Total Synthesis of (−)−Callipeltoside A

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A Total Synthesis of (−)-Callipeltoside A

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Abstract
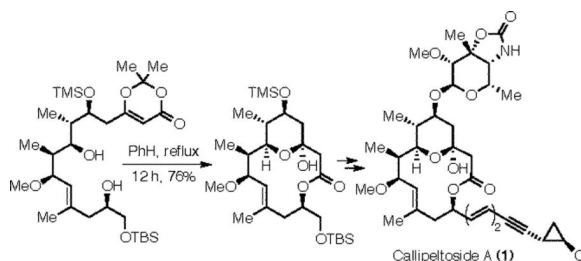
A total synthesis of (−)-callipeltoside A (**1**) has been achieved. The core macrocycle was made via a dual macrolactonization/pyran hemiketal formation reaction, which was developed to circumvent issues related to the reversible nature of acylketene formation from β-keto lactone substrates. Initial approaches to the core of the natural product that revolved around ring-closing metathesis (RCM) and relay ring-closing metathesis (RRCM) reactions are also described.

Introduction

Callipeltoside A (**1**) is a cytotoxic macrolide isolated in 1996 from the marine lithistida sponge (*Callipelta* sp.).[1] The stereochemical features of callipeltoside A were deduced on the basis of extensive NMR studies. When we initiated the research described here, issues still remained with respect to i) the absolute configuration and ii) the relative configuration of C(13) and C(20)/C(21) vis-à-vis those in the remainder of the molecule. The relative configuration of C(13) was established by Paterson and coworkers.[2] The first total synthesis, which established the remaining relative configurational issues of C(20)/C(21) as well as the overall absolute configuration of (−)-callipeltoside A (**1**) was reported by the Trost labs in 2002.[3a] Additional total syntheses have been reported,[3b–g] and numerous related studies have appeared.[4]

Results/Discussion

Our approach to **1** involved a convergent union of the three key intermediates: macrolactone **2**, carbohydrate **3**, and phosphonate **4** (Scheme 1). Our initial approach to the synthesis of **2** aimed to utilize a RCM reaction from a suitable precursor, such as **5**.[5] Unfortunately, neither **5** or its C(13) epimer (**epi-5**) could be ring-closed to give a macrocyclic product (Scheme 2). Using Grubbs' first generation metathesis initiator (**7**),[6] no initiation was observed at room temperature, as evidenced by lack of styrene formation by analysis of the NMR spectrum and recovery of starting material. Attempts to alter the reactivity of the substrate by using a more constrained, and perhaps geometrically favorable, conformer (cf. **6**) also failed.[7] At

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elevated temperatures (50–70 °C, benzene solvent) the catalyst [either **7** or the second generation initiator (**8**)][8] decomposed and starting material (**5**–**6**) could be recovered.

Believing that the main problem with the lack of reactivity of substrates **5** and **6** was due to slow initiation, we hypothesized that the use of a relay strategy would be advantageous.[5b,9] The concept, outlined in Scheme 3, was to use allyloxymethyl relays on substrates **9** and **10**. Ruthenium loading onto the terminal alkene of the relay was envisioned to give intermediates **11** and **12**. Intramolecular cyclization of each would give **13** or **14**, respectively, with concomitant formation of 3,4-dihydrofuran. Finally, cyclization of **13** and **14** would give the desired β-keto lactone **15** and regenerate a ruthenium methylidene as the active catalyst. Since we had no way of knowing whether intermediate **13** or **14** would be more likely to macrocyclize, we chose to undertake the synthesis of both substrates **9** and **10**.

The synthesis of relay substrate **9** is outlined in Scheme 4. Known Weinreb amide **16** was protected as a PMB ether using PMB-trichloroacetimidate and catalytic CSA.[10] Hydroboration/oxidation (9-BBN), followed by TBS protection and DIBAL-H reduction of the Weinreb amide gave aldehyde **17**. Lithium-halogen exchange of alkenyl iodide **18** followed by addition to aldehyde **17** gave a 1:1.5 ratio of newly formed secondary alcohols. Subsequent methylation with methyl iodide gave the relay-armed substrate **19**. Deprotection of the primary TBS ether using TBAF, oxidation with Dess-Martin periodinane, vinylogous Mukaiyama aldol reaction with diene **20**[,11] and TMS protection gave dioxinone substrate **21**. Refluxing this substrate in benzene with secondary alcohol **22**[,12] followed by TMS deprotection with PPTS in acetonitrile gave **9**.

The synthesis of the alternative relay substrate **10** is outlined in Scheme 5. The allyl ether of known bromo alkene **23**[13] was used, after lithium-halogen exchange (cat. CuI), to ring-open the TBS protected epoxide **24**[14] to give relay-armed alcohol **25**. Aldehyde **17** was elaborated by addition of vinyl magnesium bromide, giving a separable mixture of diastereomeric (dr 1:1) alcohols. Methylation with methyl iodide, TBAF deprotection, and oxidation with Dess-Martin periodinane gave aldehyde **26**. The vinylogous Mukaiyama aldol reaction of **26** with diene **20** and TMS protection of the C(5)-hydroxyl gave dioxinone **27**. Refluxing a mixture of alcohol **25** and dioxinone **27** in benzene, followed by TMS deprotection, gave relay substrate **10**.

Unfortunately for our cause, subjection of either **9** or **10** to the metathesis initiator **8** did not lead to the formation of desired product **15**, but instead gave **5**, the substrate for the initial RCM study. The process leading to **5** is outlined in Scheme 6; an event we refer to as truncation. When metathesis initiator **8** reacts with **10**, the relay to produce **28** presumably proceeds as planned, as evidenced by formation of 3,4-dihydrofuran (^{1}H NMR). In order for macrocyclic ring closure to occur within **28**, the rate of its intramolecular cyclization (k_{intra}) must be faster than the rate of bimolecular attack on the more reactive alkene in another molecule of **10** (k_{inter}). Since truncation is bimolecular, we recognized that running the reaction at higher dilution would result in a more favorable k_{intra}/k_{inter} ratio, but even at 10^{-5} M, only the truncation product **5** was observed.[7]

We examined other ways to favorably bias the ratio of k_{intra} to k_{inter} during this RRCM reaction. Since disubstituted alkenes are slower to engage in cross-metathesis (CM), it was hoped that using a 1,1-disubstituted alkene within the relay arm would slow the bimolecular truncation rate sufficiently so that macrocyclization could prevail. To this end, substrates **29** and **30** (Scheme 7) were synthesized in an analogous manner. While our reasoning was apparently sound, as evidenced by a significantly slower overall rate of reaction, no desired product was formed using these substrates having the modified relay subunit. Instead the

truncation products **5** and **6** were observed, respectively. The clear implication is that the initial relay event occurred to deliver ruthenium to the more hindered carbon atom of the otherwise inactive alkene. As these results illustrate, the use of a RRCM strategy by no means guarantees a successful outcome. If the inherent rate of the crucial metathesis cyclization event is slower than competing events (e.g, CM or [Ru] decomposition), as is the case here, then the cyclization will not be efficient regardless of the process by which the key ruthenium alkylidene intermediate is formed.[9c]

We then turned to a strategy in which the Boeckman lactonization[15] of an acylketene intermediate would be used to close the core macrocycle.[5b] This strategy formed the bases of both the Trost synthesis of **1**[3a,c] and the Marshall synthesis[16] of the aglycone. Reaction of the TBS protected epoxide **31** with lithium TMS-acetylide, followed by a two-step deprotection gave diol **32**.[17,18] Negishi carboalumination/iodination[19] and sequential protection of the 1,2-diol as TBS and PMB ethers gave **33**. Lithium-halogen exchange in **33** and addition to aldehyde **34** gave a 1:1 mixture of separable secondary alcohols.[20] Recycling of the undesired epimer by oxidation with Dess-Martin periodinane, followed by reduction with lithium triethylhydridoborate gave the desired epimer in a 10:1 dr. Subsequent methylation gave alkene **35**, which was subjected to hydroboration/oxidation (9-BBN). The resulting primary alcohol was subjected to Dess-Martin periodinane oxidation and vinylogous Mukaiyama aldol reaction with diene **20**. Each of the two new stereocenters at C(5) and C(6) were formed with essentially full diastereocontrol. Protection of the C(5)-OH with MOMCl and PMB removal at C(13) with DDQ gave the lactonization precursor **36**.

