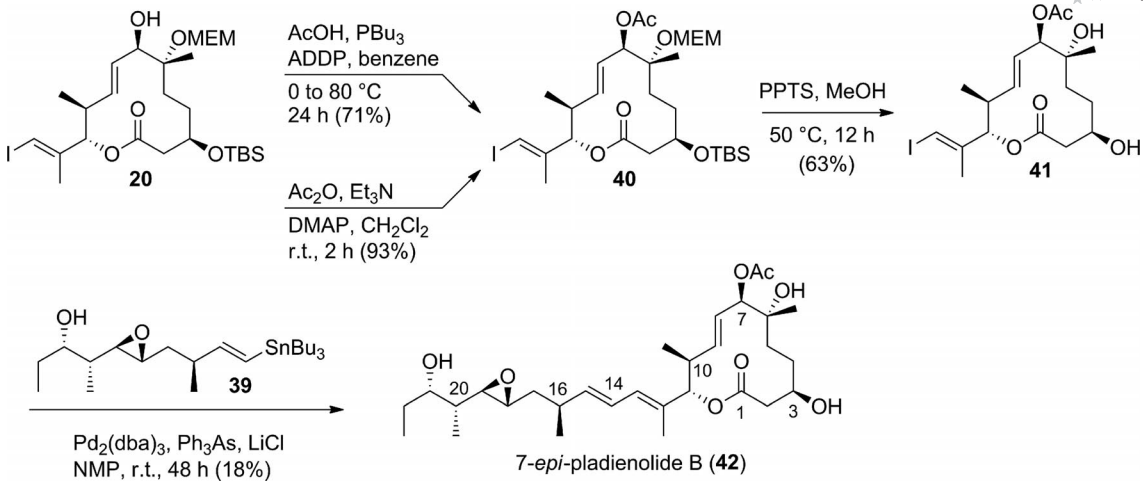
Prior to the coupling with the macrocyclic core, allylic alcohol **20** was subjected to a Mitsunobu reaction by using acetic acid in the presence of azodicarboxylic acid dipiperidide and tributylphosphine[27,28] (see Scheme 3). Combining macrolactone **40** with pyridinium *p*-toluenesulfonate in methanol delivered macrocyclic diol **41**. The subsequent Stille cross-coupling reaction between stannane **39** and alkenyl iodide **41** gave a compound with the correct mass. However, the NMR spectrum of **42** showed distinct differ-



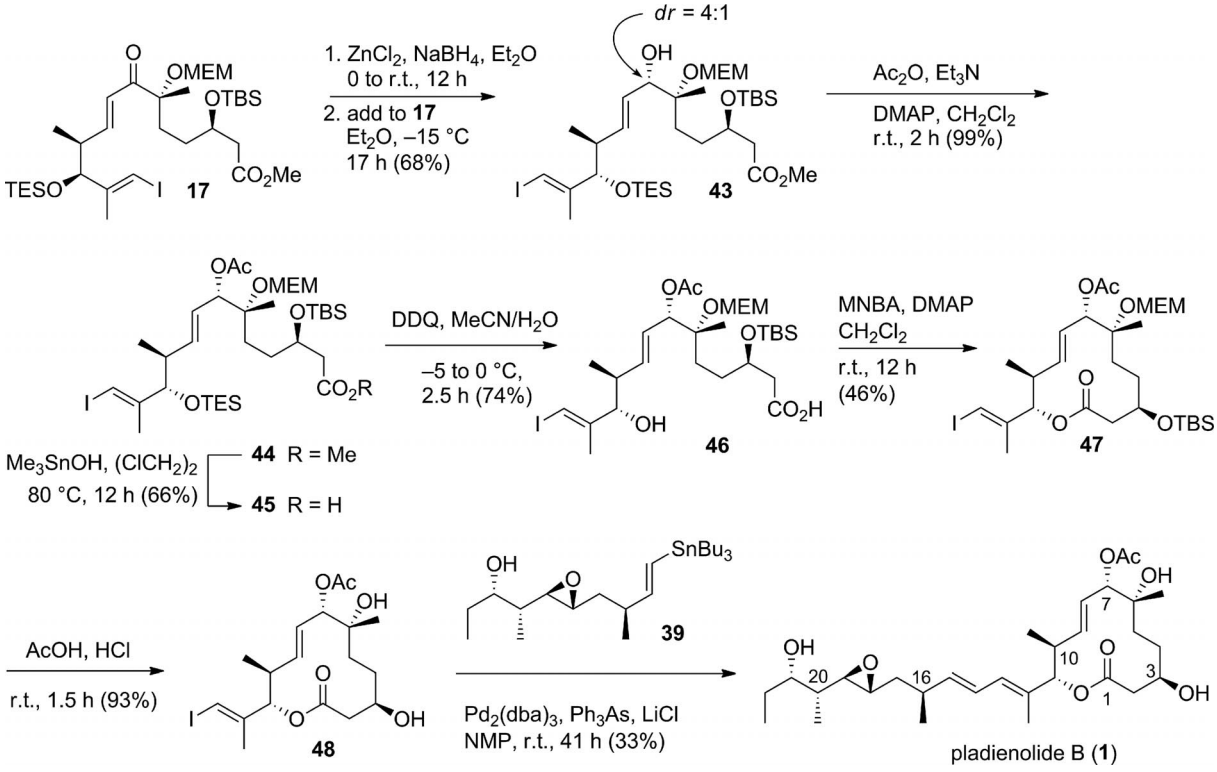
Scheme 2. Synthesis of the pladienolide B side chain **39** from aldol product **23** (DMP = Dess–Martin periodinane, tetrahydrofuran (THF), EDTA = ethylenediaminetetraacetic acid).

ences to the published one. Although the proton signals of the side chain, for example, from the diene part, were largely unaffected, there were significant differences in the shift of some of the lactone protons [for **42**, 5.17 (7-H), 5.87 (8-H), 5.23 (9-H), 4.99 (11-H) ppm; for **1**, 5.04 (7-H), 5.69 (8-H), 5.55 (9-H), 5.04 (11-H) ppm]. Careful reconsideration of the previous steps led to the conclusion that something was wrong with the Mitsunobu reaction. Thus, the Mitsunobu reaction of **21** and also of **20** apparently proceeded under retention instead of the expected inversion of configuration.[29] This was simply proven by subjecting alcohol **20** to an acylation by treatment with acetic anhydride/Et_3N to lead to the same compound **40**. Thus, this route had produced 7-*epi*-pladienolide B (**42**). The unexpected retention of the configuration in the Mitsunobu reaction of the allylic alcohol might be a consequence of the neighboring group participation by the MEM group or macrocyclic control.[30] Most likely, an allylic cation is formed (S_N1 mechanism) as an intermediate in this transformation.

To obtain natural pladienolide B (**1**), we initially tried to find conditions that would give the correct stereoisomer from the reduction of macrocyclic enone **19**. However, we were unable to find conditions that would give the correct allylic alcohol as the major product. We surmised that this might be a consequence of macrocyclic control.[30] Accordingly, we turned to the reduction of an acyclic precursor. In the event, the chelation-controlled reduction of enone **17** ($ZnCl_2$, $NaBH_4$, Et_2O, –15 °C) gave the correct allylic alcohol **43** as the major diastereomer (4:1), as determined by the product mass following the chromatographic separation (see Scheme 4 and Supporting Information, Table S1). After acetylation, the ester group was hydrolyzed with trimethyltin hydroxide[31] followed by the subsequent cleavage



Scheme 3. Acetylation of allylic alcohol **20** to give acetate **40** with retention of configuration under Mitsunobu and esterification conditions. Subsequent coupling of the vinyl iodide to give 7-*epi*-pladienolide B (**42**; dba = dibenzylideneacetone, NMP = *N*-methylpyrrolidone).



Scheme 4. Chelation-controlled reduction of enone **17** followed by its conversion to macrolactone **48** and the final cross-coupling reaction between vinyl iodide **48** and vinylstannane **39** to lead to pladienolide B (**1**, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

of the triethylsilyl (TES) ether to provide *seco*-acid **46**. Unfortunately, the yield of the subsequent Shiina macrolactonization remained a moderate 46% (unoptimized). Next, the protecting groups could be removed under acidic conditions to give the correct macrocyclic core **48**. The final Stille coupling reaction between vinylstannane **39** and vinyl iodide **48** delivered pladienolide B (**1**, 2.5 mg, 33%; see Scheme 4). Its NMR and other spectroscopic data matched those from the literature.

