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Callipeltoside A: Total Synthesis, Assignment of the Absolute and Relative Configuration, and Evaluation of Synthetic Analogues

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Abstract: The total synthesis of the novel antitumor agent callipeltoside A, as well as several analogues, is accomplished and allows assignment of the stereochemistry not previously established. A convergent strategy is employed wherein the target is dissected into three units—the core macrolactone, the sugar callipeltose, and a cyclopropyl bearing chain. The strategy for the synthesis of the macrolactone derives from employment of diastereoselective aldol reactions that emanate from an 11 carbon piece. The stereochemistry of the latter derives from the chiral pool and two asymmetric reactions—a ketone reduction using CBS−oxazaborolidine and a Pd catalyzed asymmetric allylic alkylation (AAA). The novelty of the latter protocol is its control of regioselectivity as well as absolute configuration. The trisubstituted olefin is generated using an alkene−alkyne coupling to create a trisubustituted olefin with complete control of geometry. The excellent chemo- and regioselectivity highlights the synthetic potential of this new ruthenium catalyzed process. The macrolactonization employs in situ formation of an acylketene generated by the thermolysis of a *m*-dioxolenone. Two strategies evolved for attachment of the side chain—one based upon olefination and a second upon olefin metathesis. The higher efficiency of the latter makes it the method of choice. A novel one pot olefin metathesis−Takai olefination protocol that should be broadly applicable is developed. The sugar is attached by a glycosylation by employing the *O*-trichloroacetimidate. This route provided both C-13 epimers of the macrolactone by using either enantiomeric ligand in the Pd AAA reaction. It also provided both *trans*-chlorocyclopropane diastereomers of callipeltoside A which allows the C-20 and C-21 configuration to be established as *S* and *R*, respectively. The convergent nature of the synthesis in which the largest piece, the macrolatone, require only 16 linear steps imparts utility to this strategy for the establishment of the structure−activity relationship. Initial biological testing demonstrates the irrelevance of the chloro substituent and the necessity of the sugar.

Introduction and Retrosynthetic Analysis

Callipeltoside A (**1**) was isolated in 1996 by Minale and coworkers from the shallow-water lithistid sponge *callipelta* sp., collected off the east coast of New Caledonia.[1] It was found to inhibit the proliferation of NSCLC-L6 human bronchopulmonary nonsmall-cell lung carcinoma (11.26 μg mL^{-1}) and P388 (15.26 μg mL^{-1}) cells in vitro.[1a] Results indicate this activity to be cell-cycle dependent, blocking proliferation in the G1 phase, highlighting callipeltoside A as a putative, mechanism-based lead. Unfortunately, the isolation process is extremely low yielding, and only 3.5 mg of callipeltoside A was obtained and consumed since. This initial isolation led to the determination of its structure by extensive NMR spectroscopy studies and to the initial report of its biological activity. To study this fascinating new macrolide and its biological properties, an efficient synthesis is required. Furthermore, there are several unresolved stereochemical issues: (1) the relative stereochemical relationship of callipeltose to the macrolactone rests only on two nuclear Overhauser effects (nOe's), (2) the relative configuration of the *trans*-chlorocyclopropane with regard to the macrolactone is not known, and (3) the absolute configuration remains to be assigned. Despite these structural ambiguities, many groups have embarked on the total synthesis of this compound, with different stereoisomers as targets.[2] In previous communications, we reported the total synthesis of deschlorocallipeltoside A (**2**),[3] as well as the first total synthesis of callipeltoside A **(1)**.[4] In this article, we report a full account of

