

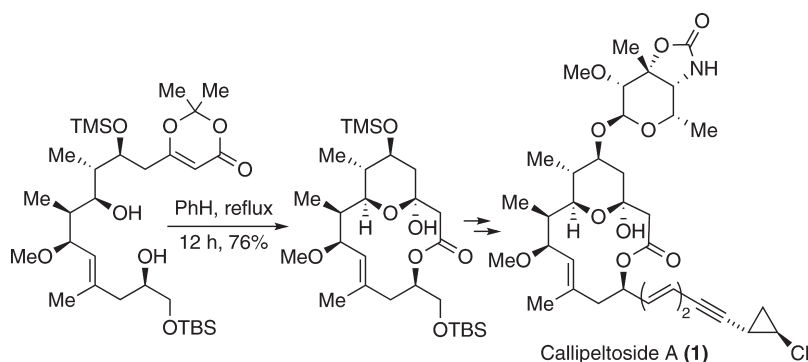
Total Synthesis of (–)-Callipeltoside A

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Received August 14, 2010



A total synthesis of (–)-callipeltoside A (**1**) has been achieved. The core macrocycle was made via a dual macrolactonization/pyran hemiketal formation reaction, 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 co-workers.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 laboratories in 2002.^{3a} Additional total syntheses have been reported,^{3b–g} and numerous related studies have appeared.⁴

Results and 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

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(2) Paterson, I.; Davies, R. D. M.; Marquez, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 603–607.

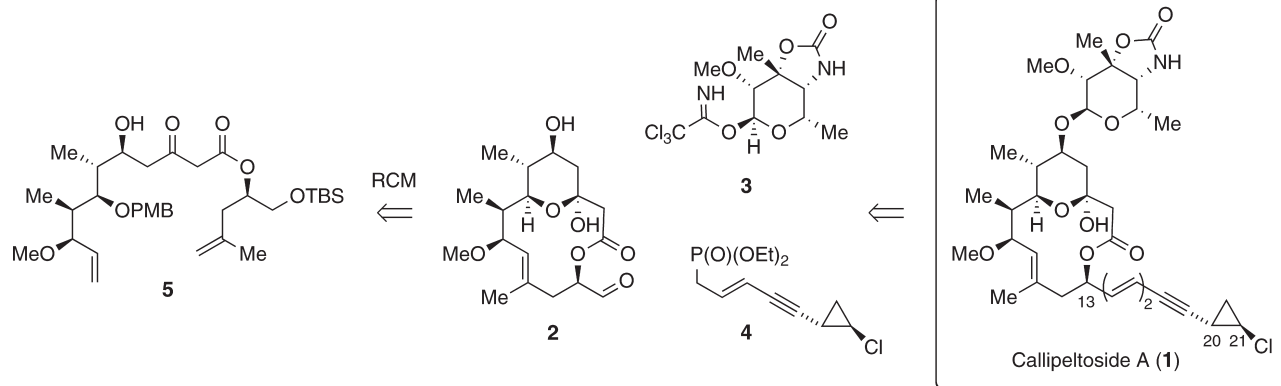
(3) Total syntheses: (a) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841–843. (b) Evans, D. A.; Hu, J.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654–5655. (c) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415. (d) Paterson, I.; Davies, R. D. M.; Heimann, A. C.; Marquez, R.; Meyer, A. *Org. Lett.* **2003**, *5*, 4477–4480. (e) Huang, H.; Panek, J. S. *Org. Lett.* **2004**, *6*, 4383–4385. (f) Evans, D. A.; Burch, J. D.; Hu, E.; Jaeschke, G. *Tetrahedron* **2008**, *64*, 4671–4699. (g) Carpenter, J.; Northrup, A. B.; Chung, D.; Wiener, J. J. M.; Kim, S.-G.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3568–3572.