In cytotoxicity tests that were performed with the two samples, 7-*epi*-pladienolide B (**42**) turned out to be completely inactive.[32] In contrast, the synthetic pladienolide B (**1**) displayed the expected strong cytotoxicity [IC_{50} = 4 ng mL^{-1} (7.5 nM), L929 mouse fibroblast cells].

Conclusions

In summary, we developed a concise synthesis of the pladienolide B side chain that featured the conversion of aldol product **23** into allylic iodide **28**. The latter was used to alkylate propionyloxazolidinone **29**. Its conversion into alk-

yne **33** was followed by a Shi epoxidation of alkenol **35**. The derived vinylstannane **39** was coupled with the two diastereomeric lactones 7-*epi*-**41** and **48** to lead to analogue **42** (7-*epi*-pladienolide B) and pladienolide B (**1**), respectively. The 7-*epi*-lactone **40** was initially formed by a Mitsunobu reaction that unexpectedly proceeded with retention of configuration. The correct configuration at C-7 resulted from reduction of acyclic enone **17** under chelation-controlled reaction conditions. The results of the biological studies indicate the importance of the correct configuration and the presence of the acetate at C-7. Starting from (*R*)-(–)-linalool, both *epi*-pladienolide B (**42**) and pladienolide B (**1**) were obtained in 17 steps in moderate overall yields that were mostly a result of the low yields of the final Stille coupling (overall yields, 0.58% for **42** and 0.63% for **1**). The synthesis of the side chain (vinylstannane **39**) required 14 steps (3.5% overall yield).

Experimental Section

Diethyl (Diazomethyl)phosphonate: Preparation was carried out from diethyl 1-diazo-2-oxopropylphosphonate according to literature procedures[22,24] (see also Supporting Information).

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpentan-1-ol (24): To a solution of the TBS-protected aldol product **23** (25.84 g, 63.70 mmol) in Et_2O (600 mL) were added MeOH (3 mL) and $LiBH_4$ (1.67 g, 76.44 mmol) at 0 °C followed by stirring the resulting mixture at 0 °C for 1.5 h. A solution of NaOH (3 M, 3 mL) was added, and the mixture was stirred at 0 °C for an additional 10 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3× 300 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/Et_2O, 6:1) delivered the desired alcohol **24** (14.50 g, 97%) as a colorless liquid; R_f = 0.49 (petroleum ether/EtOAc, 7:1). $[\alpha]_D^{22}$ = –3.3 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 [s, 3 H, $Si(CH_3)_2$], 0.08 [s, 3 H, $Si(CH_3)_2$], 0.80 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 0.89 (t, *J* = 6.8 Hz, 3 H, 5-H), 0.88 [s, 9 H, $C(CH_3)_3$], 1.46–1.53 (m, 2 H, 4-H), 1.91–2.00 (m, 1 H, 2-H), 2.46 (br. s, 1 H, OH), 3.50 (dd, *J* = 10.5, 5.2 Hz, 1 H, 1-H), 3.65–3.70 (m, 2 H, 1-H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [$Si(CH_3)_2$], –4.4 [$Si(CH_3)_2$], 10.7 (C-5), 11.8 (2-CH_3), 18.0 [$C(CH_3)_3$], 25.1 (C-4), 25.8 [$C(CH_3)_3$], 39.2 (C-2), 66.1 (C-1), 77.2 (C-3) ppm. HRMS (ESI): calcd. for $C_{12}H_{28}O_2Si$ $[M + H]^+$ 233.19313; found 233.193147.

(2*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpentanal (25): To a solution of alcohol **24** (14.81 g, 63.70 mmol) in CH_2Cl_2 (300 mL) were added $NaHCO_3$ (15.99 g, 191.15 mmol) and DMP (29.10 g, 68.64 mmol). The resulting suspension was stirred at room temp. for 1 h, and then saturated $NaHCO_3$ solution (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et_2O, 10:1) delivered the desired aldehyde **25** (9.93 g, 68%) as a colorless liquid; R_f = 0.30 (petroleum ether/EtOAc, 10:1). $[\alpha]_D^{25}$ = –20.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $C(CH_3)_3$], 0.89 (t, *J* = 7.5 Hz, 3 H, 5-H), 1.04 (d, *J* = 7.1 Hz, 3 H, 2-CH_3), 1.43–1.60 (m, 2 H, 4-H), 2.42–2.48 (m, 1 H, 2-H), 4.00–4.04 (m, 1 H, 3-H), 9.75 (d, *J* = 1.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7 [$Si(CH_3)_2$], –4.2 [$Si(CH_3)_2$], 7.5 (2-CH_3), 10.1 (C-5), 18.0 [$C(CH_3)_3$], 25.7 [$C(CH_3)_3$], 27.4 (C-4), 50.8 (C-2), 73.4 (C-3), 205.5 (C-1) ppm.

(4*S*,5*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylhept-1-en-3-ol (26): To a solution of aldehyde **25** (0.737 g, 3.20 mmol) in THF (11 mL) was added vinylmagnesium bromide (1 M in THF, 11.20 mL, 11.20 mmol) at –80 °C. Afterwards, the solution was warmed to –45 °C and then stirred for 1 h at this temperature. The reaction was quenched by the addition of a saturated NH_4Cl solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 15:1) delivered the desired allylic alcohol **26** (0.59 g, 71%, mixture of diastereomers) as a colorless oil; R_f = 0.34 (petroleum ether/Et_2O, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08–0.10 [m, 12 H, $Si(CH_3)_2$], 0.76–0.87 (m, 12 H, 7-H, 4-CH_3), 0.89 [s, 9 H, $C(CH_3)_3$], 0.90 [s, 9 H, $C(CH_3)_3$], 1.51–1.74 (m, 6 H, 4-H, 2-H), 2.85 (d, *J* = 1.8 Hz, 1 H, OH), 3.74–3.82 (m, 2 H, 5-H), 4.02 (t, *J* = 7.9 Hz, 1 H, 3-H), 4.28–4.31 (m, 1 H, 3-H), 5.10–5.11 (m, 1 H, 1-H), 5.13–5.14 (m, 1 H, 1-H), 5.24–5.25 (m, 1 H, 1-H), 5.29–5.30 (m, 1 H, 1-H), 5.74–5.88 (m, 2 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6 [$Si(CH_3)_2$], –4.4 [$Si(CH_3)_2$], –3.7 [$Si(CH_3)_2$], 5.7 (C-7), 9.9 (4-CH_3), 11.1 (4-CH_3), 18.0 [$C(CH_3)_3$], 18.0 [$C(CH_3)_3$], 25.8 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 27.5 (C-6), 39.9 (C-4), 42.3 (C-4), 75.7 (C-3), 76.1 (C-3), 78.0 (C-5), 78.4 (C-5), 114.4 (C-1), 115.8 (C-1), 140.1 (C-2), 140.5 (C-2) ppm. HRMS (ESI): calcd. for $C_{14}H_{30}O_2Si$ $[M + Na]^+$ 281.19073; found 281.19119.

(5*E*,3*S*,4*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-chloro-4-methylhept-5-en-3-ol (27): Alcohol **26** (6.66 g, 25.77 mmol) was dissolved in a mixture of Et_2O/*n*-hexane (3:2, 233 mL), and the resulting solution was cooled to –90 °C. After the addition of $SOCl_2$ (12 mL, 165.42 mmol), the mixture was warmed to 5 °C and then stirred overnight at this temperature. The reaction mixture was then added by syringe to a cooled solution (0 °C) of saturated $NaHCO_3$ (350 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (*n*-hexane) to obtain allylic chloride **27** (4.70 g, 66%) as a colorless liquid; R_f = 0.20 (petroleum ether). $[\alpha]_D^{20}$ = –31.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 3 H, $Si(CH_3)_2$], 0.03 [s, 3 H, $Si(CH_3)_2$], 0.85 (t, *J* = 7.5 Hz, 3 H, 1-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.96 (d, *J* = 6.8 Hz, 3 H, 4-CH_3), 1.32–1.50 (m, 2 H, 2-H), 2.27–2.37 (m, 1 H, 4-H), 3.43–3.48 (m, 1 H, 3-H), 4.04 (d, *J* = 7.1 Hz, 2 H, 7-H), 5.54–5.61 (m, 1 H, 5-H), 5.78 (dd, *J* = 15.3, 7.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 9.6 (C-1), 14.7 (4-CH_3), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 26.5 (C-2), 40.8 (C-4), 45.6 (C-7), 76.9 (C-3), 125.2 (C-6), 138.9 (C-5) ppm. HRMS (ESI): calcd. for $C_{14}H_{29}ClOSi$ $[M + Na]^+$ 299.15684; found 299.15698.