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(1) (a) Zampella, A.; D'Auria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085. (b) Zampella, A.; D'Auria, M. V.; Minale, L. *Tetrahedron* **1997**, *53*, 3243.
(2) For synthetic work towards callipeltoside aglycon, see: (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 169. (b) Velazquez, F.; Olivo, H. V. *Org. Lett.* **2000**, *2*, 1931. (c) Paterson, I.; Davies, R. D. M.; Marquez, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 603. For synthetic work toward the side chain, see: (d) Olivo, H. F.; Velazquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055. (e) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503. For synthetic work toward callipeltose, see: (f) Smith, G. R.; Finley, J. J., IV; Giuliano, R. M. *Carbohydr. Res.* **1998**, *308*, 223. (g) Gurjar, M. K.; Reddy, R. *Carbohydr. Lett.* **1998**, *3*, 169. (h) Pihko, A. J.; Nicolaou, K. C.; Koskinen, A. M. P. *Tetrahedron: Asymmetry* **2001**, *12*, 937. (i) Evans, D. A.; Hu, E.; Tedrow, J. S. *Org. Lett.* **2001**, *3*, 3133. After submission of this paper, an elegant total synthesis of callipeltoside A appeared: Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. *J. Am. Chem. Soc.* **2002**, *124*, 5654.
(3) Trost, B. M.; Gunzner, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 9449.
(4) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841.

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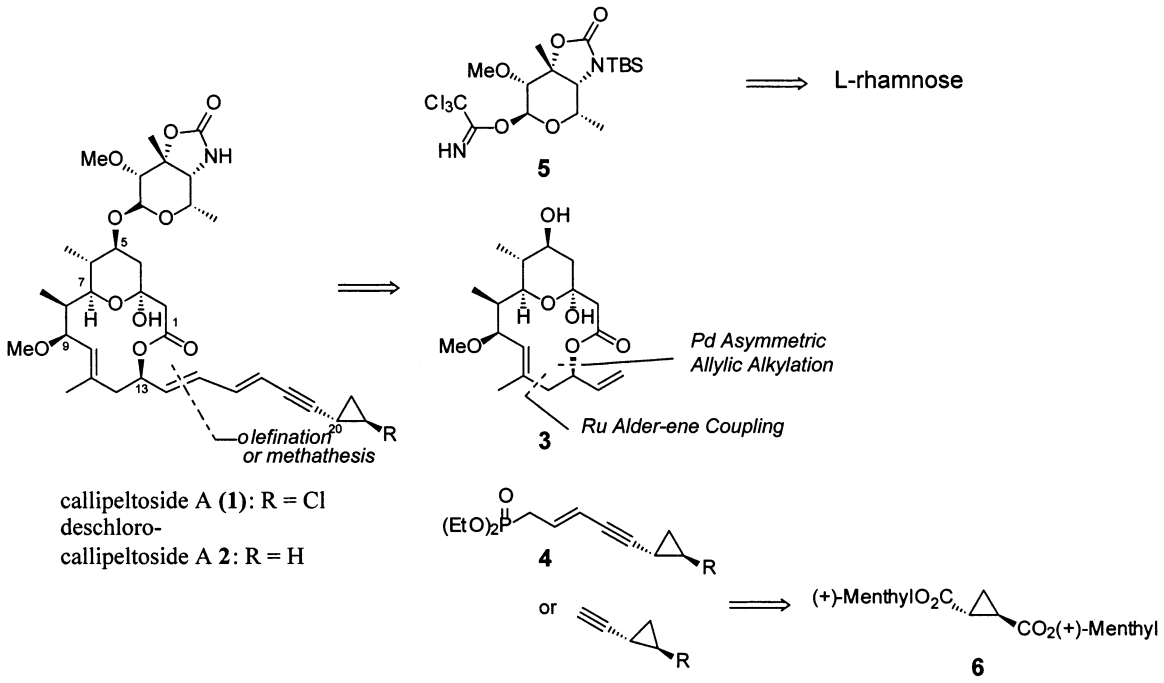


Figure 1. Retrosynthetic analysis of callipeltoside A (**1**).

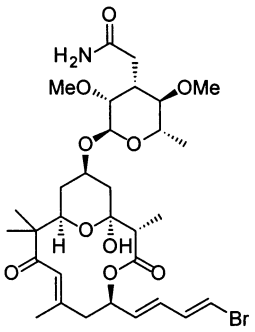


Figure 2. Structure of auriside B.

these syntheses as well as a second generation total synthesis of these molecules.