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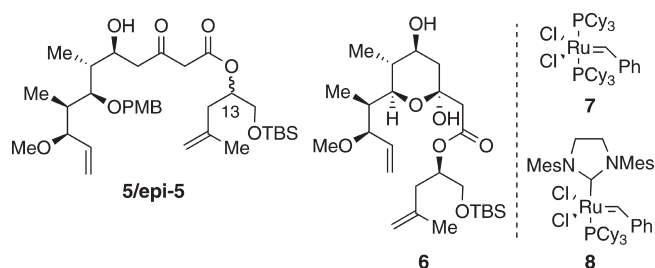
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SCHEME 1. Callipeltoside Retrosynthesis



SCHEME 2. RCM Substrates

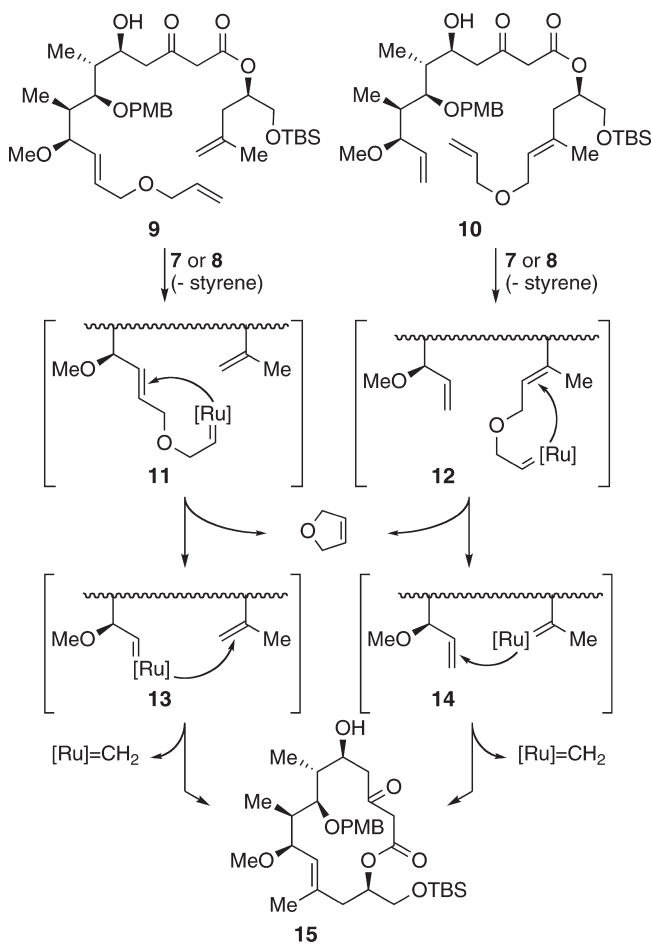


failed.⁷ At elevated temperatures (50–70 °C, benzene solvent) the catalyst [either **7** or the second generation initiator (**8**)]⁸ decomposed and starting material (**5** and **6**) could be recovered.