The dioxinone-containing substrate **36** was heated in refluxing toluene to effect thermal extrusion of acetone and concomitant generation of the acylketene **37**. Macrolactonization involves cylization of the C(13) hydroxyl group to give enol **38**. Two products were isolated: the keto lactone **39** and the methyl ketone **40** (64% and 15%, respectively) (Scheme 9). The latter arises from competitive addition of water to **37** and subsequent decarboxylation of the resulting β-ketoacid, a phenomenon that has been observed by others.[21] The relative amount of **40** increased over time. This suggests that the unimolecular lactonization of the acylketene **37** outcompetes its trapping by water and that the ketolactone **39** is able to revert via **38** to acylketene **37**.[22] While concentration effects are undoubtedly also important, it is relevant that i) addition of an O–H bond to an acylketene is a concerted event (cf., **37** to **38**)[23] and ii) the O–H bond dissociation energy of water is substantially higher than those of alcohols (119 vs. 104–107 kcal mol^{-1}).[24] We hypothesized that the detrimental outcome of competitive water addition could be mitigated if the β-ketone in a macrolactone like **39** could be sequestered. An attractive possibility was that it be trapped as its corresponding pyran-hemiketal by a free hydroxyl group at C(7).[22]

To test this idea, we elected to prepare diol **43** (Scheme 10).[25] Thus, the vinyllithium species derived from **ent-33** was added to aldehyde **41** to give a 1:1 ratio of diols. Separation and methylation with methyl iodide gave alkene **42**. Hydroboration/oxidation, Dess-Martin oxidation, and vinylogous Mukaiyama aldol reaction with diene **20** was performed. Protection of the resulting secondary alcohol, followed by DDQ removal of both PMB ethers afforded the dioxinone diol **43**.

To our delight, when refluxed in benzene for 12 hours, dioxinone **43** produced the desired dual macrocyclic pyran-hemiketal **44** in 76% yield (Scheme 11). We suspect that pyran-hemiketal formation within either enol **46** or ketone **47** follows macrolactonization (**45** to **46**). It is noteworthy that no products indicative of competitive trapping of the acylketene **45** by water could be detected (and no 8-membered lactone from reaction of the C(7)-OH with the ketene carbon was observed). It is clear that in situ protection of the C(3)-ketone as its hemiketal is advantageous.[22]

The completion of the synthesis, following established lines, is outlined in Scheme 12. A three-step protecting group manipulation was used to convert **44** into **48**. Parikh-Doerin'g oxidation afforded the corresponding aldehyde, from which aglycone **49** was obtained by Horner-Emmons olefination with the known phosphonate **4,**[26] followed by deprotection of the TMS ether at C(5). Glycosidation[3a] with known acetimidate **3**[27] provided (−)-callipeltoside A (**1**).

In conclusion, we have completed a total synthesis of (−)-callipeltoside A (**1**). Initial attempts using an RCM reaction on substrates **5** and **6** were not successful; presumably these compounds are simply too hindered to load ruthenium to the requisite (and more hindered) alkene carbon atom. This led to the evolution of the RRCM strategy, which was explored via substrates **9, 10, 29**, and **30**. In each case, relay activation allowed ruthenium to be transiently installed to the necessary site (cf. **13, 14**, and **28**), but bimolecular truncation of these species thwarted the (inherently slow) final ring-closing event. Ultimately, the synthesis of **1** (20 linear steps from TBS-glycidol **24**, 0.7% yield) was enabled by a highly efficient acylketene mediated dual macrolactonization/pyran-hemiketal formation reaction, converting the linear precursor **43** directly to the bridged bicyclic macrolactone **44**.

Experimental Section

General. ^{1}H NMR chemical shifts in CDCl$_3$ are referenced to TMS (0.00 ppm) and in PhH-d_6 to 7.16. ^{13}C NMR chemical shifts in CDCl$_3$ are referenced to chloroform (77.2 ppm). The following format has been used to report peaks: chemical shift in ppm [multiplicity, coupling constant(s) in Hz, integral]. MPLC refers to medium pressure liquid chromatography (25–60 psi) using hand-packed columns of E. Merck silica gel (230–400 mesh), a pump, and a differential refractive index detector. Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in oven-dried glassware. Dry diethyl ether and benzene were distilled from sodium benzophenone ketyl. Toluene was distilled from Na/K. Anhydrous THF and methylene chloride were passed through a column of activated alumina. Triethylamine and pyridine were distilled from KOH just prior to use. DMF was stored over 4 Angstrom molecular sieves. The structure of each intermediate numbered here as **S##** can be found in the Supporting Information.

(+)-(2*S*)-4-Pentyne-1,2-diol (32)[28]

To epoxide **31** (13.3 g, 71.0 mmol), TMS-acetylene (15 mL, 106.0 mmol), and THF (141 mL) was added *n*-BuLi (3.2 M in hexanes, 40.0 mL, 92.0 mmol) dropwise at −78 °C, followed by BF$_3$•OEt$_2$ (13.4 mL, 106.0 mmol) dropwise at the same temperature. The solution was stirred for 45 min at −78 °C before being quenched with aqueous NH$_4$Cl (20 mL). The mixture was allowed to warm to rt and diluted with H$_2$O (150 mL). The aqueous layer was extracted with DCM (3 × 100 mL) and the combined organic portions were dried over Na$_2$SO$_4$ and concentrated to give crude TMS alkyne as a colorless oil. This alkyne was immediately subjected to desilylation. To the crude oil was added K$_2$CO$_3$ (29.3 g, 212 mol) and MeOH (100 mL), and this mixture was stirred for 24 h at rt. The suspended K$_2$CO$_3$ was filtered through celite on a sintered glass funnel with MeOH. The filtrate was concentrated to afford the crude alkyne as a mixture of primary and secondary TBS ethers. The crude products were carried into the next step without purification. To the mixture of alkynes was added MeOH (40 mL), THF (40 mL), and KF (24 g, 420 mmol); and the resulting slurry was refluxed at 65 °C for 48 h. The mixture was cooled to rt, concentrated, placed on a flash column, and purified via flash chromatography (hexanes:EtOAc = 1:1 followed by 100% EtOAc) to provide a pale yellow oil that crystallized in a freezer overnight to afford diol **32** as white needles (3.2 g, 77%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.91 (dddd, *J* = 3.7, 6.2, 6.2, and 6.2 Hz, 1H), 3.77 (dd, *J* = 3.7 and 11.1 Hz, 1H), 3.62 (dd, *J* = 6.2 and 10.0 Hz, 1H), 2.45 (dd, *J* = 2.7 and 6.2 Hz, 2H), 2.35 (bs, 1H), 1.90 (bs, 1H), and 2.08 (t, *J* = 2.7 Hz, 1H). [13]C

NMR (125 MHz, CDCl$_3$) δ 80.3, 70.7, 70.2, 65.3, and 23.2. GC-MS T$_R$ = 2.66 min.; m/z: 100, 69, and 61. IR (neat) 3300, 3292, 2113, 1719, 1416, 1085, and 1044 cm^{-1}. mp 44–51 °C. TLC R$_f$ = 0.35, 100% EtOAc. [α]^{RT} +8.22° (c = 1.1, CHCl$_3$).

(−)-(2*S*,4*E*)-1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-iodo-2-[(4-methoxyphenyl)methoxy]-4-methyl-4-pentene (33)

To zirconocene dichloride (2.5 g, 9.6 mmol) and 1,2-dichloroethane (90 mL) was added AlMe$_3$ (2.0 M in toluene, 36 mL, 72 mmol) dropwise at rt followed by diol **32** (2.4 g, 24 mmol) in 1,2-dichloroethane (20 mL). The solution was stirred at 50 °C for 48 h and then cooled to −40 °C. Iodine (9.1 g, 36 mmol) in THF (26 mL) was added dropwise by cannula. The resulting dark brown solution was allowed to warm and was stirred for 30 min at rt before being poured into a mixture of hexanes and sodium potassium tartrate. The aqueous layer was extracted with EtOAc (1 × 50 mL), saturated with NaCl, and extracted again with EtOAc (3 × 50 mL). The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and chromatographed (100% EtOAc) to provide iodo diol (Rf = 0.13 in 1:1 hexanes:EtOAc) as a pale yellow oil (3.4 g, 58%). The diol (3.0 g, 12.4 mmol) was dissolved in DCM (120 mL) and treated with TEA (7.0 mL, 50.0 mmol), DMAP (230 mg 1.86 mmol), and TBSCl (3.0 g 20.0 mmol). The resulting solution was stirred 24 h at rt before being quenched with aqueous NH$_4$Cl (50 mL), diluted with H$_2$O (100 mL) and extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and chromatographed (hexanes:EtOAc = 19:1) to provide a primary TBS ether (Rf = 0.25 in 9:1 hexanes:EtOAc) as a colorless oil (3.2 g, 72%). To this ether (310 mg, 0.87 mmol) in DCM (5 mL) was added *para*-methoxybenzyl trichloroacetimidate (762 mg, 2.7 mmol) and CSA (46 mg, 0.2 mmol). The reaction mixture was stirred for 48 h before being quenched with aqueous NaOH (10%, 20 mL). The mixture was extracted with DCM, washed with aqueous NaOH (10%, 20 mL), dried over MgSO$_4$, and concentrated. Purification by MPLC (hexanes:EtOAc = 12:1) gave **33** (330 mg, 82%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.97 (broad s, 1H), 4.60 (d, *J* = 11.5 Hz, 1H); 4.46 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.67 (m, 1H), 3.55 (dd, *J* = 5.0 and 8.5 Hz, 1H), 3.52 (dd, *J* = 5.5 and 8.5 Hz, 1H), 2.44 (dd, *J* = 3.5 and 14.0 Hz, 1H), 2.36 (dd, *J* = 8.0 and 13.0 Hz, 1H), 1.78 (broad s, 3H), 0.90 (s, 9H), and 0.06 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 144.9, 130.6, 129.5, 113.8, 77.2, 77.1, 72.0, 65.0, 55.3, 41.8, 25.9, 24.3, 18.3, −5.32, and −5.37. IR (neat) 3063, 3032, 2996, 2958, 2931, 2857, 1612, 1512, and 1250 cm^{-1}. GC-MS TR = 12.6 min.; m/z: 419, 349, and 121. HRMS (CI, 4% NH$_3$ in CH$_4$) Calcd for (C$_{20}$H$_{33}$IO$_3$Si + NH$_4$)$^+$: 494.1582. Found: 494.1579. TLC R$_f$ = 0.3, hexanes:EtOAc = 15:1. [α]^{RT} −15.3° (c = 1.0, CHCl$_3$).