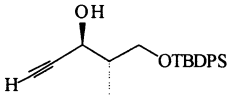
Figure 1 illustrates a simplification of the synthetic target to three building blocks: the macrolactone **3**, the side chain **4**, and the sugar **5**. The two bond disconnections depicted facilitate the synthesis of the core **3**. The stereocenter at C-13 is envisioned to derive from a palladium catalyzed asymmetric allylic alkylation and that at C-9 by a diastereoselective reduction. The stereocenters at C-5, C-6, and C-7 were conceived to derive from diastereoselective aldol type processes. The coupling of the core with the side chain is thought to be made either by a Wittig type reaction or by an olefin cross-metathesis. The macrolactonization is envisioned to derive from a thermal conversion of a dioxolenone to an acylketene as the reactive acylating agent. The stereocenters at C-20 and C-21 are envisioned to derive from **6** by conversion of one of the carboxylic acids to a chloride.

Our choice for the absolute configuration of the macrolactone that we synthesized has been dictated by analogy with a structurally similar molecule, auriside B (Figure 2). The absolute configuration of this marine macrolide has been determined by degradation studies, and its sugar moiety matches L-**rhamnose.**[5] Therefore we chose L-rhamnose as starting material for the sugar synthesis. We also evolved a strategy that could provide either enantiomer with equal facility. To the extent that the nOe correlation between the carbohydrate and the macrolactone in the original structural determination is valid, the absolute configuration of the macrolactone then is also indicated.

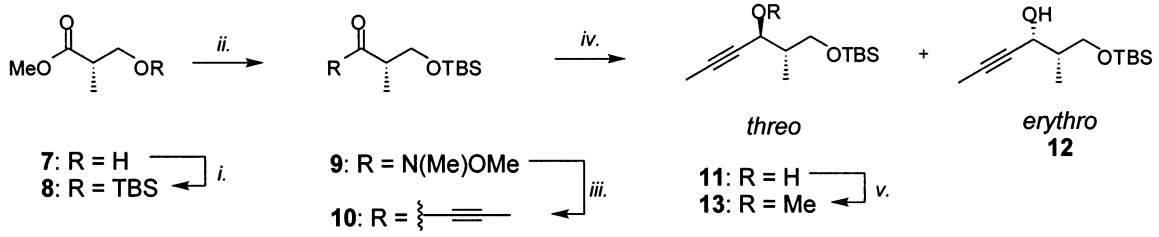
Synthesis of the C-7 to C-11 Fragment

Scheme 1 begins the journey with the synthesis of the C-7 to C-11 fragment starting with the commercially available methyl (*S*)-3-hydroxy-2-methyl propionate (**7**), which is protected as its *tert*-butyldimethylsilyl ether **8**. Various conditions were screened for the formation of the Weinreb amide **9**. Aluminum reagents gave moderate yields on the *tert*-butyldiphenylsilyl ether analogue of **8** (Me_3Al, PhMe, 80 °C, or Me_2AlCl, PhMe, room temperature, 65% yield), and poor yields on **8** itself. A solution was found by using the method developed by Merck (*i*PrMgCl, tetrahydrofuran (THF), −20 °C) which gave the desired amide **9** in 99% yield after 15 min.[6] Formation of the propynyl ketone **10** occurred smoothly by treatment of the Weinreb amide **9** with 1-propynylmagnesium bromide at 0 °C. The resulting ketone needs to be selectively reduced to afford the desired *threo* alcohol **11**. Unfortunately, diastereoselective reduction of **10** with the achiral reducing agent DIBAL-H proved disappointing with *threo*/*erythro* ratios ranging from 0.7/1.0 (butylated hydroxytoluene (BHT), THF, −78 °C) to 1.4/1.0 (PhMe, −78 °C).[7] Using 2-methyl-(*S*)-CBS-

(5) Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956.
(6) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(7) The stereochemistry was assigned on the basis of ^{1}H NMR coupling constants in correlation with those reported in: Williams, D. R.; Kissel, W. S. Total Synthesis of (+)-Amphidinolide J. *J. Am. Chem. Soc.* **1998**, *120*, 11198. These are reported for