(5*E*,3*S*,4*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-iodo-4-methylhept-5-ene (28): To a solution of allylic chloride **27** (4.68 g, 16.89 mmol) in acetone (60 mL) was added NaI (15.19 g, 101.36 mmol) at room temp., and the mixture was stirred at this temperature for additional 20 h. After the addition of *n*-hexane (20 mL) and H_2O (20 mL), the layers were separated, and the aqueous layer was extracted with *n*-hexane (3× 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (*n*-hexane) delivered the desired iodide **28** (4.99 g, 80%) as an orange oil; R_f = 0.55 (petroleum ether). $[\alpha]_D^{25}$ = –11.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 0.02 [s, 6 H, $Si(CH_3)_2$], 0.84 (t, J = 7.5 Hz, 3 H, 1-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.93 (d, J = 6.8 Hz, 3 H, 4-CH_3), 1.33–1.47 (m, 2 H, 2-H), 2.25–2.33 (m, 1 H, 4-H), 3.42–3.46 (m, 1 H, 3-H), 3.87–3.88 (m, 2 H, 7-H), 5.68–5.71 (m, 2 H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 7.1 (C-7), 9.5 (C-1), 14.8 (4-CH_3), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 26.5 (C-2), 40.8 (C-4), 77.0 (C-3), 127.1 (C-6), 137.9 (C-5) ppm. HRMS (ESI): calcd. for $C_{14}H_{29}IOSi$ [M + Na]$^+$ 391.09246; found 391.09205.

(4*R*)-4-Benzyl-3-[(2′*S*,4′*E*,6′*S*,7′*S*)-7′-{[*tert*-butyl(dimethyl)silyl]oxy}-2′,6′-dimethylnon-4′-enoyl]-1,3-oxazolidin-2-one (30): A solution of oxazolidinone **29** (6.30 g, 27.03 mmol) in THF (55 mL) was cooled to –78 °C, and then sodium hexamethyldisilazide (NaHMDS, 1 M in THF, 34 mL, 33.80 mmol) was added dropwise. The resulting yellow solution was stirred at –78 °C for 1 h. Afterwards, a solution of iodide **28** (4.97 g, 13.52 mmol) in THF (20 mL) was added slowly at the same temperature, and the resulting mixture was stirred overnight. The reaction was quenched by the addition of a saturated NH_4Cl solution (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 10:1) to obtain oxazolidinone **30** (4.85 g, 76%, 98% *de*) as a colorless liquid; R_f = 0.26 (petroleum ether/EtOAc, 10:1). $[\alpha]_D^{20}$ = –36.8 (c = 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, $Si(CH_3)_2$], 0.83 (t, J = 7.5 Hz, 3 H, 9-H), 0.87 [s, 9 H, $C(CH_3)_3$], 0.92 (d, J = 6.9 Hz, 3 H, 6′-CH_3), 1.15 (d, J = 5.8 Hz, 3 H, 2′-CH_3), 1.39–1.45 (m, 2 H, 8′-H), 2.10–2.17 (m, 1 H, 3′-H), 2.23–2.30 (m, 1 H, 6′-H), 2.43–2.51 (m, 1 H, 3′-H), 2.68 (dd, J = 13.3, 9.9 Hz, 1 H, $PhCH_2$), 3.28 (dd, J = 13.3, 3.2 Hz, 1 H, $PhCH_2$), 3.38–3.42 (m, 1 H, 7′-H), 3.73–3.82 (m, 1 H, 2′-H), 4.12–4.20 (m, 2 H, 5-H), 4.64–4.70 (m, 1 H, 4-H), 5.34–5.41 (m, 1 H, 4′-H), 5.45–5.51 (m, 1 H, 5′-H), 7.20 (d, J = 6.8 Hz, 2 H, Ar), 7.26–7.34 (m, 3 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 9.2 (C-9′), 15.9 (6′-CH_3), 16.3 (2′-CH_3), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 26.6 (C-8′), 37.0 ($PhCH_2$), 37.7 (C-3′), 38.1 (C-2′), 41.3 (C-6′), 55.4 (C-4), 66.0 (C-5), 77.1 (C-7′), 126.0 (C-4), 127.3 (Ar), 128.9 (Ar), 129.4 (Ar), 135.4 (C-5′), 136.3 (Ar), 153.1 (C=O), 176.8 (C=O) ppm. HRMS (ESI): calcd. for $C_{27}H_{43}NO_4Si$ [M + Na]$^+$ 496.28536; found 496.28550.

(2*S*,4*E*,6*S*,7*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,6-dimethylnon-4-en-1-ol (31): To a solution of oxazolidinone **30** (4.82 g, 10.19 mmol) in Et_2O (34 mL) were added MeOH (0.5 mL) and $LiBH_4$ (0.26 g, 11.72 mmol) at 0 °C, and the reaction mixture was stirred at this temperature for 1.5 h. A solution of NaOH (3 M, 15 mL) was added, and the resulting mixture was stirred at 0 °C for an additional 10 min. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et_2O, 10:1) delivered primary alcohol **31** (2.50 g, 82%) as a colorless liquid; R_f = 0.17 (petroleum ether/Et_2O, 10:1). $[\alpha]_D^{21}$ = –22.6 (c = 1, $CHCl_3$); ref.[12] $[\alpha]_D^{25}$ = –2.2 (c = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 6 H, $Si(CH_3)_2$], 0.84 (t, J = 7.5 Hz, 3 H, 9-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.89–0.94 (m, 6 H, 2-CH_3, 6-CH_3), 1.36–1.48 (m, 2 H, 8-H), 1.65–1.73 (m, 1 H, 2-H), 1.85–1.91 (m, 1 H, 3-H), 2.03–2.12 (m, 1 H, 3-H), 2.21–2.29 (m, 1 H, 6-H), 3.39–3.45 (m, 2 H, 7-H, 1-H), 3.48–3.52 (m, 1 H, 1-H), 5.37–5.41 (m, 2 H, 4-H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 9.3 (C-9), 16.0 (6-CH_3), 16.4 (2-CH_3), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 26.6 (C-8), 36.0 (C-2), 36.8 (C-3), 41.4 (C-6), 68.1 (C-1), 77.3 (C-7), 127.5 (C-4), 135.1 (C-5) ppm. HRMS (ESI): calcd. for $C_{17}H_{36}O_2Si$ [M + Na]$^+$ 323.23768; found 323.23771.

(2*S*,4*E*,6*S*,7*S*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,6-dimethylnon-4-enal (32): To a solution of alcohol **31** (2.50 g, 8.33 mmol) in CH_2Cl_2 (42 mL) was added $NaHCO_3$ (2.09 g, 24.99 mmol) followed by DMP (5.30 g, 12.50 mmol). The resulting suspension was stirred at 0 °C for 1 h, and then a saturated $NaHCO_3$ solution (20 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 20:1) to give aldehyde **32** (1.79 g, 72%) as a colorless oil; R_f = 0.75 (petroleum ether/EtOAc, 10:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 3 H, $Si(CH_3)_2$], 0.02 [s, 3 H, $Si(CH_3)_2$], 0.83 (t, J = 7.5 Hz, 3 H, 9-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.92 (d, J = 6.8 Hz, 3 H, 6-CH_3), 1.07 (d, J = 6.8 Hz, 3 H, 2-CH_3), 1.33–1.47 (m, 2 H, 8-H), 2.04–2.13 (m, 1 H, 3-H), 2.21–2.29 (m, 1 H, 6-H), 2.36–2.43 (m, 2 H, 2-H, 3-H), 3.40 (q, J = 5.3 Hz, 1 H, 7-H), 5.28–5.36 (m, 1 H, 4-H), 5.44–5.50 (m, 1 H, 5-H), 9.64 (d, J = 1.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 9.4 (C-9), 13.0 (2-CH_3), 15.8 (6-CH_3), 18.2 [$C(CH_3)_3$], 25.9 [$C(CH_3)_3$], 26.5 (C-8), 33.8 (C-3), 41.4 (C-6), 46.3 (C-2), 77.1 (C-7), 125.5 (C-4), 136.4 (C-5), 205.0 (C-1) ppm. HRMS (ESI): calcd. for $C_{17}H_{34}O_2Si$ [M + CH_3OH + Na]$^+$ 353.24824; found 353.24818.