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**

SCHEME 3. Relay Ring-Closing Metathesis



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

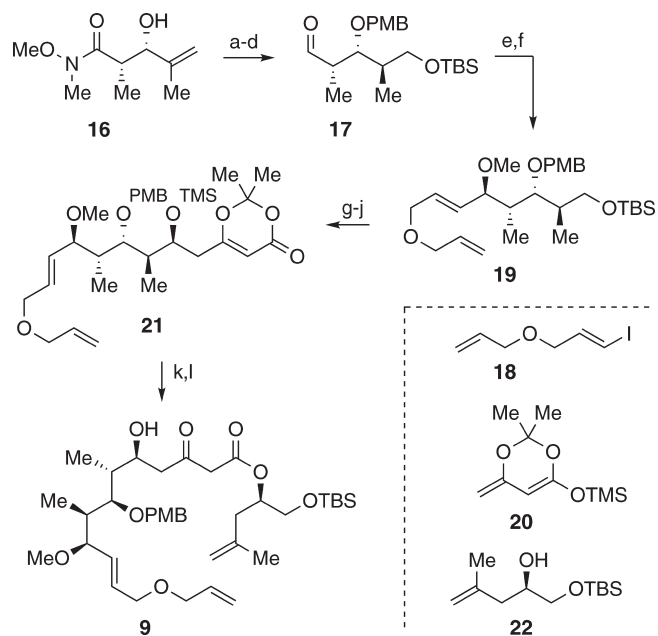
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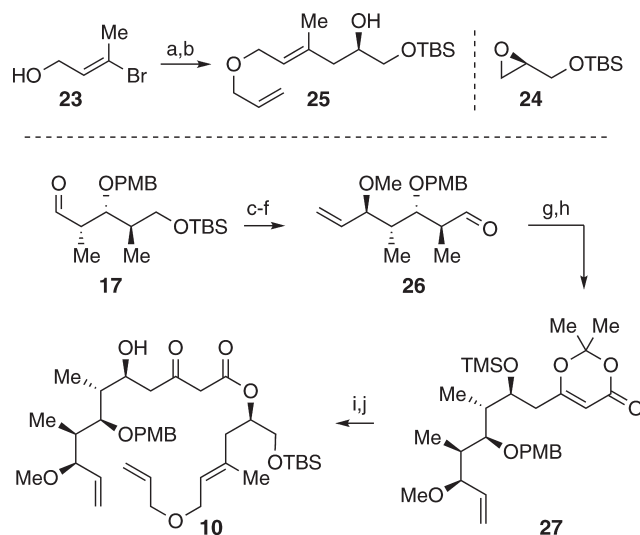
SCHEME 4. Synthesis of Relay Substrate 9^a

^aKey: (a) PMB acetimidate, CSA, 92%; (b) 9-BBN, then NaOH/H₂O₂, 56%; (c) TBSCl, TEA, 60%; (d) DIBAL-H, 95%; (e) ^tBuLi, then **18**, dr = 1:1.5; SiO₂ separation; 22%/33%; (f) MeI, NaH, DMF, 64%; (g) TBAF, THF; (h) DMP; (i) **20**, BF₃·OEt₂; (j) TMSCl, 65% over four steps; (k) **22**, benzene reflux; (l) PPTS, ACN 69% over two steps.

with secondary alcohol **22**,¹² followed by TMS deprotection with PPTS in acetonitrile gave **9**.

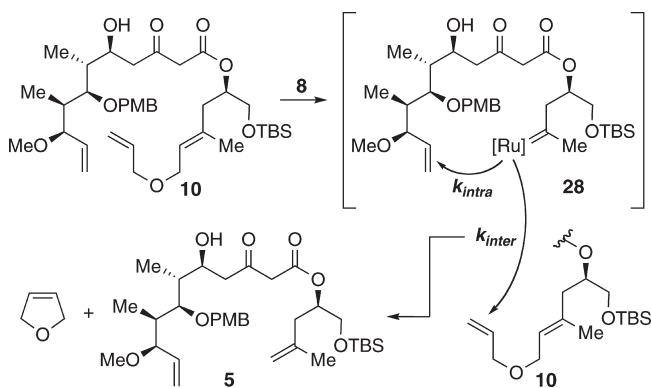
The synthesis of the alternative relay substrate **10** is outlined in Scheme 5. The allyl ether of known bromo alkene **23**¹³ was used, after lithium–halogen exchange (cat. CuI), to ring-open the TBS protected epoxide **24**¹⁴ to give relay-armed alcohol **25**. Aldehyde **17** was elaborated by addition 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, 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 (¹H 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

SCHEME 5. Synthesis of Relay Substrate 10^a

^aKey: (a) allyl bromide, NaH, 81%; (b) ^tBuLi, CuI, **24**; (c) vinylMgBr, dr = 1:1; SiO₂ separation; 34%/34%; (d) MeI, NaH, DMF, 89%; (e) TBAF, THF, 87%; (f) DMP, 92%; (g) **20**, BF₃·OEt₂, 90%; (h) TMSCl, TEA, 65%; (i) **25**, benzene reflux; (j) PPTS, ACN, 77% over two steps.