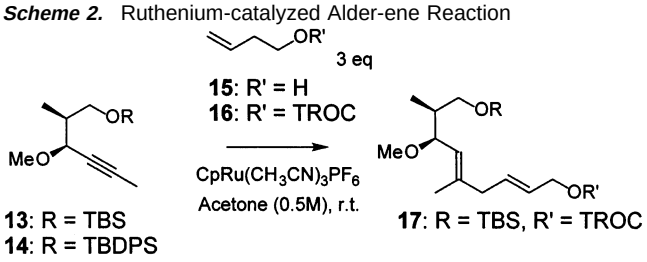
Scheme 1.[a] Synthesis of C-7 Alkyne



Entry	(*S*)-CBS equiv	Yield	11:12
A	2	99%	10:1
B	0.35	97%	5:1

[a] Reagents and conditions: (i) TBDMSCl, imidazole, CH_2Cl_2, room temperature, 2 h, 99%; (ii) MeNHOMe·HCl, *i*-PrMgCl, THF, −20 °C, 15 min, 99%; (iii) 1-propynylmagnesium bromide, THF, 0 °C, 2 h, 89%; (iv) 2-methyl (*S*)-CBS-oxazaborolidine, BH_3·SMe_2, THF, −30 °C, 1 h, 10/1 dr, 99%; (v) MeI, Ag_2O, Et_2O, room temperature, 4 h, 92%.

Scheme 2. Ruthenium-catalyzed Alder-ene Reaction



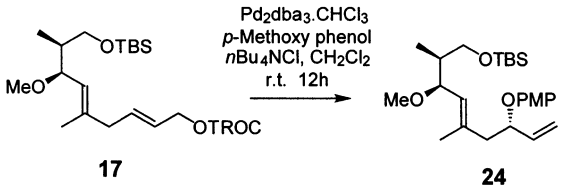
Entry	R	R'	mol % Ru cat	Time	Yield
A	TBDPS	H	10	2h	86%
B	TBS	H	10	2h	62%
C	TBS	TROC	5	30 min	85%

oxazaborolidine, the reduction was nearly quantitative along with a 10/1 ratio using 2 equiv of the chiral reagent, but the selectivity eroded to 5/1 when a substoichiometric amount (35 mol %) was used.[8] A methylation using silver oxide and methyl iodide completes the C-7 to C-11 fragment synthesis. This synthesis is very efficient and has been carried out on multigram quantities.

Synthesis of the Callipeltoside Core

The extension of the C-7 to C-11 fragment requires the stereoselective formation of the trisubstituted double bond, which is sought to be achieved by a regioselective ruthenium catalyzed Alder-ene reaction.[9] To our delight, all the reactions carried out were completely regioselective, affording only the linear product (Scheme 2). When the reactions were carried out using the free homoallylic alcohol **15**, better results were obtained with the substrate bearing the more robust protecting group (compare entries A and B). However, we were gratified to find that using lower catalyst loading (5 mol % instead of 10) and shorter reaction times (30 min instead of 2 h), **14** could react with the homoallylic carbonate **16** to give exclusively the linear product in 85% yield. This reaction is one of few examples of a ruthenium catalyzed Alder-ene with exclusive linear selectivity.[9a] This exceptional selectivity could be explained by the coordination of the propargylic methyl ether in ruthenacycle B (Scheme 3), and/or the inductive effect of the homoallylic oxygen which might speed up the β-hydride elimination step, thereby decreasing the equilibration of the oxidative addition step.