(−)-[3*S*-(3*R**,4*S**,5*S**,9*S**),6*E*]-5-Methoxy-3,9-Bis-[(4-methoxyphenyl)methoxy]-2,4,7-trimethyl-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,6-decadiene (42)

To vinyl iodide ***ent-33*** (600 mg, 1.26 mmol, prepared by the same sequence described above) and diethyl ether (10 mL, stirred over CaH$_2$ for 1 h) in a round bottom flask was added solid CaH$_2$ (5 mg), and the mixture was stirred for 10 min at rt. The cloudy solution was cooled to −78 °C and *n*-BuLi (2.1 M in hexane, 0.66 mL, 1.38 mmol) was added dropwise and stirred for 10 min. At the same temperature aldehyde **41**[29] (342 mg, 1.38 mmol) in diethyl ether (2 mL) was added to the flask by cannula, and the solution was stirred for 15 min before warming to 0 °C. The reaction mixture was poured into a separatory funnel containing aqueous NH$_4$Cl, diluted with water, and extracted with DCM. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and purified by MPLC (hexanes:EtOAc = 7:3) to afford (−)-[3*S*-(3*R**,4*S**,5*S**,9*S**),6*E*]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,9-bis-[(4-methoxyphenyl)methoxy]-2,4,7-trimethyldeca-1,6-dien-5-ol (**S30**, 255 mg, 34%) and its C5-epimer (**S30b**, 265 mg, 34%), each as a colorless oil. **S30**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 7.24 (d,

J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.23 (broad d, J = 8.4 Hz, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.59 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.29 (ddd, J = 4.6, 7.3, and 9.0 Hz, 1H), 4.21 (d, J = 11.4 Hz, 1H), 4.00 (d, J = 4.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.54 – 3.69 (m, 3H), 2.25 (dd, J = 4.3 and 13.9 Hz, 1H), 2.18 (dd, J = 7.7 and 13.9 Hz, 1H), 2.18 (d, J = 4.6 Hz, 1H), 1.73 (ddq, J = 4.3, 7.2 and 7.2 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 0.90 (s, 9H), 0.82 (d, J = 7.1 Hz, 3H), and 0.05 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 159.0, 142.8, 135.7, 131.0, 130.6, 129.5, 129.2, 113.8, 113.6, 112.5, 82.0, 78.1, 71.7, 70.4, 70.3, 65.6, 55.2, 42.1, 41.3, 25.9, 19.5, 18.3, 17.2, 10.7, −5.31, and −5.38. IR (neat) 3476, 2952, 2928, 2856, 1613, 1514, 1248, 1090, 1037, and 836 cm$^{−1}$. HRMS (FAB) Calcd for (C$_{35}$H$_{54}$O$_6$Si + Na)$^+$: 621.3582, found: 621.3593. TLC R$_f$ = 0.3 in hexanes:EtOAc 4:1 [α]^{RT} −10.31° (c = 0.38, DCM). **S30b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.26 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.37 (broad d, J = 8.2 Hz, 1H), 5.07 (s, 1H), 5.04 (s, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.44 (ddd, J = 2.9, 2.9, and 8.2, 1H), 4.19 (d, J = 11.2 Hz, 1H), 3.83 (d, J = 5.6 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.53–3.66 (m, 3H), 2.25 (dd, J = 5.1 and 13.9 Hz, 1H), 2.17 (d, J = 2.9, 1H), 2.16 (dd, J = 7.2 and 13.9 Hz, 1H), 1.73 (ddq, J = 3.0, 5.6, and 6.9 Hz, 1H), 1.70 (s, 3H), 1.57 (s, 3H), 0.97 (d, J = 7.3 Hz, 3H), 0.90 (s, 9H), and 0.05 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.1, 159.0, 142.6, 134.8, 131.0, 130.5, 129.4, 129.3, 129.2, 113.8, 113.7, 113.4, 85.6, 78.4, 71.8, 70.7, 70.3, 65.6, 55.2, 41.9, 41.0, 25.9, 18.5, 18.3, 17.3, 8.0, −5.31, and −5.38. IR (neat) 3476, 2952, 2928, 2855, 1612, 1513, 1464, 1247, 1081, 1037, and 836 cm$^{−1}$. TLC R$_f$ = 0.3 in hexanes:EtOAc 4:1. [α]^{RT} −34.06° (c = 0.31, DCM).

To alcohol **S30** (300 mg, 0.502 mmol) in DMF (3 mL) was added MeI (0.37 mL, 6.00 mmol) and NaH (25% dispersion in mineral oil, 240 mg, 2.51 mmol) at rt. The mixture was stirred for 24 h, quenched with aqueous NH$_4$Cl (10 mL), diluted with H$_2$O, extracted with Et$_2$O (3 × 10 mL), washed with H$_2$O, and dried over Na$_2$SO$_4$. MPLC (hexanes:EtOAc = 19:1) separation gave **42** (245 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.06 (broad d, J = 9.7 Hz, 1H), 4.98 (app s, 2H), 4.60 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.19 (d, J = 11.3 Hz, 1H), 4.00 (d, J = 3.9 Hz, 1H), 3.80 (s, 3H), 3.79 (dd, J = 8.4 and 9.4 Hz, 1H), 3.78 (s, 3H), 3.57–3.69 (m, 3H), 3.07 (s, 3H), 2.30 (dd, J = 4.6 and 14.0 Hz, 1H), 2.23 (dd, J = 6.7 and 14.0 Hz, 1H), 1.73 (ddq, J = 3.9, 8.4, and 7.0 Hz, 1H), 1.68 (app s, 6H), 0.90 (s, 9H), 0.75 (d, J = 7.1 Hz, 3H), and 0.05 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.0, 158.9, 143.5, 137.8, 131.5, 131.0, 129.3, 129.2, 126.8, 113.65, 113.62, 111.6, 81.2, 78.3, 77.8, 71.8, 70.7, 65.6, 55.5, 55.3, 55.2, 42.2, 40.4, 25.9, 19.3, 18.3, 17.5, 9.6, −5.32, and −5.39. IR (neat) 2952, 2928, 2856, 1613, 1513, 1463, 1247, 1082, and 837 cm$^{−1}$. HRMS (FAB) Calcd for (C$_{36}$H$_{56}$O$_6$Si + Na)$^+$: 635.3738, found: 635.3772. TLC Rf = 0.5, hexanes:EtOAc = 4:1. [α]^{RT} −3.00° (c = 0.95, DCM).