SCHEME 6. Truncation of Relay Substrate 10



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

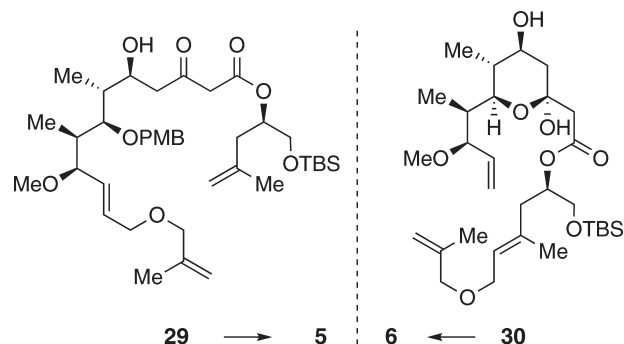
We examined other ways to favorably bias the ratio of *k*_{intra} to *k*_{inter} during this RRCM reaction. Since disubstituted alkenes are slower to engage in cross-metathesis (CM), it was hoped that using a 1,1-disubstituted alkene within the relay arm would slow the bimolecular truncation rate sufficiently 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

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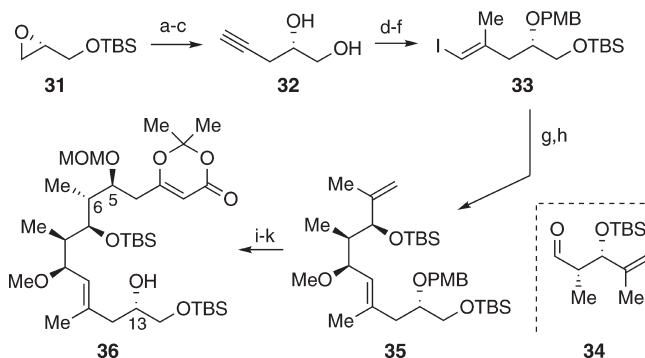
SCHEME 7. Additional RRCM Substrates



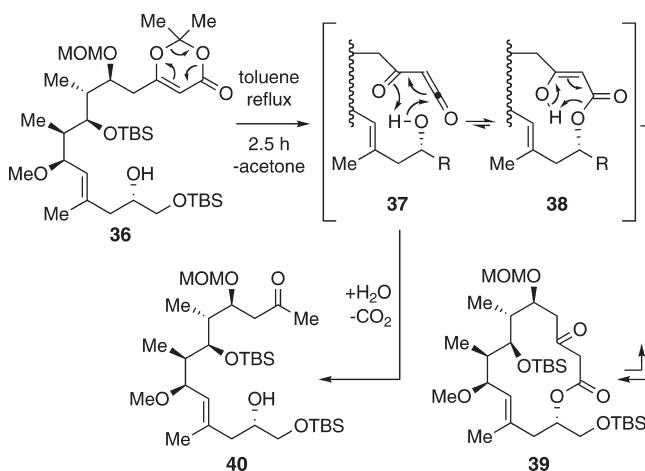
the cyclization will not be efficient regardless of the process by which the key ruthenium alkylidene intermediate is formed.^{9c}

We then turned to a strategy in which the Boeckman lactonization¹⁵ 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 synthesis¹⁶ of the aglycon. Reaction of the TBS-protected epoxide **31** with lithium TMS-acetylide, followed by a two-step deprotection gave diol **32**.^{17,18} Negishi carboalumination/iodination¹⁹ 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 cyclization of the C(13) hydroxyl group to give enol **38** (Scheme 8). 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 -keto acid, 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

SCHEME 8. Synthesis of Lactonization Precursor **36**^a

^aKey: (a) Li-TMS-acetylide, $\text{BF}_3 \cdot \text{OEt}_2$; (b) K_2CO_3 , MeOH; (c) KF, MeOH reflux, 77% over three steps; (d) AlMe_3 , ZrCp_2Cl_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_2O_2 , 99%; (j) DMP, 79%; (k) **20**, $\text{BF}_3 \cdot \text{OEt}_2$, 70%; (l) MOMCl, 95%; (m) DDQ, 100%.