With allyl carbonate **17** in hand, the palladium catalyzed asymmetric allylic alkylation was explored using *p*-methoxyphenol as the nucleophile (eq 1). The use of a chiral ligand



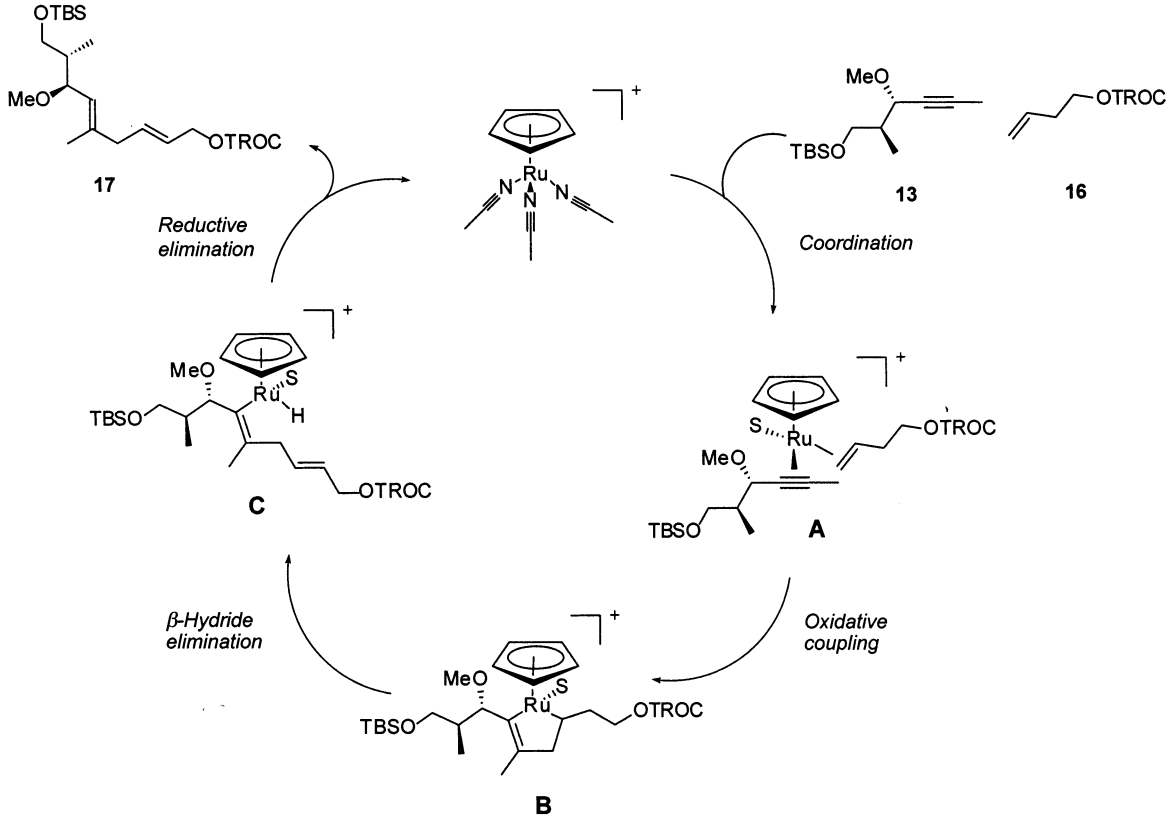
(1)

was anticipated to control the regio- and the diastereoselectivity to set the C-13 stereocenter.[10] To this end, ligands **18**−**23** (Figure 3) have been screened (Table 1).[11] The best result was obtained using the (*R*,*R*)-diphenyl ligand **19** with 100% conversion, 3/1 branched to linear regioselectivity and 19/1 diastereomeric ratio (dr). THF and acetonitrile were unsuccessfully tried as solvents, and lowering the temperature to 0 °C stopped the reaction. Previous examples which used (*R*,*R*) ligands with a substrate similar to **17** gave (*R*)-stereochemistry at the newly generated stereocenter. However, when we checked the absolute configuration of C-13 using the *O*-methylmandelate method at a later stage molecule of the synthesis, we found that the (*S*)-diastereomer was formed, opposite to what was expected (Scheme 4).[12]

The mechanism of this reaction is depicted in Scheme 5. Coordination of the olefin leads to ionization of the carbonate and formation of a π-allylpalladium intermediate which undergoes diastereofacial exchange. The addition of chloride ion (nBu$_4$NCl) speeds up the equilibration by coordination to the palladium, thereby allowing the coordination of the allyl substrate to switch from η^3 to η^1. The σ-bond formation at the

(8) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.
(9) (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739.
(10) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545.
(11) For recent reviews on the palladium catalyzed asymmetric allylic alkylation (AAA) reactions using the Trost ligands, see: (a) Trost, B. M. *Bull. Chem. Pharm.* **2002**, *50*, 1. (b) Trost, B. M.; Lee. C. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593−651.
(12) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.