(−)-6-{[2*S*-(2*R**,3*R**,4*R**,5*R**,6*S**,10*S**),7*E*]-4,10-Dihydroxy-6-methoxy-3,5,8-trimethyl-11-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-[(trimethylsilyl)oxy]-undec-7-enyl}-2,2-dimethyl-4H-1,3-dioxin-4-one (43)

A flask containing **42** (235 mg, 0.384 mmol) was brought into a dry box where solid 9-BBN dimer (235 mg, 1.91 mmol) was added. The flask was taken out of the dry box, THF (4 mL) was added at −78 °C, and the solution was warmed to rt. The system was stirred for 18 h before H$_2$O$_2$ (30%, 0.6 mL) and aqueous NaOH (10%, 3.8 mL) were added at 0 °C. After 45 min the reaction mixture was extracted with DCM and dried over MgSO$_4$. Separation by flash chromatography (hexanes:EtOAc = 7:3) gave a mixture of both diastereomers (7:1 ratio). MPLC (hexanes:EtOAc = 7:3) separation afforded the desired alcohol (+)-[2*R*-(2*R**, 3*R**,4*R**,5*R**,9*R**),6*E*]-5-methoxy-3,9-bis-[(4-methoxyphenyl)-methoxy]-2,4,7-trimethyl-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-deca-6-en-1-ol (**S31**, 168 mg, 70%)

and a minor amount of the C2-epimer (**S32**), each as a colorless oil. **S31**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.01 (dq, *J* = 9.1 and 1.2 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 3.85 (dd, *J* = 1.8 and 9.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.75 (dd, *J* = 9.7 and 9.7 Hz, 1H) 3.50–3.71 (m, 5H), 3.17 (s, 3H), 2.73 (dd, *J* = 3.3 and 8.7 Hz, 1H), 2.33 (dd, *J* = 5.1 and 14.0 Hz, 1H), 2.25 (dd, *J* = 7.5 and 14.0 Hz, 1H), 1.92 (ddq, *J* = 4.0, 9.0, and 7.0 Hz, 1H), 1.65 (ddq, *J* = 1.4, 8.3, and 6.8 Hz, 1H), 1.68 (d, *J* = 1.5 Hz, 3H), 0.90 (s, 9H), 0.83 (d, *J* = 7.1 Hz, 3H), 0.80 (d, *J* = 7.1 Hz, 3H), 0.061 (s, 3H), and 0.059 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 159.1, 138.2, 131.0, 130.9, 129.3, 129.3, 127.6, 113.9, 113.6, 81.8, 78.4, 78.2, 74.2, 71.8, 67.2, 65.5, 55.3, 55.3, 55.1, 42.2, 40.4, 38.3, 25.9, 18.3, 17.4, 14.1, 9.8, −5.33, and −5.40. IR (neat) 3470, 2953, 2928, 2857, 1613, 1513, 1248, 1090, 1036, and 837 cm^{-1}. HRMS (FAB) Calcd for (C$_{36}$H$_{58}$O$_7$Si + Na)$^+$: 653.3844, found: 653.3851. TLC Rf = 0.2, hexanes:EtOAc = 7:3. [α]^{RT} +23.2° (c = 0.45, DCM). **S32**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.01 (d, *J* = 9.8 Hz, 1H), 4.62 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 10.4 Hz, 1H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.51 (d, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (dd, *J* = 2.3 and 7.0 Hz, 1H), 3.50 – 3.70 (m, 6H), 3.12 (s, 3H), 2.31 (dd, *J* = 5.1 and 14.2 Hz, 1H), 2.24 (dd *J* = 7.2 and 14.2 Hz, 1H), 1.96 (ddq, *J* = 6.0, 7.0, and 7.0 Hz, 1H), 1.72 (ddq, *J* = 2.1, 6.6, and 9.0 Hz, 1H), 1.67 (d, *J* = 1.5 Hz, 3H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), and 0.06 (s, 6H). IR (neat) 3434, 2953, 2928, 2856, 1613, 1513, 1247, 1096, and 837 cm^{-1}. HRMS (FAB) Calcd for (C$_{36}$H$_{58}$O$_7$Si + Na)$^+$: 653.3844, Found: 653.3857. TLC Rf = 0.2, hexanes:EtOAc = 7:3. [α]^{RT} +6.62° (c = 0.64, DCM).

Dess-Martin periodinane (158 mg, 0.37 mmol) was added to alcohol **S31** (158 mg, 0.25 mmol) and DCM (12 mL) at rt. The resulting cloudy mixture was stirred 1 h before being placed directly onto a flash column. Flash chromatography (hexanes:EtOAc = 9:1 to 4:1) afforded (+)−[2*S*-(2*R**,3*R**,4*S**,5*S**,9*S**),6*E*]-5-methoxy-3,9-bis-[(4-methoxyphenyl)-methoxy]-2,4,7-trimethyl-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-decenal (**S33**, 119 mg, 76%) as a colorless oil. **S33** ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.73 (d, *J* = 3.0 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.51 (s, 2H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.15 (dd, *J* = 2.2 and 9.3 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.82 (m, 1H), 3.57–3.70 (m, 3H), 3.17 (s, 3H), 2.67 (ddq, *J* = 3.0, 9.3, and 7.0 Hz, 1H), 2.33 (dd, *J* = 5.0 and 14.0 Hz, 1H), 2.25 (dd, *J* = 7.4 and 14.0 Hz, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.62 (ddq, *J* = 2.2, 9.1, and 7.0 Hz, 1H), 0.97 (d, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.80 (d, *J* = 7.5 Hz, 3H), 0.061 (s, 3H), and 0.059 (s, 3H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.1, 159.1, 159.2, 138.5, 130.9, 130.9, 129.3, 129.2, 127.4, 113.8, 113.7, 78.4, 78.1, 77.7, 73.9, 71.8, 65.5, 55.28, 55.27, 55.0, 49.8, 42.2, 40.5, 25.9, 18.3, 17.4, 11.1, 9.5, −5.32, and −5.39. IR (neat) 2952, 2932, 2856, 1724, 1613, 1513, 1248,1036, and 837 cm^{-1}. Anal. Calcd for C$_{36}$H$_{56}$O$_7$Si: C, 68.75; H: 8.97. found: C, 69.14; H, 8.65. TLC Rf = 0.4, hexanes:EtOAc = 4:1. [α]^{RT} +2.0° (c = 0.84, DCM).

BF$_3$•Et$_2$O (45 μL, 0.36 mmol) was added over 2 min to aldehyde **S33** (113 mg, 0.18 mmol) and ketene acetal **20** (385 mg, 1.8 mmol) in DCM (9 mL) at −78 °C. After 45 min the reaction mixture was allowed to warm to room temperature before being quenched with saturated aqueous NaHCO$_3$. The resulting mixture was extracted with DCM, dried over MgSO$_4$, and concentrated. Flash chromatography (hexanes:EtOAc = 7:3 to 1:1) gave (+)-6-{[2*S*-(2*R**,3*S**,4*S**,5*S**,6*S**,10*S**),7*E*]-2-hydroxy-6-methoxy-5,10-bis-[(4-methoxyphenyl)methyl]-3,5,8-trimethyl-11-[[(1,1-dimethylethyl)dimethylsilyl]-oxy]-undec-7-enyl}-2,2-dimethyl-4H-1,3-dioxin-4-one (**S34**, 125 mg, 90%). **S34** ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.27 (s, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.63 (d, *J* = 10.6 Hz, 1H),

4.61 (d, J = 10.6 Hz, 1H), 4.51 (d, J = 10.6 Hz, 1H), 4.50 (d, J = 10.6 Hz, 1H), 4.16 (m, 1H), 3.87 (dd, J = 2.4 and 8.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (dd, J = 9.6 and 9.6 Hz, 1H), 3.58–3.72 (m, 3H), 3.20 (s, 3H), 2.38 (dd, J = 9.45 and 14.4 Hz, 2H), 2.35 (dd, J = 4.53 and 12.8 Hz, 1H), 2.33 (d, J = 5.8 Hz, 1H), 2.26 (dd, J = 6.8 and 12.8 Hz, 1H), 2.23 (dd, J = 4.15 and 14.4 Hz, 1H), 1.70 (m, 2H), 1.69 (s, 3H), 0.91 (s, 9H), 0.85 (d, J = 7.0 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), and 0.06 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.9, 161.1, 159.3, 159.0, 138.3, 130.8, 130.7, 129.4, 129.3, 127.3, 113.8, 113.6, 106.4, 94.7, 79.9, 78.4, 78.1, 74.2, 71.7, 68.7, 65.4, 55.2, 55.2, 55.0, 42.1, 40.8, 40.7, 39.3, 25.9, 25.2, 24.7, 18.2, 17.4, 10.6, 9.8, −5.37, and −5.43. IR (neat) 3457, 2928, 2856, 1726, 1634, 1613, 1512, 1389, and 1375 cm^{-1}. HRMS (FAB) Calcd for (C$_{43}$H$_{66}$O$_{10}$Si + Na)$^+$: 793.4318, found: 793.4336. TLC Rf = 0.35, hexanes:EtOAc = 1:1. [α]^{RT} +7.2° (c = 0.31, DCM).