SCHEME 9. Boeckman Cyclization and Competitive Hydrolysis of **36**

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 macro-lactone 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 vinyl lithium 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

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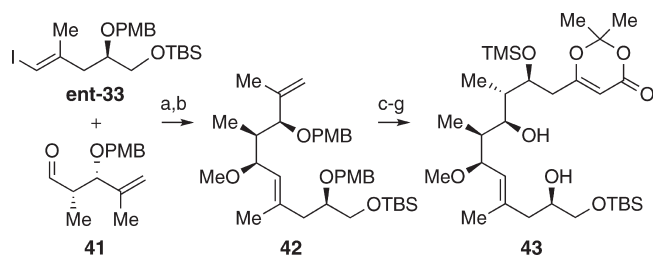
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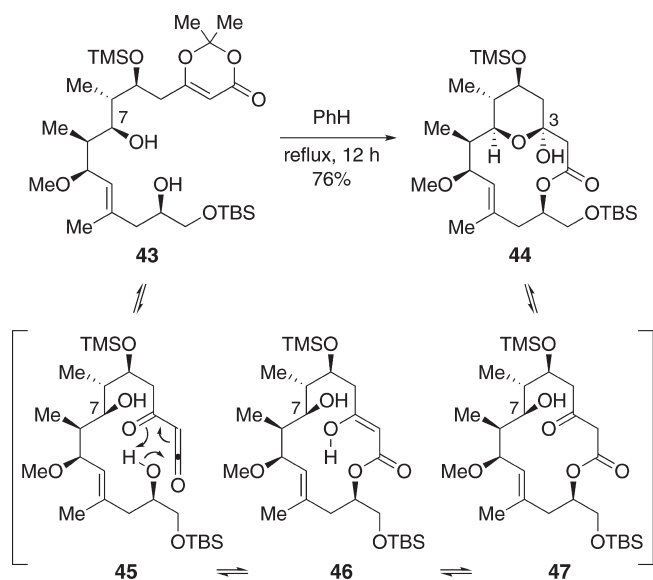
(24) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255–263.

(25) By this juncture, the configuration at C(13) in **1** had been established,² so our subsequent studies described here all involved intermediates directed toward the 13*R* configuration.

SCHEME 10. Synthesis of Dual Macrolactonization/Pyran–Hemiketal Precursor 43^a

^aReagents and conditions: (a) *n*-BuLi, **ent-33**; then **41**, dr = 1:1, SiO₂ separation, 34%/34%; (b) MeI, NaH, 80%; (c) 9-BBN, then NaOH/H₂O₂, 70%; (d) DMP, 76%; (e) **20**, BF₃·OEt₂, 90%; (f) TMSCl; (g) DDQ, 78% over two steps.

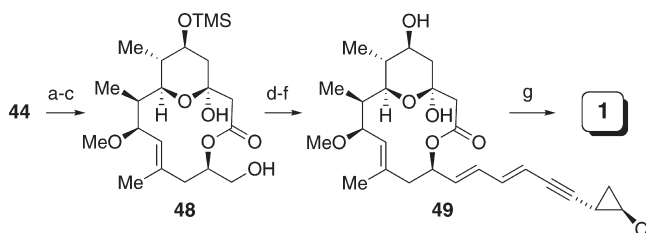
SCHEME 11. Formation of Pyran–Hemiketal 44