(3*S*,4*S*,5*E*,8*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4,8-dimethyldec-5-en-9-yne (33): To a –78 °C solution of KO*t*Bu (0.14 g, 1.12 mmol) in THF (3 mL) was slowly added a solution of diethyl (diazomethyl)phosphonate (0.20 g, 1.12 mmol) in THF (3 mL). The resulting mixture was stirred at the same temperature for 20 min, and then a solution of aldehyde **32** (0.25 g, 0.83 mmol) in THF (2.5 mL) was added over a period of 15 min. After stirring at –78 °C for 1 h, a saturated NH_4Cl solution (3 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude alkyne was purified by flash chromatography (petroleum ether/EtOAc, 10:1), and alkyne **33** (0.17 g, 70%) was obtained as a colorless liquid; R_f = 0.27 (petroleum ether). $[\alpha]_D^{21}$ = –8.5 (c = 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 6 H, $Si(CH_3)_2$], 0.84 (t, J = 7.5 Hz, 3 H, 1-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.94 (d, J = 6.8 Hz, 3 H, 4-CH_3), 1.15 (d, J = 6.8 Hz, 3 H, 8-CH_3), 1.39–1.47 (m, 2 H, 2-H), 2.03 (d, J = 2.3 Hz, 1 H, 10-H), 2.08–2.30 (m, 3 H, 7-H, 4-H), 2.40–2.49 (m, 1 H, 8-H), 3.42 (q, J = 5.6 Hz, 1 H, 3-H), 5.35–5.49 (m, 2 H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 9.3 (C-1), 15.9 (4-CH_3), 18.2 [$C(CH_3)_3$], 20.3 (8-CH_3), 25.9 [$C(CH_3)_3$], 26.0 (C-8), 26.6 (C-2), 39.8 (C-4), 41.4 (C-7), 68.3 (C-10), 77.3 (C-3), 88.9 (C-9), 126.2 (C-6), 135.9 (C-5) ppm. HRMS (ESI): calcd. for $C_{18}H_{34}OSi$ [M + Na]$^+$ 317.22711; found 317.22663.

(3*S*,4*S*,5*E*,8*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4,8-dimethyl-10-(trimethylsilyl)dec-5-en-9-yn-3-ol (34): To a solution of alkyne **33** (0.14 g, 0.47 mmol) in THF (2.5 mL) was slowly added *n*BuLi (2.5 M in THF, 0.47 mL, 1.17 mmol) at –78 °C, and the resulting mixture was stirred at this temperature for 30 min. Freshly distilled trimethylsilyl chloride (TMSCl, 0.15 mL, 1.17 mmol) was added dropwise, and again the mixture was stirred at –78 °C for 30 min. The reaction was quenched by the addition of a saturated NH_4Cl solution (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (pentane) delivered the TMS-pro-

tected alkyne **34** (0.16 g, 94%) as a colorless oil; R_f = 0.24 (pentane). $[\alpha]_D^{26}$ = +4.7 (c = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 6 H, $Si(CH_3)_2$], 0.13 [s, 9 H, $Si(CH_3)_3$], 0.84 (t, J = 7.5 Hz, 3 H, 1-H), 0.89 [s, 9 H, $C(CH_3)_3$], 0.94 (d, J = 6.8 Hz, 3 H, 4-CH_3), 1.12 (d, J = 7.6 Hz, 3 H, 9-CH_3), 1.40–1.47 (m, 2 H, 2-H), 2.05–2.19 (m, 2 H, 8-H), 2.22–2.30 (m, 1 H, 4-H), 2.43–2.49 (m, 1 H, 8-H), 3.41 (q, J = 5.6 Hz, 1 H, 3-H), 5.41–5.44 (m, 2 H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4 [$Si(CH_3)_2$], –4.3 [$Si(CH_3)_2$], 0.2 [$Si(CH_3)_3$], 9.3 (C-1), 16.0 (4-CH_3), 18.2 [$C(CH_3)_3$], 20.4 (8-CH_3), 25.9 [$C(CH_3)_3$], 26.6 (C-2), 27.2 (C-8), 40.0 (C-4), 41.4 (C-7), 77.2 (C-3), 84.1 (C-10), 111.8 (C-9), 126.6 (C-6), 135.5 (C-5) ppm. HRMS (ESI): calcd. for $C_{21}H_{42}OSi_2$ $[M + Na]^+$ 389.26664; found 389.26621.

(3*S*,4*S*,5*E*,8*S*)-4,8-Dimethyl-10-(trimethylsilyl)dec-5-en-9-yn-3-ol (35): To a solution of TMS-protected alkyne **34** (0.16 g, 0.44 mmol) in MeOH (4.5 mL) was added PPTS (0.22 g, 0.88 mmol), and the mixture was heated to 50 °C. After stirring at this temperature for 12 h, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 2 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et_2O, 10:2) delivered alkenol **35** (0.11 g, 98%) as a colorless oil; R_f = 0.26 (petroleum ether/Et_2O, 10:2). $[\alpha]_D^{21}$ = +17.5 (c = 0.17, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.13 [s, 9 H, $Si(CH_3)_3$], 0.95 (t, J = 7.3 Hz, 3 H, 1-H), 1.00 (d, J = 7.1 Hz, 3 H, 4-CH_3), 1.14 (d, J = 6.8 Hz, 3 H, 8-CH_3), 1.34–1.42 (m, 1 H, 2-H), 1.50–1.57 (m, 2 H, OH, 2-H), 2.11–2.15 (m, 2 H, 7-H), 2.22–2.30 (m, 1 H, 4-H), 2.45–2.54 (m, 1 H, 8-H), 3.35–3.39 (m, 1 H, 3-H), 5.41–5.55 (m, 2 H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.2 [$Si(CH_3)_3$], 10.5 (C-1), 14.3 (4-CH_3), 20.6 (8-CH_3), 26.7 (C-2), 27.3 (C-8), 39.8 (C-7), 42.0 (C-4), 76.1 (C-3), 84.6 (C-10), 111.4 (C-9), 128.3 (C-5), 135.0 (C-6) ppm. HRMS (ESI): calcd. for $C_{15}H_{28}OSi$ $[M + Na]^+$ 275.18016; found 275.17996.

(2*R*,3*S*)-2-{(2′*R*,3′*R*)-3′-[(2′′*S*)-2′′-Methyl-4′′-(trimethylsilyl)but-3′′-ynyl]oxiran-2′-yl}pentan-3-ol (37): To a solution of alkene **35** (0.09 g, 0.36 mmol) in MeCN (5 mL) and sodium tetraborate decahydrate (0.05 M)-Na_2EDTA (0.4 mM) solution (5 mL) was added Shi's catalyst (ketone **36**, 0.28 g, 1.08 mmol) at 0 °C. K_2CO_3 (0.60 g, 4.31 mmol) and Oxone® (0.44 g, 1.44 mmol) were added in small portions over a period of 1 h. After stirring for 1 h at 0 °C, Et_2O (2 mL) and H_2O (2 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3× 2 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/Et_2O, 10:2) delivered epoxide **37** (0.076 g, 78%, single diastereomer) as a colorless oil; R_f = 0.17 (petroleum ether/Et_2O, 10:2). $[\alpha]_D^{26}$ = +38.4 (c = 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.14 [s, 9 H, $Si(CH_3)_3$], 0.94–0.99 (m, 6 H, 5-H, 2-CH_3), 1.21 (d, J = 7.1 Hz, 3 H, 2′′-H), 1.45–1.70 (m, 5 H, 4-H, 2-H, 1′′-H), 1.95 (s, 1 H, OH), 2.61–2.71 (m, 1 H, 2′′-H), 2.78 (dd, J = 6.8, 2.3 Hz, 1 H, 2′-H), 2.94 (ddd, J = 5.9, 2.3 Hz, 1 H, 3′-H), 3.61–3.63 (m, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.1 [$Si(CH_3)_3$], 10.2 (C-5), 10.6 (2-CH_3), 21.6 (2′′-CH_3), 24.6 (C-2′′), 27.2 (C-4), 39.5 (C-1′′), 40.0 (C-2), 56.1 (C-3′), 61.8 (C-2′), 74.4 (C-3), 85.2 (C-4′′), 110.6 (C-3′′) ppm. HRMS (ESI): calcd. for $C_{15}H_{28}O_2Si$ $[M + Na]^+$ 291.17508; found 291.17552.