Scheme 3. Proposed Mechanism of the Ruthenium-Catalyzed Alder-ene Reaction



secondary π-allyl position permits syn to anti-π-allyl interconversion. Only once the palladium is bound to the substrate with a σ-bond at the primary position can it readily undergo diastereofacial exchange.[13] Due to the chirality of the ligand, one of these two intermediates is more stable and has an open space for the nucleophile to enter for attack upon the π-allyl moiety. One possible explanation for this reverse selectivity is that the substituted end of the π-allyl is much larger than the previously reported substrates. This additional steric bulk in the substrate might cause the reactive π-allyl to switch from the syn to the anti form. If the anti-π-allyl is the one being attacked, the opposite configuration at C-13 will be obtained. Alternatively, the trisubstituted olefin could also be coordinating to the palladium causing the unexpected reversal in selectivity. After the nucleophilic attack, decomplexation of the palladium occurs to release the product and regenerate the catalyst.

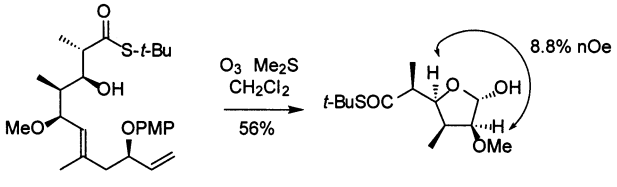
This reverse selectivity is, however, inconsequential for our synthesis since a simple switch of the configuration of the ligand (*ent*-**19**) allows us to obtain the desired diastereoisomer **28** with 20/1 dr and a somewhat reduced branched to linear 2/1 regioselectivity from which the desired diastereomer was isolated in 51% yield (see Scheme 6).[14] The synthesis of the core was then completed. The silyl ether in **28** was cleanly removed by treatment with tetrabutylammonium flouride (TBAF) (96% yield), and the resulting alcohol **29** was oxidized to aldehyde **30** with the use of Dess−Martin periodinane (84% yield). The kinetically formed *E* lithium enolate of *tert*-butyl thiopropionate adds to aldehyde **30** to provide the Cram type addition product **31** with 5/1 diastereoselectivity in 82% yield.[15,16] Aldol product **31** was protected as the *tert*-butyldimethylsilyl ether **33** and the thioester was selectively reduced to aldehyde **34** through the use of DIBAL-H. Felkin-Ahn type addition to aldehyde **34** of the dienyl silyl ether **35**[17] produced a single diastereoisomer **36** in 94% yield. To suppress any dehydration, a hindered base (2,6-di-*tert*-butylpyridine) had to be used in the protection step. The silyl ether **37** formed was then subjected to CAN to liberate the C-13 hydroxyl group for the macrolactonization. The macrocyclization was performed using Boeckman's method which involves the thermolysis of the dioxolenone functionality through a retro−hetero-Diels−Alder reaction, thus generating a ketene intermediate which is intramolecularly trapped by a hydroxyl group to form a 14-membered macrolide **39**.[18] This process proceeded smoothly

(13) When the reaction is carried out, all conditions are equal, but with no chloride ion source, the regioselectivity drops from 3/1 to 1.5/1.

(14) Compound **17** and ligand **19** are a diastereomeric matched pair, whereas **17** and *ent*-**19** are a mismatched pair giving rise to a lower regioselectivity.

(15) For similar aldol reactions with ethyl thiopropiolate, see: (a) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247. (b) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 2219. (c) Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 6449.

(16) To determine the stereochemistry of one of the newly formed stereocenters, aldol product **31** was subjected to an ozonolysis cleavage to afford lactol **32** in 56% yield. After assigning each proton through a COSY spectrum followed by acquisition of nOe data on lactol **32**, it was clear that the newly formed hydroxyl group (tied up as the ring oxygen on **32**) had the desired stereochemistry due to the 8.8% nOe across the ring.