TMSCl (0.046 mL, 0.36 mmol) was added to a solution of **S34** (28 mg, 0.036 mmol), Et$_3$N (0.15 mL, 1.08 mmol), and DCM (0.3 mL) at rt. The resulting mixture was stirred until the reaction was deemed complete by TLC, ca. 4 h, at which time the solution had taken on a pink color. The mixture was quenched with aqueous NaHCO$_3$, extracted with DCM, dried over Na$_2$SO$_4$, and concentrated to furnish crude silyl ether, which was carried forward without purification. This oil was first dissolved in wet DCM (1.2 mL) and H$_2$O (100 μL). DDQ (65 mg, 0.29 mmol) was added at rt, and the mixture was stirred for 0.5 h. Aqueous NaHCO$_3$ was added, the mixture was stirred for 5 min, diluted with water, and extracted with DCM. The organic layers were dried over Na$_2$SO$_4$ and concentrated. Flash chromatography (hexanes:EtOAc = 7:3 to 100% EtOAc) furnished diol **43** (17 mg, 78%) as a colorless oil. **43** ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.29 (s, 1H), 5.20 (d, J = 9.3 Hz, 1H), 4.36 (ddd, J = 2.2, 4.3, 8.6 Hz, 1H), 3.95 (dd, J = 6.7 and 9.4 Hz, 1H), 3.83 (ddd, J = 1.5, 1.5, and 9.7 Hz, 1H), 3.81 (m, 1H), 3.63 (dd, J = 3.6, 9.9 Hz, 1H), 3.46 (dd, J = 6.8 and 9.5 Hz, 1H), 3.44 (d, J = 1.8 Hz, 1H), 3.25 (s, 3H), 2.47 (dd, J = 8.8 and 13.8 Hz, 2H), 2.41 (d, J = 3.6, 1H), 2.31 (dd, J = 4.3 and 13.8 Hz, 1H), 2.21 (bs, 1H), 2.19 (bs, 1H), 1.75 (d, J = 1.4 Hz, 3H), 1.70 (s, 3H), 1.68 (s, 3H), 1.63 (m, 2H) 0.91 (s, 9H), 0.86 (d, J = 7.2 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H), 0.12 (s, 9H), and 0.07 (s, 6H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.6, 161.1, 137.0, 127.6, 106.4, 95.2, 80.2, 70.9, 70.9, 69.7, 66.9, 56.1, 43.6, 40.6, 39.6, 39.2, 26.2, 25.8, 24.0, 18.3, 17.0, 10.6, 8.4, 0.19, −5.38, and −5.41. IR (neat) 3502, 2953, 2931, 2857, 1734, 1635, 1464, 1390, 1375, 1273, 1251, 1085 and 840 cm^{-1}. HRMS (FAB) Calcd for (C$_{30}$H$_{58}$O$_8$Si$_2$ + Na)$^+$: 625.3562, found: 625.3570. TLC Rf = 0.6, hexanes:EtOAc = 1:1. [α]^{RT} −22.8° (c = 0.29, DCM).

(−)-[1S*(1R*,5S*,9S*,10S*,11R*,12R*,13R*)7E)-1-Hydroxy-9-methoxy-7,10,12-trimethyl-5-[[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-13-[(trimethylsilyl)oxy]-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (44)

Benzene (200 mL) was placed in a round bottom flask equipped with a Dean-Stark trap. The flask was heated and 40 mL of benzene was removed through the trap. The condenser was removed and diol **43** (16 mg, 0.027 mmol) in benzene (2 mL) was transferred into the flask. The condenser was replaced and the mixture was refluxed for 12 h. The reaction mixture was cooled to rt, concentrated, and purified by flash chromatography (hexanes:EtOAc = 9:1) to afford macrolactone **44** (11 mg, 78%). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.37 (dddd, J = 11.6, 6.8, 4.4, 2.5 Hz, 1H), 5.28 (dq, J = 9.5, 1.2 Hz, 1H), 5.07 (d, J = 2.5 Hz, 1H), 3.80 (dd, J = 9.3, 2.4 Hz, 1H), 3.77 (m, 1H), 3.70 (dd, J = 11.0, 6.7 Hz, 1H), 3.66 (dd, J = 11.1, 4.5 Hz, 1H), 3.61 (dd, J = 10.4, 2.7 Hz, 1H), 3.24 (s, 3H), 2.50 (d, J = 12.8 Hz, 1H), 2.40 (d, J = 12.8 Hz, 1H), 2.24 (dd, J = 13.4, 2.6 Hz, 1H), 2.20 (ddq, J = 2.4, 2.4, 7.0 Hz, 2H), 2.16 (dd, J =13.4, 11.7 Hz, 1H), 1.97 (dd, J = 12.0, 4.7 Hz, 1H), 1.72 (s, 3H), 1.42 (ddq, J = 10.2, 10.2, 6.1 Hz, 1H), 1.35 (ddd, J = 11.9, 10.7, 2.4 Hz, 1H), 0.97 (d, J = 7.1 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.13 (s, 9H), 0.05 (s, 3H), and 0.05 (s, 3H). ^{13}C NMR (125

MHz, CDCl$_3$) δ 172.4, 132.6, 127.3, 95.4, 79.9, 72.7, 70.1, 65.17, 65.12, 55.2, 44.6, 44.4, 42.6, 40.1, 37.1, 25.7, 18.2, 16.1, 12.3, 6.6, −0.02, −5.30, and −5.33. IR (neat) 3451, 2956, 2929, 2859, 1706, 1251, 1075, and 838 cm^{-1}. HRMS (FAB) calcd for (C$_{27}$H$_{52}$O$_7$Si$_2$ + Na)$^+$: 567.3144, found: 567.3159. TLC R$_f$ = 0.4, hexanes:EtOAc = 9:1. [α]^{rt} −19.8° (c = 0.93, DCM).

(−)-[1*S**(1*R**,5*S**,9*S**,10*S**,11*R**,12*R**,13*R**)7*E*]-1-Hydroxy-5-(hydroxymethyl)-9-methoxy-7,10,12-trimethyl-13-[(trimethylsilyl)oxy]-4,15-dioxabicyclo[9.3.1]-pentadec-7-en-3-one (48)

TBAF (0.28 mL, 1.0 M in THF, 0.28 mmol) was added to **44** (11 mg, 0.020 mmol) in THF (0.5 mL) at rt and stirred for 10 min. The solution was placed on a pipette column and purified by flash chromatography (100% EtOAc) to afford a diol that was immediately carried into the next reaction. TMSCl (0.05 mL, 0.40 mmol) was added to a mixture of the diol, NEt3 (0.17 mL, 1.21 mmol), and DCM (0.2 mL) at rt. The mixture was stirred for 2 h, quenched with aqueous NaHCO$_3$, diluted with water, extracted with DCM, dried over Na$_2$SO$_4$, and concentrated to give a crude oil. This lactone was dissolved in MeOH (1 mL), NaHCO$_3$ (5 mg) was added, and the resulting mixture was stirred for 2 h. The mixture was diluted with water, extracted with DCM, dried over Na$_2$SO$_4$, and concentrated. Purification by flash chromatography (hexanes:EtOAc = 19:1) afforded **48** (6 mg, 70% over three steps). ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.42 (dddd, J = 2.4, 3.7, 6.2, and 8.7 Hz, 1H), 5.31 (d, J = 9.4 Hz, 1H), 5.00 (d, J = 2.4 Hz, 1H), 3.8 (dd, J = 2.2 and 9.6 Hz, 1H), 3.76 (m, 3H), 3.61 (dd, J = 2.5, 10.3 Hz, 1H), 3.24 (s, 3H), 2.54 (d, J = 13.0 Hz, 1H), 2.44 (d, J = 13.0 Hz, 1H), 2.30 (dd, J = 12.0 and 12.0 Hz, 1H), 2.21 (m, 2H), 1.98 (dd, J = 4.6 and 12.0 Hz, 1H), 1.74 (s, 3H), 1.61 (dd, J = 5.9 and 5.9 Hz, 1H), 1.43 (ddq, J = 10.3, 10.3, and 6.5 Hz, 1H), 1.36 (ddd, J = 2.4, 10.7, and 12.0 Hz, 1H), 0.97 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.4, 132.2, 127.7, 99.4, 79.8, 75.1, 72.8, 70.0, 64.9, 55.2, 44.7, 44.3, 42.4, 40.1, 37.0, 16.2, 12.4, 6.6, and 0.30. IR (neat) 3434, 2962, 2930, 2874, 1704, 1251, 1227, 1182, 1075, 891, and 841 cm^{-1}. HRMS (FAB) Calcd for (C$_7$H$_{38}$O$_7$Si + Na)$^+$: 453.2279, found: 453.2291. TLC R$_f$ = 0.5, hexanes:EtOAc = 1:1. [α]^{RT} −23.9° (c = 0.33, DCM).