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 h, 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–Doering oxidation afforded the corresponding aldehyde, from which aglycon **49** was obtained by Horner–Emmons olefination with the known phosphonate **4**,²⁶ followed by deprotection

SCHEME 12. Completion of the Synthesis^a

^aReagents and conditions: (a) TBAF, THF; (b) TMSCl, TEA, DCM; (c) NaHCO₃, MeOH, 70% over three steps; (d) SO₃·pyr, DMSO, TEA; (e) **4**, LiHMDS, THF; (f) TBAF, THF, 54% over three steps; (g) **5**, TMSOTf, DCM, 70%.

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** (21 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 Methods. ¹H NMR chemical shifts in CDCl₃ are referenced to TMS (0.00 ppm) and in PhH-d₆ to 7.16. ¹³C NMR chemical shifts in CDCl₃ 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 Å 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 BF₃·OEt₂ (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 NH₄Cl (20 mL). The mixture was allowed to warm to rt and

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diluted with H₂O (150 mL). The aqueous layer was extracted with DCM (3 × 100 mL), and the combined organic portions were dried over Na₂SO₄ and concentrated to give crude TMS alkyne as a colorless oil. This alkyne was immediately subjected to desilylation. To the crude oil were added K₂CO₃ (29.3 g, 212 mol) and MeOH (100 mL), and this mixture was stirred for 24 h at rt. The suspended K₂CO₃ 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 were 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%): ¹H NMR (300 MHz, CDCl₃) 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), 2.08 (t, *J* = 2.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 80.3, 70.7, 70.2, 65.3, 23.2; GC–MS *t*_R = 2.66 min; *m/z* 100, 69, 61; IR (neat) 3300, 3292, 2113, 1719, 1416, 1085, 1044 cm⁻¹; mp 44–51 °C; TLC *R*_f = 0.35, 100% EtOAc; [α]_D²⁵ +8.22 (*c* = 1.1, CHCl₃).

(–)-(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 AlMe₃ (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 Na₂SO₄, concentrated, and chromatographed (100% EtOAc) to provide iodo diol (*R*_f = 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 NH₄Cl (50 mL), diluted with H₂O (100 mL), and extracted with DCM. The combined organic layers were dried over Na₂SO₄, concentrated, and chromatographed (hexanes/EtOAc = 19:1) to provide a primary TBS ether (*R*_f = 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) were added *p*-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 MgSO₄, and concentrated. Purification by MPLC (hexanes/EtOAc = 12:1) gave **33** (330 mg, 82%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) 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), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 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, –5.37; IR (neat) 3063, 3032, 2996, 2958, 2931, 2857, 1612, 1512, 1250 cm⁻¹; GC–MS *t*_R = 12.6 min; *m/z* 419, 349, 121; HRMS (CI, 4% NH₃ in CH₄) calcd for (C₂₀H₃₃IO₃Si + NH₄)⁺ 494.1582, found 494.1579; TLC *R*_f = 0.3, hexanes/EtOAc = 15:1; [α]_D²⁵ –15.3 (*c* = 1.0, CHCl₃).

(–)-[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 CaH₂ for 1 h) in a round-bottom flask was added solid CaH₂ (5 mg), and the mixture was stirred for 10 min at rt. The cloudy solution was cooled to –78 °C, *n*-BuLi (2.1 M in hexane, 0.66 mL, 1.38 mmol) was added dropwise, and the mixture was 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 NH₄Cl, diluted with water, and extracted with DCM. The combined organic layers were dried over Na₂SO₄, 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**: ¹H NMR (500 MHz, CDCl₃) 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), 0.05 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 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, –5.38; IR (neat) 3476, 2952, 2928, 2856, 1613, 1514, 1248, 1090, 1037, 836 cm⁻¹; HRMS (FAB) calcd for (C₃₅H₅₄O₆Si + Na)⁺ 621.3582, found 621.3593; TLC *R*_f = 0.3 in hexanes/EtOAc 4:1 [α]_D²⁵ –10.31 (*c* = 0.38, DCM). **S30b**: ¹H NMR (500 MHz, CDCl₃) 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 Hz, 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 Hz, 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), 0.05 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 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, –5.38; IR (neat) 3476, 2952, 2928, 2855, 1612, 1513, 1464, 1247, 1081, 1037, 836 cm⁻¹; TLC *R*_f = 0.3 in hexanes/EtOAc 4:1; [α]_D²⁵ –34.06 (*c* = 0.31, DCM).