(2*R*,3*S*)-2-{(2′*R*,3′*R*)-3′-[(2′′*S*)-2′′-Methylbut-3′′-ynyl]oxiran-2′-yl}pentan-3-ol (38): Silylated alkyne **37** (0.068 g, 0.253 mmol) was dissolved in MeOH (1.3 mL), and the resulting mixture was cooled to 0 °C. After the addition of K_2CO_3 (0.017 g, 0.127 mmol), the mixture was warmed to room temp. and stirred overnight. Et_2O (0.5 mL) and a saturated NH_4Cl solution (0.5 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3× 1 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/Et_2O, 2:1) to provide alkyne **38** (0.043 g, 86%) as a colorless liquid; R_f = 0.26 (petroleum ether/Et_2O, 2:1). $[\alpha]_D^{19}$ = +38.9 (c = 1.5, $CHCl_3$); ref.[12] $[\alpha]_D^{25}$ = +5.72 (c = 1.31, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.99 (m, 6 H, 5-H, 2-CH_3), 1.23 (d, J = 7.1 Hz, 3 H, 2′′-CH_3), 1.47–1.55 (m, 3 H, 4-H, 2-H), 1.62–1.64 (m, 2 H, 1′′-H), 1.88 (br. s, 1 H, OH), 2.09 (d, J = 2.3 Hz, 1 H, 4′′-H), 2.61–2.70 (m, 1 H, 2′′-H), 2.77 (dd, J = 7.3, 2.3 Hz, 1 H, 2′-H), 2.95 (ddd, J = 5.9, 2.3 Hz, 1 H, 3′-H), 3.61 (d, J = 2.53 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3 (2-CH_3), 10.5 (C-5), 21.3 (2′′-CH_3), 23.5 (C-2′′), 27.2 (C-4), 39.4 (C-1′′), 40.2 (C-2), 56.1 (C-3′), 61.7 (C-2′), 69.3 (C-4′′), 74.5 (C-3), 87.8 (C-3′′) ppm. HRMS (ESI): calcd. for $C_{12}H_{20}O_2$ $[M + Na]^+$ 219.135551; found 219.135647.

(2*R*,3*S*)-2-{(2′*R*,3′*R*)-3′-[(2′′*S*,3′′*E*)-2′′-Methyl-4′′-(tributylstannyl)but-3′′-enyl]oxiran-2′-yl}pentan-3-ol (39): To a solution of alkyne **38** (0.015 g, 0.076 mmol) in THF (1.5 mL) were added $PdCl_2(PPh_3)_2$ (0.003 g, 0.004 mmol) and Bu_3SnH (0.022 mL, 0.083 mmol) at 0 °C. Thereafter, the mixture was warmed to room temp. and stirred for 30 min. The reaction was quenched by the addition of a saturated $NaHCO_3$ solution (1 mL). Then, the layers were separated, and the aqueous layer was extracted with EtOAc (3× 1 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 1:1 and 5 drops of Et_3N) delivered the desired vinylstannane **39** (0.027 g, 73%) as a colorless liquid; R_f = 0.52 (petroleum ether/Et_2O, 1:1). The ^1H NMR spectrum of **39** (slightly impure) is included in the Supporting Information. HRMS (ESI): calcd. for $C_{24}H_{48}O_2Sn$ $[M + Na]^+$ 511.257293; found 511.257155.

(3*R*,6*R*,7*R*,8*E*,10*S*,11*S*,12*E*)-Macrolactone 40: To a solution of lactone **20** (0.030 g, 0.048 mmol) in CH_2Cl_2 (0.3 mL) were added DMAP (0.001 g, 0.008 mmol), Et_3N (0.008 mL, 0.057 mmol), and Ac_2O (0.007 mL, 0.072 mmol). The reaction mixture was stirred at room temp. for 2 h, and then a saturated $NaHCO_3$ solution (0.5 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3× 0.5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (petroleum ether/Et_2O, 3:1) delivered the desired acetate **40** (0.030 g, 93%) as a colorless oil; R_f = 0.40 (petroleum ether/EtOAc, 5:1). $[\alpha]_D^{19}$ = –40.3 (c = 2.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$], 0.86 (d, J = 6.8 Hz, 3-H, 10-CH_3), 0.89 [s, 3 H, $C(CH_3)_3$], 1.24 (s, 3 H, 6-CH_3), 1.40–1.48 (m, 2 H, 5-H), 1.57–1.71 (m, 2 H, 4-H), 1.79 (s, 3 H, 12-CH_3), 2.10 (s, 3 H, OAc), 2.36–2.56 (m, 3 H, 2-H, 10-H), 3.38 (s, 3 H, OCH_3), 3.53–3.56 (m, 2 H, $OCH_2CH_2OCH_3$), 3.71–3.73 (m, 2 H, $OCH_2CH_2OCH_3$), 3.78–3.83 (m, 1 H, 3-H), 4.86 (s, 1 H, OCH_2O), 5.08 (d, J = 10.6 Hz, 1 H, 11-H), 5.15–5.22 (m, 1 H, 9-H), 5.35 (s, 1 H, 7-H), 5.81 (dd, J = 15.41, 2.53 Hz, 1 H, 8-H), 6.43 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$Si(CH_3)_2$], –4.7 [$Si(CH_3)_2$], 16.6 (10-CH_3), 18.2 [$C(CH_3)_3$], 19.2 (12-CH_3), 19.9 (OAc), 21.0 (6-CH_3), 25.8 [$C(CH_3)_3$], 30.4 (C-4), 34.7 (C-5), 40.4 (C-2), 41.0 (C-10), 59.0 (OCH_3), 67.0 ($OCH_2CH_2OCH_3$), 70.7 (C-3), 71.8 ($OCH_2CH_2OCH_3$), 75.9 (C-7), 79.8 (C-6), 80.5 (C-11), 83.5 (C-13), 89.8 (OCH_2O), 127.3 (C-8), 130.2 (C-9), 144.0 (C-12), 168.9 (OAc), 169.8 (C=O) ppm. HRMS (ESI): calcd. for $C_{28}H_{49}IO_8Si$ $[M + Na]^+$ 691.213360; found 691.213535.

(3*R*,6*R*,7*R*,8*E*,10*S*,11*S*,12*E*)-Macrolactone 41: To a solution of macrolactone **40** (0.016 g, 0.024 mmol) in MeOH (0.3 mL) was added PPTS (0.018 g, 0.072 mmol). The reaction mixture was heated to 50 °C and stirred overnight. After cooling to room temp., the solvent was removed in vacuo, and the residue purified by preparative TLC (petroleum ether/EtOAc, 1:2) to give deprotected lactone **41** (0.007 g, 63%) as a colorless oil; R_f = 0.26 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{21}$ = –69.1 (*c* = 1.7, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H, 10-CH_3), 1.24 (s, 3 H, 6-CH_3), 1.55–1.66 (m, 4 H, 4-H, 5-H), 1.82 (s, 3 H, 12-CH_3), 2.13 (s, 3 H, OAc), 2.52–2.63 (m, 3 H, 2-H, 10-H), 3.72 (br. s, 1 H, 3-H), 5.13–5.21 (m, 2 H, 7-H, 9-H), 5.27 (d, *J* = 10.6 Hz, 1 H, 11-H), 5.87 (dd, *J* = 15.4, 2.3 Hz, 1 H, 8-H), 6.46 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (10-CH_3), 19.0 (12-CH_3), 21.0 (OAc), 24.8 (6-CH_3), 29.9 (C-4), 36.1 (C-5), 38.7 (C-10), 40.7 (C-2), 69.4 (C-3), 74.1 (C-13), 77.7 (C-6), 80.4 (C-7), 83.9 (C-11), 127.4 (C-8), 130.0 (C-9), 143.6 (C-12), 169.7 (C=O), 171.8 (C-1) ppm. HRMS (ESI): calcd. for $C_{18}H_{27}IO_6$ $[M + Na]^+$ 489.074453; found 489.074137.