(−)-[1*S*(1*R**,5*S**,9*S**,10*S**,11*S**,12*S**,13*R**)7*E*]-5-[(1*E*,3*E*)-6-((1*R**,2*S**)-2-Chlorocyclopropyl)-1,3-hexadien-5-yn-1-yl]-1,13-dihydroxy-9-methoxy-7,10,12-trimethyl-4-15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (49)[2,3a,3c,3d,3e]

Sulfur trioxide•pyridine (19 mg, 0.12mmol) was added to a mixture of alcohol **48** (5 mg, 0.01 mmol), TEA (24.0 μL, 0.174 mmol), DCM (100 μL), and DMSO (300 μL) at 0 °C. The mixture was stirred 0.5 h at which time it was diluted with EtOAc (500 μL), quenched with aqueous NH$_4$Cl, and diluted with H$_2$O (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), washed with water (5 mL), dried over Na$_2$SO$_4$, and concentrated. The crude product was passed through a plug of silica gel (hexanes:EtOAc = 1:1) to afford crude aldehyde, which was immediately carried on to the next reaction. A solution of n-BuLi (0.3 mL, 2.05 M, 0.67 mmol) was added to neat hexamethyldisilazane (0.14 mL, 0.67 mmol) in a round bottom flask at 0 °C. The solution was stirred for 0.5 h at which time a white precipitate had formed. THF (2.9 mL) was then added to make a 0.2 M solution of LiHMDS. Phosphonate **43**[3c,3e] (14 mg, 0.051 mmol) was placed in a vial and dissolved in THF (0.3 mL). To this solution was added LiHMDS (255 μL, 0.2 M in THF, 0.051 mmol) at −78 °C, resulting in a dark brown color. The mixture was stirred 3 min at −78 °C before the aldehyde from the previous step (in THF, 200 μL) was added. The vessel was immediately removed from the dry ice bath and allowed to warm to rt over 4 min before being quenched with aqueous NH$_4$Cl, extracted with EtOAc, dried over Na$_2$SO$_4$, and concentrated. The crude product was passed through a pipette column of silica gel (hexanes:EtOAc = 4:1) to afford the TMS protected product.

The silylated product was dissolved in THF (0.5 mL), TBAF (30 μL, 1.0 M in THF) was added, and the resulting mixture was stirred for 5 min at rt. The solvent was removed with a stream of N_2 and the resulting oil was loaded onto a flash column with DCM. Flash chromatography (hexanes:EtOAc = 7:3 to 1:1) afforded **49** (3 mg, 54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (dd, J = 10.9 and 15.4 Hz, 1H), 6.27 (dd, J = 10.9 and 15.1 Hz, 1H), 5.83 (m, 1H), 5.76 (dd, J = 6.2 and 15.1 Hz, 1H), 5.57 (dd, J = 2.2 and 15.5 Hz, 1H), 5.31 (d, J = 9.7 Hz, 1H), 5.03 (d, J = 2.4 Hz, 1H), 3.80 (dd, J = 2.4 and 9.5 Hz, 1H), 3.79 (m, 1H), 3.61 (dd, J = 2.6 and 10.2 Hz, 1H), 3.24 (s, 3H), 3.18 (ddd, J = 3.2, 5.6, and 6.2 Hz, 1H), 2.55 (d, J = 12.9 Hz, 1H), 2.44 (d, J = 12.9 Hz, 1H), 2.29 (m, 2H), 2.22 (ddq, J = 2.5, 2.5, and 6.9 Hz, 1H), 2.10 (dd, J = 4.6 and 11.8 Hz, 1H), 1.78 (m, 1H), 1.74 (s, 3H), 1.39 (m, 1H) 1.30 (m, 4H), and 0.98 (app d, J = 6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 140.1, 132.7, 132.3, 130.9, 127.8, 112.5, 95.3, 92.2, 79.8, 77.2, 75.0, 71.5, 69.5, 55.2, 46.9, 44.7, 43.7, 40.1, 36.8, 34.3, 19.3, 16.1, 12.06, 12.03, and 6.5. IR (neat) 3452, 3364, 2953, 2923, 2853, 1700, 1465, 1457, and 1225 cm^{-1}. HRMS (FAB) Calcd for ($C_{26}H_{35}ClO_6$ + Na)$^+$: 501.2014, found: 501.2037. TLC R_f = 0.5, hexanes:EtOAc = 1:1. $[\alpha]^{RT}$ −53.8° (c = 0.5, $CHCl_3$).

(−)-{3a*R*(3a*R**,4*S**,6*R*,7*R*,7a*R**)}-6-[[(1*S**,5*R**,7*E*,9*R**,10*R**,11*R**,12*R**,13*S**)-5-[(1*E*,3*E*)-6-[(1*S**, 2*R**)-2-Chlorocyclopropyl]-1,3-hexadien-5-yn-1-yl]-1-hydroxy-9-methoxy-7,10,12-trimethyl-3-oxo-4,15-dioxabicyclo[9.3.1]pentadec-7-en-13-yl]oxy]-7-methoxy-4,7a-dimethyl-4*H*-pyrano[3,4-*d*]oxazol-2(3*H*)-one (1)