To alcohol **S30** (300 mg, 0.502 mmol) in DMF (3 mL) were 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 NH₄Cl (10 mL), diluted with H₂O, extracted with Et₂O (3 × 10 mL), washed with H₂O, and dried over Na₂SO₄. MPLC (hexanes/EtOAc = 19:1) separation gave **42** (245 mg, 80%) as a colorless oil: ¹H NMR (500 MHz, CDCl₃) 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), 0.05 (s, 6H); ¹³C NMR (125 MHz,

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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 ; IR (neat) 2952, 2928, 2856, 1613, 1513, 1463, 1247, 1082, 837 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{36}\text{H}_{56}\text{O}_6\text{Si} + \text{Na})^+$ 635.3738, found 635.3772; TLC R_f = 0.5, hexanes/EtOAc = 4:1; $[\alpha]_D^{25}$ -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-4*H*-1,3-dioxin-4-one (**43**). A flask containing **42** (235 mg, 0.384 mmol) was brought into a drybox where solid 9-BBN dimer (235 mg, 1.91 mmol) was added. The flask was taken out of the drybox, THF (4 mL) was added at -78°C , and the solution was warmed to rt. The system was stirred for 18 h before H_2O_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**: ^1H 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), 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 , -5.40 ; IR (neat) 3470, 2953, 2928, 2857, 1613, 1513, 1248, 1090, 1036, 837 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{36}\text{H}_{58}\text{O}_7\text{Si} + \text{Na})^+$ 653.3844, found 653.3851; TLC R_f = 0.2, hexanes/EtOAc = 7:3; $[\alpha]_D^{25}$ +23.2 (c = 0.45, DCM). **S32**: ^1H 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), 0.06 (s, 6H); IR (neat) 3434, 2953, 2928, 2856, 1613, 1513, 1247, 1096, 837 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{36}\text{H}_{58}\text{O}_7\text{Si} + \text{Na})^+$ 653.3844, found 653.3857; TLC R_f = 0.2, hexanes/EtOAc = 7:3; $[\alpha]_D^{25}$ +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**: ^1H 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), 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 , -5.39 ; IR (neat) 2952, 2932, 2856, 1724, 1613, 1513, 1248, 1036, 837 cm^{-1} ; TLC R_f = 0.4, hexanes/EtOAc = 4:1; $[\alpha]_D^{25}$ +2.0 (c = 0.84, DCM). Anal. Calcd for $\text{C}_{36}\text{H}_{56}\text{O}_7\text{Si}$: C, 68.75; H, 8.97. Found: C, 69.14; H, 8.65.

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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)methoxy]-3,5,8-trimethyl-11-[(1,1-dimethylethyl)dimethylsilyl]oxy]undec-7-enyl]-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**S34**, 125 mg, 90%). **S34**: ^1H 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), 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 , -5.43 ; IR (neat) 3457, 2928, 2856, 1726, 1634, 1613, 1512, 1389, 1375 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{43}\text{H}_{66}\text{O}_{10}\text{Si} + \text{Na})^+$ 793.4318, found 793.4336; TLC R_f = 0.35, hexanes/EtOAc = 1:1; $[\alpha]_D^{25}$ +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_3N (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_2SO_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_2O (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, and the mixture was stirred for 5 min, diluted with water, and extracted with DCM. The organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (hexanes/EtOAc = 7:3 to 100% EtOAc) furnished diol **43** (17 mg, 78%) as a colorless oil. **43**: ^1H 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), 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 , -5.41 ; IR (neat) 3502, 2953, 2931, 2857, 1734, 1635, 1464, 1390, 1375, 1273, 1251, 1085, 840 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{30}\text{H}_{58}\text{O}_8\text{Si}_2 + \text{Na})^+$ 625.3562, found