7-*epi*-Pladienolide B (42): To a solution of $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Ph_3As (5 g, 0.017 mmol), LiCl (0.9 mg, 0.021 mmol), and vinylstannane **39** (11 mg, 0.023 mmol) in degassed NMP (0.4 mL) was added a solution of lactone **41** (7 mg, 0.015 mmol) in NMP (0.4 mL). The resulting green reaction mixture was stirred at room temp. for 24 h. Then $Pd_2(dba)_3$ (1 mg, 0.001 mmol) and Ph_3As (5 mg, 0.017 mmol) were added again, and the mixture was stirred for an additional 24 h. The reaction was quenched by the addition of H_2O (0.5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3× 0.5 mL). The combined organic layers were washed with a saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/EtOAc, 3:7) to afford 7-*epi*-pladienolide B (**42**, 2.2 mg, 18%) as a white oil; R_f = 0.20 (*n*-hexane/EtOAc, 3:7). $[\alpha]_D^{27}$ = +2.3 (*c* = 0.05, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.86 (d, *J* = 6.8 Hz, 3 H, 10-CH_3), 0.89 (d, *J* = 7.1 Hz, 3 H, 20-H), 0.93 (t, *J* = 7.5 Hz, 3 H, 23-H), 1.08 (d, *J* = 6.8 Hz, 3 H, 16-CH_3), 1.16–1.21 (m, 1 H, 20-H), 1.19 (s, 3 H, 6-CH_3), 1.42–1.53 (m, 6 H, 4-H, 5-H, 17-H, 22-H), 1.60–1.68 (m, 2 H, 4-H, 17-H), 1.74 (s, 3 H, 12-CH_3), 2.12 (s, 3 H, OAc), 2.44–2.57 (m, 3 H, 2-H, 16-H), 2.56–2.66 (m, 1 H, 10-H), 2.62–2.66 (m, 1 H, 19-H), 2.70–2.73 (m, 1 H, 18-H), 3.43–3.53 (m, 1 H, 21-H), 3.73–3.79 (m, 1 H, 3-H), 4.99 (d, *J* = 10.6 Hz, 1 H, 11-H), 5.17 (s, 1 H, 7-H), 5.23 (ddd, *J* = 15.5, 9.7, 2.0 Hz, 1 H, 9-H), 5.64 (dd, *J* = 15.0, 8.5 Hz, 1 H, 15-H), 5.87 (dd, *J* = 15.4, 2.5 Hz, 1 H, 8-H), 6.08 (d, *J* = 10.9 Hz, 1 H, 13-H), 6.32 (dd, *J* = 14.6, 10.9 Hz, 1 H, 14-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 10.8 (20-CH_3), 10.9 (12-CH_3), 11.9 (C-23), 17.2 (10-CH_3), 20.9 (OAc), 21.7 (16-CH_3), 24.6 (6-CH_3), 28.6 (C-22), 30.8 (C-4), 36.7 (C-16), 37.2 (C-5), 40.7 (C-2), 40.7 (C-17), 41.7 (C-10), 42.8 (C-20), 58.5 (C-18), 63.0 (C-19), 70.8 (C-3), 74.6 (C-6), 75.3 (C-21), 79.3 (C-7), 84.3 (C-11), 125.9 (C-14), 128.1 (C-8), 132.0 (C-13), 132.2 (C-9), 132.8 (C-12), 142.2 (C-15), 171.6 (C=O), 171.9 (C-1) ppm. HRMS (ESI): calcd. for $C_{30}H_{48}O_8$ $[M + Na]^+$ 559.32414; found 559.32383.

Methyl (3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-hydroxy-13-iodo-6-[(2-methoxyethoxy)methoxy]-6,10,12-trimethyl-11-[(triethylsilyl)oxy]trideca-8,12-dienoate (43): To a solution of $ZnCl_2$ (1 M in Et_2O, 0.15 mmol) in Et_2O (1 mL) was added $NaBH_4$ (0.010 g, 0.31 mmol) at 0 °C. The resulting mixture was stirred at room temp. for 12 h and then cooled again to –15 °C. Then, a solution of enone **17** (0.030 g, 0.03 mmol) in Et_2O (0.8 mL) was added dropwise to the $Zn(BH_4)_2$ solution. The mixture was stirred at –15 °C overnight and then at –10 °C for an additional 5 h. The mixture was then treated with a saturated NH_4Cl solution (0.5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3× 0.5 mL). The combined organic layers were washed with a saturated NaCl solution, dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 5:1) delivered the desired allylic alcohol **43** (0.023 g, 68%; *dr* 4:1, determined by mass after separation of the isomers) as a colorless oil; R_f = 0.18 (petroleum ether/Et_2O, 2:1). $[\alpha]_D^{25}$ = –16.0 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.54 [q, *J* = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.85 [s, 9 H, $C(CH_3)_3$], 0.89–0.93 [m, 12 H, 10-CH_3, $Si(CH_2CH_3)_3$], 1.11 (s, 3 H, 6-CH_3), 1.48–1.63 (m, 3 H, 4-H, 5-H), 1.73 (d, *J* = 1.0 Hz, 3 H, 12-CH_3), 1.76–1.86 (m, 1 H, 5-H), 2.26–2.35 (m, 1 H, 10-H), 2.42–2.44 (m, 2 H, 2-H), 3.37 (s, 3 H, OCH_3), 3.54 (t, *J* = 4.4 Hz, 2 H, $OCH_2CH_2OCH_3$), 3.64 (s, 3 H, 1-OCH_3), 3.66–3.73 (m, 1 H, $OCH_2CH_2OCH_3$), 3.75–3.82 (m, 1 H, $OCH_2CH_2OCH_3$), 3.90 (d, *J* = 6.32 Hz, 1 H, 11-H), 4.01 (d, *J* = 7.1 Hz, 1 H, 7-H), 4.11–4.16 (m, 1 H, 3-H), 4.72 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 4.86 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 5.38 (dd, *J* = 15.4, 6.8 Hz, 1 H, 8-H), 5.72 (dd, *J* = 15.4, 7.5 Hz, 1 H, 9-H), 6.10 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.4 [$Si(CH_3)_2$], 4.7 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)_3$], 15.3 (10-CH_3), 18.0 [$C(CH_3)_3$], 20.2 (12-CH_3), 20.5 (6-CH_3), 25.8 [$C(CH_3)_3$], 29.1 (C-4), 30.9 (C-5), 41.0 (C-2), 42.3 (C-10), 51.4 (1-OCH_3), 59.0 (OCH_3), 65.9 (C-3), 67.6 ($OCH_2CH_2OCH_3$), 69.7 ($OCH_2CH_2OCH_3$), 71.7 (C-7), 77.8 (C-11), 78.4 (C-13), 81.4 (C-6), 89.9 (OCH_2O), 128.2 (C-8), 135.5 (C-12), 149.3 (C-9), 172.3 (C-1) ppm. HRMS (ESI): calcd. for $C_{33}H_{65}IO_8Si_2$ $[M + Na]^+$ 795.315487; found 795.315977.

Methyl (3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-7-(Acetyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-13-iodo-6-[(2-methoxyethoxy)methoxy]-6,10,12-trimethyl-11-[(triethylsilyl)oxy]trideca-8,12-dienoate (44): Alcohol **43** (0.075 g, 0.097 mmol) was dissolved in CH_2Cl_2 (0.5 mL), and DMAP (0.174 g, 0.467 mmol), Et_3N (0.016 mL, 0.116 mmol) and Ac_2O (0.014 mL, 0.145 mmol) were added. The resulting reaction mixture was stirred at room temp. for 2 h. Afterwards, a saturated $NaHCO_3$ solution (1 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3× 1 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/Et_2O, 3:1) to obtain the desired acetate **44** (0.078 g, 99%) as colorless oil; R_f = 0.26 (petroleum ether/Et_2O, 2:1). $[\alpha]_D^{26}$ = +6.7 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.53 [q, *J* = 7.8 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.85 [s, 9 H, $C(CH_3)_3$], 0.88–0.92 [m, 12 H, 10-CH_3, $Si(CH_2CH_3)_3$], 1.17 (s, 3 H, 6-CH_3), 1.34–1.41 (m, 1 H, 5-H), 1.56–1.66 (m, 3 H, 4-H, 5-H), 1.72 (d, *J* = 0.7 Hz, 3 H, 12-CH_3), 2.04 (s, 3 H, OAc), 2.28–2.32 (m, 1 H, 10-H), 2.36–2.48 (m, 2 H, 2-H), 3.37 (s, 3 H, OCH_3), 3.51 (t, *J* = 4.7 Hz, 2 H, $OCH_2CH_2OCH_3$), 3.60–3.74 (m, 2 H, $OCH_2CH_2OCH_3$), 3.65 (s, 3 H, 1-OCH_3), 3.89 (d, *J* = 6.3 Hz, 1 H, 11-H), 4.08–4.15 (m, 1 H, 3-H), 4.69 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 4.86 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 5.27 (d, *J* = 6.6 Hz, 1 H, 7-H), 5.38–5.44 (m, 1 H, 8-H), 5.71–5.76 (m, 1 H, 9-H), 6.09 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 4.7 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)_3$], 16.3 (10-CH_3), 17.9 [$C(CH_3)_3$], 20.1 (OAc), 20.2 (12-CH_3), 21.2 (6-CH_3), 25.7 [$C(CH_3)_3$], 30.8 (C-4), 31.1 (C-5), 40.9 (C-2), 42.4 (C-10), 51.5 (1-OCH_3), 59.0 (OCH_3), 67.0 ($OCH_2CH_2OCH_3$), 69.5 (C-3), 71.8 ($OCH_2CH_2OCH_3$), 77.6 (C-7), 78.6 (C-11), 78.7 (C-13), 81.3 (C-6), 90.1 (OCH_2O), 124.5 (C-8), 136.7 (C-9), 149.2 (C-12), 169.7 (OAc), 172.1 (C-1) ppm. HRMS (ESI): calcd. for $C_{35}H_{67}IO_9Si_2$ $[M + Na]^+$ 837.326051; found 837.326287.