To a mixture of the aglycon **49** (2 mg, 0.004 mmol), carbohydrate **34**[3f] (3 mg, 0.008), and powdered molecular sieves (20 mg) in DCM (300 μL) was added TMSOTf (0.055 M in DCM, 15 μL, 0.836 μmol) at 0 °C. TLC still showed starting material after stirring for 30 min and so additional carbohydrate **3** (1.5 mg, 0.004 mmol) was added. After the addition, TLC showed absence of starting material within 10 min. The mixture was quenched with saturated aqueous $NaHCO_3$. The resulting solution was diluted with H_2O, extracted with DCM, dried over Na_2SO_4, and purified by HPLC (100% EtOAc) to afford (−)-callipeltoside A (**1**) (2 mg, 70%). ^{1}H NMR (500 MHz, CD_3OD) δ 6.49 (dd, J = 10.8 and 15.4 Hz, 1H), 6.33 (dd, J = 10.8 and 14.1 Hz, 1H), 5.83 (m, 1H), 5.80 (m, 1H), 5.64 (dd, J = 1.9 and 15.4 Hz, 1H), 5.26 (d, J = 9.7 Hz, 1H), 4.71 (d, J = 6.2 Hz, 1H), 3.95 (dd, J = 1.9 and 6.5 Hz, 1H), 3.87 (dd, J = 2.4 and 9.5 Hz, 1H), 3.72 (dd, J = 4.7, 10.7, and 10.7 Hz, 1H), 3.64 (dd, J = 2.4 and 10.4 Hz, 1H), 3.59 (s, 3H), 3.44 (d, J = 1.9 Hz, 1H), 3.42 (d, J = 6.1 Hz, 1H), 3.24 (m), 3.21 (s, 3H), 2.52 (d, J = 12.8 Hz, 1H), 2.46 (d, J = 12.8 Hz), 2.33 (bd, J = 13.3 Hz, 1H), 2.26 (dd, J = 11.1 and 13.3 Hz, 1H), 2.21 (m, 1H), 2.21 (ddq, 2.3, 2.3, and 7.2 Hz, 1H), 1.80 (m, 1H), 1.74 (s, 3H), 1.50 (s, 3H), 1.50 (ddq, J = 3.9, 10.3, and 6.6 Hz, 1H), 1.39 (dd, J = 11.1 and 12.2 Hz, 1H), 1.27 (m, 2H), 1.08 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H), and 0.95 (d, J = 7.0 Hz, 3H). ^{13}C NMR* (125 MHz, CD_3OD) δ 172.9, 141.6, 134.4, 134.3, 132.0, 128.4, 113.5, 103.6, 96.6, 92.8, 83.9, 83.0, 81.4, 78.7, 78.4, 76.4, 72.7, 65.3, 62.7, 62.0, 55.4, 47.8, 46.1, 44.5, 36.8, 39.9, 38.2, 35.9, 35.1, 30.8, 23.0, 19.8, 16.3, 15.9, 12.7, and 6.8. *The weak carbamate carbonyl resonance at δ 161.1 ppm reported for the natural sample of callipeltoside A was not observed. IR (neat) 3452, 3266, 2921, 2852, 1750, 1699, 1464, 1358, and 988 cm^{-1}. HRMS (FAB) Calcd for ($C_{35}H_{48}ClNO_{10}$ + Na)$^+$: 700.2864, Found: 700.2883. TLC R_f = 0.5, hexanes:EtOAc = 1:1. $[\alpha]^{RT}$ −53.8° (c = 0.5, CHCl3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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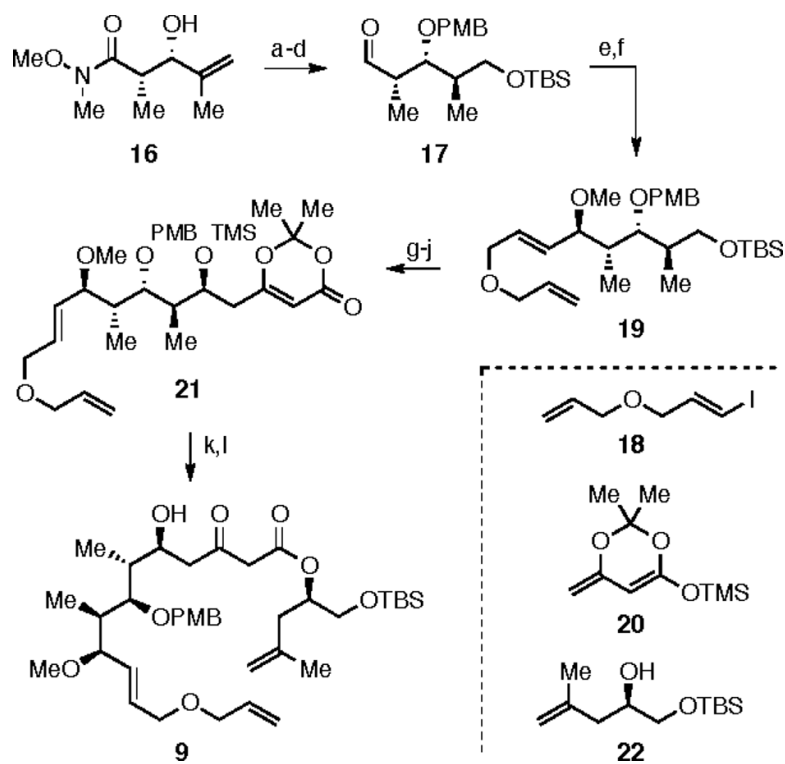(29). Hoffman RW, Stuermer R. Chem. Ber 1994;127:2511–2518.
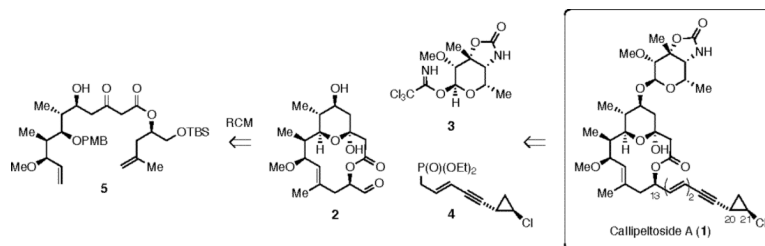
Scheme 1.
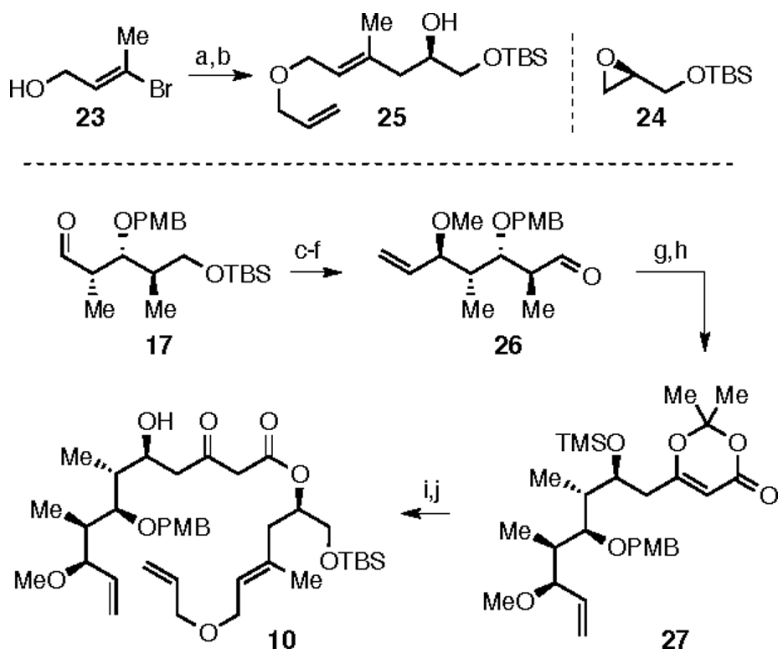Callipeltoside Retrosynthesis.
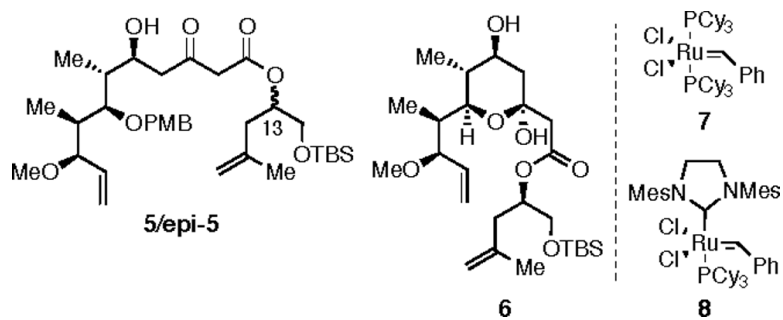
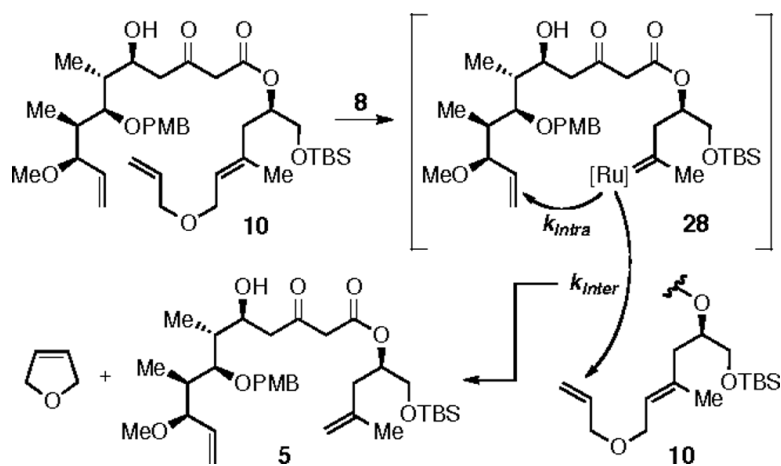**Scheme 2.**
RCM Substrates.
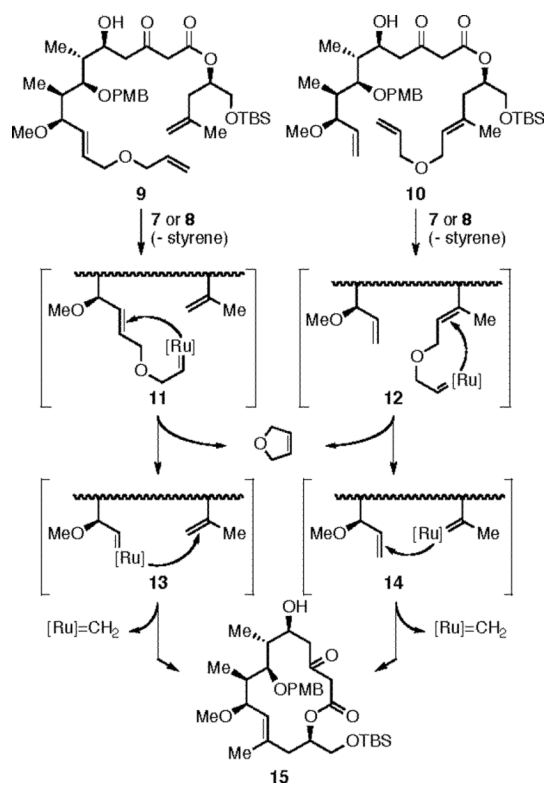
Scheme 3.
Relay Ring-Closing Metathesis.