625.3570; TLC R_f = 0.6, hexanes/EtOAc = 1:1; $[\alpha]_D^{25}$ –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%): ^1H 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), 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, –5.33; IR (neat) 3451, 2956, 2929, 2859, 1706, 1251, 1075, 838 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{27}\text{H}_{52}\text{O}_7\text{Si}_2 + \text{Na})^+$ 567.3144, found 567.3159; TLC R_f = 0.4, hexanes/EtOAc = 9:1; $[\alpha]_D^{25}$ –19.8 (c = 0.93, DCM).

(–)-[1S*(1R*,5S*,9S*,10S*,11R*,12R*,13R*)7E]-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 pipet 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, NEt_3 (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_2SO_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_2SO_4 , and concentrated. Purification by flash chromatography (hexanes/EtOAc = 19:1) afforded **48** (6 mg, 70% over three steps): ^1H 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, 0.30; IR (neat) 3434, 2962, 2930, 2874, 1704, 1251, 1227, 1182, 1075, 891, 841 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{21}\text{H}_{38}\text{O}_7\text{Si} + \text{Na})^+$ 453.2279, found 453.2291; TLC R_f = 0.5, hexanes/EtOAc = 1:1; $[\alpha]_D^{25}$ –23.9 (c = 0.33, DCM).

(–)-[1S*(1R*,5S*,9S*,10S*,11S*,12S*,13R*)7E]-5-[(1E,3E)-6-[(1R*,2S*)-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–3e}. Sulfur trioxide·pyridine (19 mg, 0.12 mmol) 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_4Cl , and diluted with H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 \times 5 mL). The combined organic layers were washed with brine (5 mL), washed with water (5 mL), dried over Na_2SO_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 $n\text{-BuLi}$ (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 formed. THF (2.9 mL) was then added to make a 0.2 M solution of LiHMDS. Phosphonate **43**^{3c,e} (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_4Cl , extracted with EtOAc, dried over Na_2SO_4 , and concentrated. The crude product was passed through a pipet 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%): ^1H 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), 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, 6.5; IR (neat) 3452, 3364, 2953, 2923, 2853, 1700, 1465, 1457, 1225 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{26}\text{H}_{35}\text{ClO}_6 + \text{Na})^+$ 501.2014, found 501.2037; TLC R_f = 0.5, hexanes/EtOAc = 1:1; $[\alpha]_D^{25}$ –53.8 (c = 0.5, CHCl_3).

(–)-{3aR(3aR*,4S*,6R*,7R*,7aR*)}-6-[(1S*,5R*,7E,9R*,10R*,11R*,12R*,13S*)-5-[(1E,3E)-6-[(1S*,2R*)-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-4H-pyrano[3,4-d]oxazol-2(3H)-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 an 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%): ^1H 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), 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, 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, 988 cm^{-1} ; HRMS (FAB) calcd for $(\text{C}_{35}\text{H}_{48}\text{ClNO}_{10} + \text{Na})^+$ 700.2864, found 700.2883; TLC $R_f = 0.5$, hexanes/EtOAc = 1:1; $[\alpha]_D^{25} -53.8$ ($c = 0.5$, CHCl_3).

Acknowledgment. These studies were supported by the National Cancer Institute (CA-76497) of the United States National Institutes of Health. We thank Mr. Aaron M. Johnson for his preparation of intermediates enroute to fragments **3** and **4**.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.