(3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-7-(Acetyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-13-iodo-6-[(2-methoxyethoxy)methoxy]-6,10,12-trimethyl-11-[(triethylsilyl)oxy]trideca-8,12-dienoic Acid (45): To a solution of ester **44** (0.078 g, 0.038 mmol) in 1,2-dichloroethane (1 mL) was added Me_3SnOH (0.129 g, 0.715 mmol). After stirring the mixture at 80 °C overnight, it was diluted with a $KHSO_4$ solution (5% in water, 0.5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/EtOAc, 3:1) gave acid **45** (0.050 g, 66%) as a colorless oil; R_f = 0.17 (petroleum ether/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 [s, 3 H, $Si(CH_3)_2$], 0.08 [s, 3 H, $Si(CH_3)_2$], 0.53 [q, J = 8.0 Hz, 6 H, $Si(CH_2CH_3)_3$], 0.87 [s, 9 H, $C(CH_3)_3$], 0.88–0.92 [m, 12 H, 10-CH_3, $Si(CH_2CH_3)_3$], 1.18 (s, 3 H, 6-CH_3), 1.34–1.42 (m, 1 H, 5-H), 1.52–1.57 (m, 3 H, 4-H, 5-H), 1.72 (s, 3 H, 12-CH_3), 2.04 (s, 3 H, OAc), 2.26–2.35 (m, 1 H, 10-H), 2.49 (d, J = 5.6 Hz, 2 H, 2-H), 3.37 (s, 3 H, OCH_3), 3.52 (t, J = 4.7 Hz, 2 H, $OCH_2CH_2OCH_3$), 3.59–3.64 (m, 1 H, $OCH_2CH_2OCH_3$), 3.71–3.76 (m, 1 H, $OCH_2CH_2OCH_3$), 3.89 (d, J = 6.6 Hz, 1 H, 11-H), 4.07–4.13 (m, 1 H, 3-H), 4.68 (d, J = 7.8 Hz, 1 H, OCH_2O), 4.87 (d, J = 7.6 Hz, 1 H, OCH_2O), 5.27 (d, J = 6.8 Hz, 1 H, 7-H), 5.37–5.44 (m, 1 H, 8-H), 5.71–5.77 (m, 1 H, 9-H), 6.09 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.5 [$Si(CH_3)_2$], 4.7 [$Si(CH_2CH_3)_3$], 6.8 [$Si(CH_2CH_3)_3$], 16.4 (10-CH_3), 17.7 [$C(CH_3)_3$], 17.9 (OAc), 20.1 (12-CH_3), 21.2 (6-CH_3), 25.7 [$C(CH_3)_3$], 30.5 (C-4), 31.3 (C-5), 40.9 (C-2), 41.7 (C-10), 59.0 (OCH_3), 67.1 ($OCH_2CH_2OCH_3$), 69.6 (C-3), 71.8 ($OCH_2CH_2OCH_3$), 77.6 (C-7), 78.6 (C-11), 78.7 (C-13), 81.3 (C-6), 90.1 (OCH_2O), 124.4 (C-8), 137.0 (C-9), 145.1 (C-12), 169.7 (OAc), 170.5 (C-1) ppm.

(3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-7-(Acetyloxy)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-11-hydroxy-13-iodo-6-[(2-methoxyethoxy)methoxy]-6,10,12-trimethyltrideca-8,12-dienoic Acid (46): To a solution of *seco* acid **45** (0.050 g, 0.062 mmol) in CH_3CN/H_2O (10:1, 0.7 mL) was added DDQ (0.016 g, 0.069 mmol) at –5 °C. The mixture was stirred for 5 min and was then subsequently warmed to 0 °C. After stirring at 0 °C for 2.5 h, a saturated $NaHCO_3$ solution (0.5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 0.5 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 2:1) delivered the desired hydroxy acid **46** (0.03 g, 74%) as a colorless oil; R_f = 0.26 (petroleum ether/EtOAc, 2:1). $[\alpha]_D^{26}$ = +33.6 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 [s, 3 H, $Si(CH_3)_2$], 0.08 [s, 3 H, $Si(CH_3)_2$], 0.87 [s, 9 H, $C(CH_3)_3$], 0.88–0.90 (m, 3 H, 10-CH_3), 1.22 (s, 3 H, 6-CH_3), 1.54–1.64 (m, 3 H, 4-H, 5-H), 1.67–1.75 (m, 1 H, 5-H), 1.79 (d, J = 1.0 Hz, 3 H, 12-CH_3), 2.06 (s, 3 H, OAc), 2.30–2.39 (m, 1 H, 10-H), 2.49 (d, J = 5.6 Hz, 2 H, 2-H), 3.37 (s, 3 H, OCH_3), 3.52 (t, J = 4.7 Hz, 2 H, $OCH_2CH_2OCH_3$), 3.61–3.66 (m, 1 H, $OCH_2CH_2OCH_3$), 3.70–3.75 (m, 1 H, $OCH_2CH_2OCH_3$), 3.84 (d, J = 8.1 Hz, 1 H, 11-H), 4.03–4.08 (m, 1 H, 3-H), 4.73 (d, J = 7.6 Hz, 1 H, OCH_2O), 4.87 (d, J = 7.6 Hz, 1 H, OCH_2O), 5.19 (d, J = 6.1 Hz, 1 H, 7-H), 5.53–5.64 (m, 1 H, 8-H, 9-H), 6.22 (s, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9 [$Si(CH_3)_2$], –4.6 [$Si(CH_3)_2$], 16.6 (10-CH_3), 17.9 [$C(CH_3)_3$], 19.3 (OAc), 19.9 (12-CH_3), 21.3 (6-CH_3), 25.7 [$C(CH_3)_3$], 30.5 (C-4), 31.3 (C-5), 40.8 (C-2), 41.7 (C-10), 59.0 (OCH_3), 67.1 ($OCH_2CH_2OCH_3$), 69.5 (C-3), 71.8 ($OCH_2CH_2OCH_3$), 77.2 (C-7), 78.7 (C-13), 80.2 (C-11), 83.3 (C-6), 90.2 (OCH_2O), 126.6 (C-8), 137.2 (C-9), 148.1 (C-12), 170.0 (OAc), 178.0 (C-1) ppm. HRMS (ESI): calcd. for $C_{28}H_{51}IO_9Si$ $[M + Na]^+$ 709.223924; found 709.223603.