Scheme 4. Synthesis of Relay Substrate 9
a) PMB acetimidate, CSA, 92%; b) 9-BBN, then NaOH/H_2O_2, 56%; c) TBSCl, TEA, 60%; d) DIBAL-H, 95%; e) ^{t}BuLi, then **18**, dr = 1:1.5; SiO_2 separation; 22%/33%; f) MeI, NaH, DMF, 64%; g) TBAF, THF; h) DMP; i) **20**, $BF_3 \cdot OEt_2$; j) TMSCl, 65% over 4 steps; k) **22**, benzene reflux; l) PPTS, ACN 69% over 2 steps.
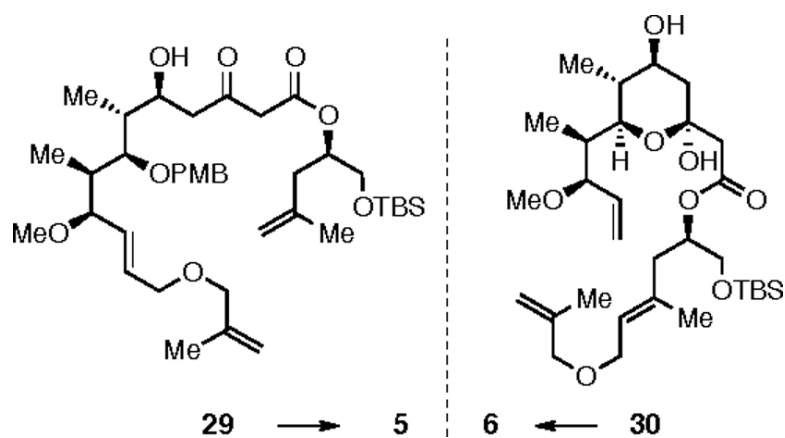
Scheme 5. Synthesis of Relay Substrate 10
a) allyl bromide, NaH, 81%; b) ^{t}BuLi, CuI, **24**; c) vinylMgBr, dr = 1:1; SiO$_2$ separation;
34%/34%; d) MeI, NaH, DMF, 89%; e) TBAF, THF, 87%; f) DMP, 92%; g) **20**, BF$_3$·OEt$_2$,
90%; h) TMSCl, TEA, 65%; i) **25**, benzene reflux; j) PPTS, ACN, 77% over two steps.
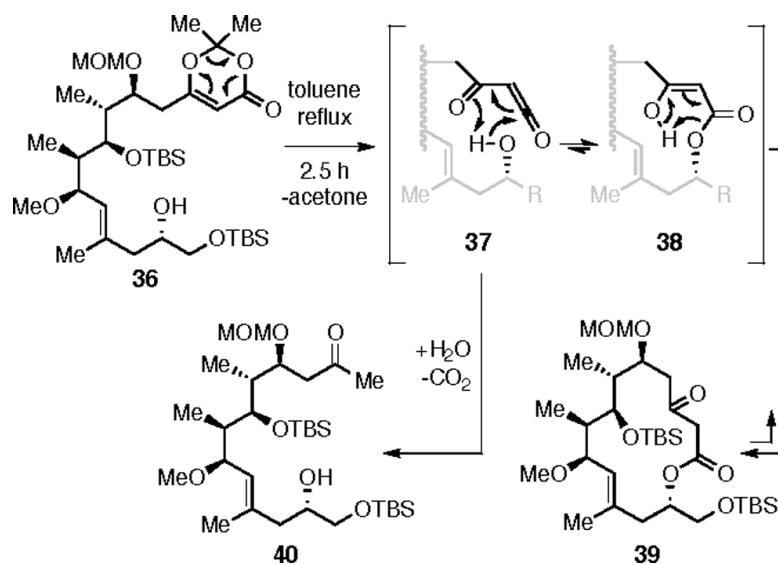
Scheme 6.
Truncation of Relay Substrate 10.
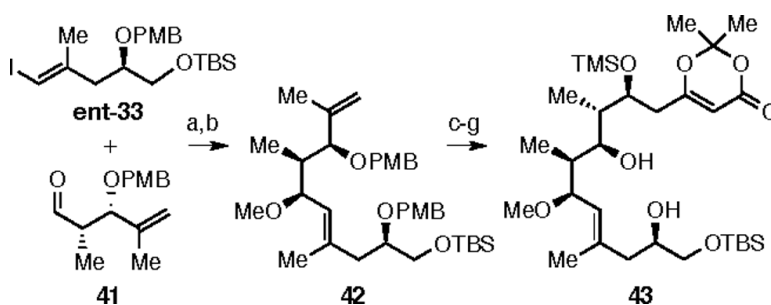
Scheme 7.
Additional RRCM Substrates.
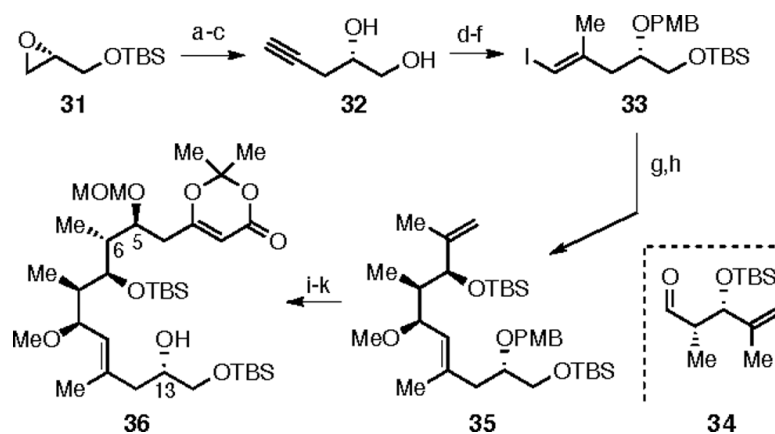
Scheme 8. Synthesis of Lactonization Precursor 38

a) Li-TMS-acetylide, BF$_3$•OEt$_2$; b) K$_2$CO$_3$, MeOH; c) KF, MeOH reflux, 77% over 3 steps; d) AlMe$_3$, ZrCp$_2$Cl$_2$; I$_2$, 65%; e) TBSCl, imidazole, 72%; f) PMB acetimidate, CSA, 82%; g) n-BuLi, **34**, dr = 1:1; h) MeI, NaH, 80%; i) 9-BBN, then NaOH/H$_2$O$_2$, 99%; j) DMP, 79%; k) **20**, BF$_3$·OEt$_2$, 70%; l) MOMCl, 95%; m) DDQ, 100%.
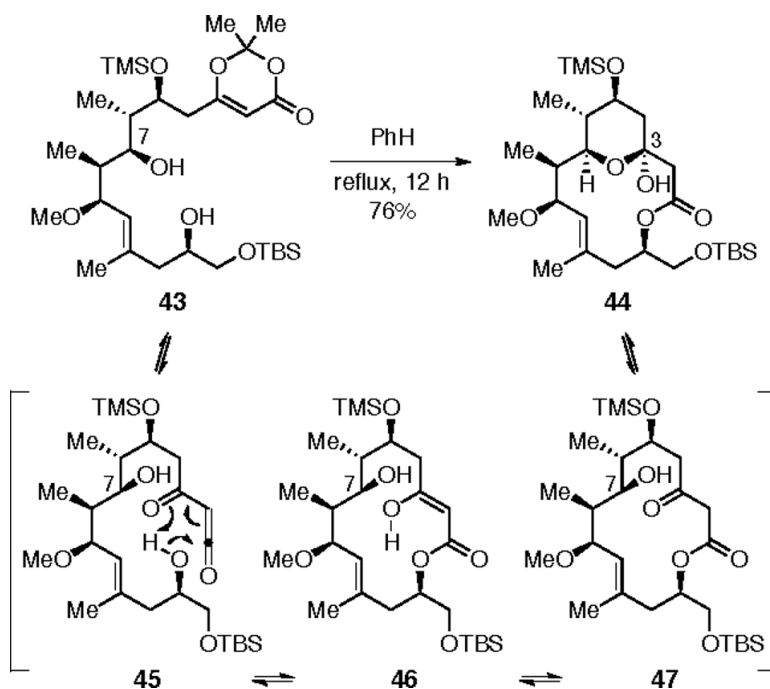
Scheme 9.
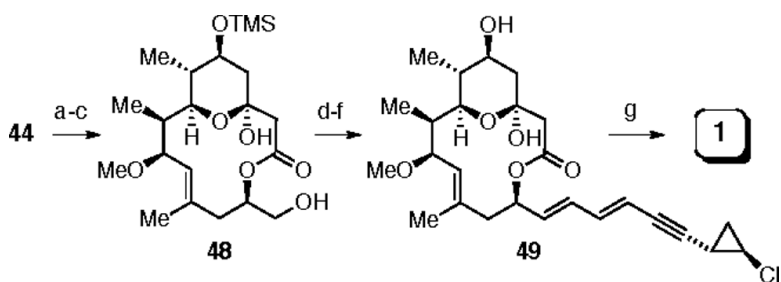Boeckman Cyclization and Competitive Hydrolysis of 36.

Scheme 10. Synthesis of Dual Macrolactonizion/Pyran-Hemiketal Precursor 43
Reagents and conditions: (a) ^{n}BuLi, **ent-33**; then **41**, dr = 1:1, SiO$_2$ separation, 34%/34%;
(b) MeI, NaH, 80%; (c) 9-BBN, then NaOH/H$_2$O$_2$, 70%; (d) DMP, 76%; (e) **20**, BF$_3$•OEt$_2$,
90%; (f) TMSCl; g) DDQ, 78% over 2 steps.

Scheme 11.
Formation of Pyran-Hemiketal 44.

Scheme 12. Completion of the Synthesis
Reagents and conditions: (a) TBAF, THF; (b) TMSCl, TEA, DCM; (c) NaHCO$_3$, MeOH, 70% over 3 steps; (d) SO$_3$•pyr, DMSO, TEA; (e) **4**, LiHMDS, THF; (f) TBAF, THF, 54% over 3 steps; (g) **5**, TMSOTf, DCM, 70%.