(3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-Macrolactone 47: To a stirred solution of MNBA (0.023 g, 0.068 mmol) and DMAP (0.013 g, 0.108 mmol) in CH_2Cl_2 (4.5 mL) was added a solution of *seco* acid **46** (0.31 g, 0.045 mmol) in CH_2Cl_2 (12 mL) at room temp. over a period of 12 h through a syringe pump. Thereafter, a saturated $NaHCO_3$ solution (5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative TLC (petroleum ether/EtOAc, 2:1) delivered the desired macrolactone **47** (0.014 g, 46%) as colorless oil; R_f = 0.26 (petroleum ether/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 [s, 3 H, $Si(CH_3)_2$], 0.06 [s, 3 H, $Si(CH_3)_2$], 0.87–0.89 [m, 12 H, $C(CH_3)_3$, 10-CH_3], 1.28 (s, 3 H, 6-CH_3), 1.35–1.70 (m, 4 H, 4-H, 5-H), 1.78 (d, J = 1.0 Hz, 3 H, 12-CH_3), 2.05 (s, 3 H, OAc), 2.36–2.52 (m, 3 H, 2-H, 10-H), 3.38 (s, 3 H, OCH_3), 3.55 (t, J = 4.7 Hz, 2 H, $OCH_2CH_2OCH_3$), 3.68–3.73 (m, 1 H, $OCH_2CH_2OCH_3$), 3.77–3.84 (m, 2 H, $OCH_2CH_2OCH_3$, 3-H), 4.85 (d, J = 7.6 Hz, 1 H, OCH_2O), 5.02–5.10 (m, 3 H, $OCH_2CH_2OCH_3$, 7-H, 11-H), 5.55–5.64 (m, 1 H, 9-H), 5.66–5.74 (m, 1 H, 8-H), 6.44 (d, J = 1.0 Hz, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 [$Si(CH_3)_2$], 16.3 (10-CH_3), 18.1 [$C(CH_3)_3$], 19.1 (12-CH_3), 19.8 (OAc), 21.3 (6-CH_3), 25.8 [$C(CH_3)_3$], 30.4 (C-4), 35.4 (C-5), 40.2 (C-2), 40.5 (C-10), 59.0 (OCH_3), 66.7 ($OCH_2CH_2OCH_3$), 70.2 (C-3), 71.8 ($OCH_2CH_2OCH_3$), 78.8 (C-7), 79.1 (C-6), 80.3 (C-11), 83.8 (C-13), 90.4 (OCH_2O), 125.8 (C-8), 140.0 (C-9), 143.7 (C-12), 168.4 (OAc), 170.2 (C=O) ppm. HRMS (ESI): calcd. for $C_{28}H_{49}IO_8Si$ $[M + Na]^+$ 691.213360; found 691.213516.

(3*R*,6*R*,7*S*,8*E*,10*S*,11*S*,12*E*)-Macrolactone 48: To a solution of lactone **47** (10 mg, 0.015 mmol) in THF (0.2 mL) and AcOH (0.3 mL) was added dropwise aqueous HCl (2 M, 0.2 mL). The resulting reaction mixture was stirred at room temp. for 1.5 h. Thereafter, a saturated NaCl solution (0.3 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 0.2 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by preparative TLC (petroleum ether/EtOAc, 1:2) to give deprotected lactone **48** (6.5 mg, 93%) as a colorless oil; R_f = 0.28 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{19}$ = –43.7 (c = 0.54, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.8 Hz, 3 H, 10-CH_3), 1.20 (s, 3 H, 6-CH_3), 1.27–1.41 (m, 2 H, 4-H), 1.47–1.54 (m, 1 H, 5-H), 1.65–1.73 (m, 1 H, 5-H), 1.81 (d, J = 0.8 Hz, 3 H, 12-CH_3), 2.08 (s, 3 H, OAc), 2.45–2.55 (m, 2 H, 2-H, 10-H), 2.61–2.66 (m, 1 H, 2-H), 3.40 (d, J = 10.6 Hz, 1 H, OH), 3.72–3.78 (m, 1 H, 3-H), 5.05 (d, J = 9.4 Hz, 1 H, 7-H), 5.29 (d, J = 10.6 Hz, 1 H, 11-H), 5.57 (dd, J = 15.3, 9.6 Hz, 1 H, 9-H), 5.67 (dd, J = 15.3, 9.6 Hz, 1 H, 8-H), 6.47 (d, J = 1.0 Hz, 1 H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (10-CH_3), 19.0 (12-CH_3), 21.3 (OAc), 24.6 (6-CH_3), 29.7 (C-4), 35.1 (C-5), 38.2 (C-10), 40.9 (C-2), 59.0 (OCH_3), 69.1 (C-3), 73.3 (C-13), 78.7 (C-6), 80.2 (C-11), 84.2 (C-7), 126.1 (C-8), 139.6 (C-9), 143.3 (C-12), 169.6 (C=O), 170.2 (C-1) ppm. HRMS (ESI): calcd. for $C_{18}H_{27}IO_6$ $[M + Na]^+$ 489.07445; found 489.07394.

Pladienolide B (1): To a solution of $Pd_2(dba)_3$ (1 mg, 0.001 mmol), Ph_3As (5 mg, 0.015 mmol), and LiCl (0.8 mg, 0.019 mmol) in degassed NMP (0.7 mL) was added a solution of lactone **48** (6.5 mg, 0.014 mmol) in NMP (1.0 mL). Thereafter, a solution of vinylstannane **39** (10.0 mg, 0.021 mmol) in NMP (0.5 mL) was added dropwise. The resulting green solution was stirred at room temp. for 24 h, and then additional $Pd_2(dba)_3$ (1 mg, 0.001 mmol) and Ph_3As (5 mg, 0.015 mmol) were added. After the reaction mixture was stirred at room temp. for a total of 41 h, H_2O (1 mL) was added, and the layers were separated. The aqueous layer was ex-

tracted with EtOAc (3 × 0.5 mL), and the combined organic layers were washed with a saturated NaCl solution (0.5 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by preparative TLC (*n*-hexane/EtOAc, 3:7) to give pladienolide B (**1**, 2.5 mg, 33%) as a white oil; R_f = 0.25 (*n*-hexane/EtOAc, 3:7). $[\alpha]_D^{27}$ = +20.4 (*c* = 0.12, CH_3OH); ref.[10] $[\alpha]_D^{27}$ = +7.90 (*c* = 1.10, MeOH); ref.[12] $[\alpha]_D^{25}$ = +7.18 (*c* = 0.68, MeOH); ref.[11] $[\alpha]_D^{20}$ = +7.3 (*c* = 0.26, MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.87 (d, *J* = 6.8 Hz, 3 H, 10-CH_3), 0.89 (d, *J* = 7.1 Hz, 3 H, 20-CH_3), 0.93 (t, *J* = 7.5 Hz, 3 H, 23-H), 1.07 (d, *J* = 6.8 Hz, 3 H, 16-H), 1.14–1.20 (m, 1 H, 20-H), 1.18 (s, 3 H, 6-CH_3), 1.30–1.39 (m, 2-H, 4-H, 5-H), 1.41–1.53 (m, 3 H, 17-H, 22-H), 1.55–1.66 (m, 3 H, 4-H, 5-H, 17-H), 1.74 (s, 3 H, 12-CH_3), 2.05 (s, 3 H, OAc), 2.43–2.59 (m, 1 H, 16-H), 2.51 (d, *J* = 3.8 Hz, 2 H, 2-H), 2.54–2.59 (m, 1 H, 10-H), 2.65 (dd, *J* = 8.1, 2.3 Hz, 1 H, 19-H), 2.71 (ddd, *J* = 5.9, 2.3 Hz, 1 H, 18-H), 3.50 (ddd, *J* = 8.5, 4.6, 4.4 Hz, 1 H, 21-H), 3.79–3.79 (m, 1 H, 3-H), 5.04 (d, *J* = 9.9 Hz, 2 H, 7-H, 11-H), 5.55 (dd, *J* = 15.3, 9.9 Hz, 1 H, 9-H), 5.65 (dd, *J* = 15.9, 9.1 Hz, 1 H, 15-H), 5.69 (dd, *J* = 15.4, 9.7 Hz, 1 H, 8-H), 6.08 (d, *J* = 10.9 Hz, 1 H, 13-H), 6.32 (dd, *J* = 15.0, 10.7 Hz, 1 H, 14-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 10.8 (20-CH_3), 10.9 (12-CH_3), 11.9 (C-23), 16.9 (10-CH_3), 21.1 (OAc), 21.7 (16-CH_3), 24.2 (6-CH_3), 28.6 (C-22), 30.4 (C-4), 36.7 (C-16), 37.5 (C-5), 40.1 (C-2), 40.7 (C-17), 41.8 (C-10), 42.8 (C-20), 58.5 (C-18), 63.0 (C-19), 70.4 (C-3), 74.1 (C-6), 75.3 (C-21), 80.3 (C-7/11), 84.3 (C-7/11), 125.9 (C-14), 127.1 (C-8), 132.2 (C-13), 132.4 (C-12), 141.7 (C-9), 142.4 (C-15), 171.7 (C=O), 172.2 (C-1) ppm. HRMS (ESI): calcd. for $C_{30}H_{48}O_8$ $[M + Na]^+$ 559.32414; found 559.32401.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra are provided for all key intermediates and final products. Additional information as needed.

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