31 **32**

(17) Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem*. **1991**, *56*, 91.

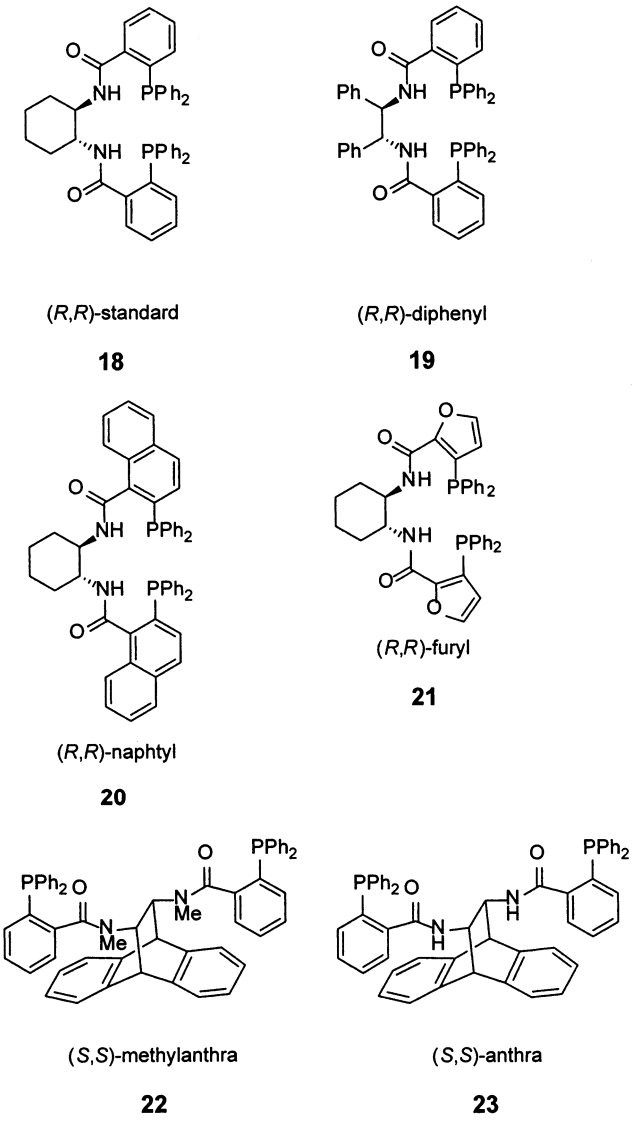


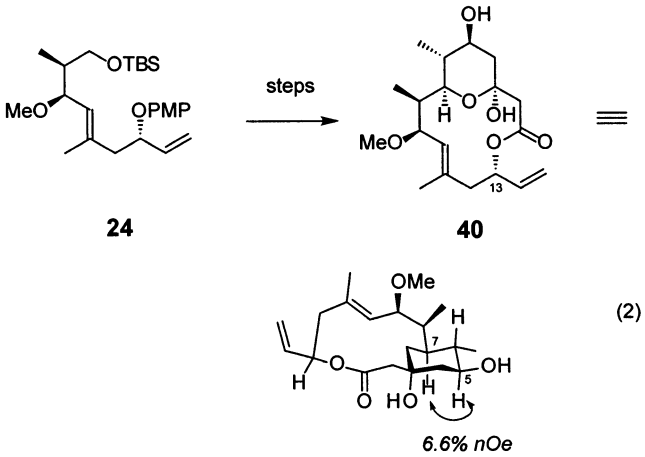
Figure 3. Chiral ligands screened for the palladium-catalyzed asymmetric allylic alkylation reaction.

Table 1. Palladium-Catalyzed Asymmetric Allylic Alkylation Reaction

entry	ligand	conversion (%)	2°/1°
A	**18**	100	1.6/1
B	**19**	100	3/1
C	**20**	100	0.5/1
D	**21**	26	0/1
E	**22**	0	na
F	**23**	0	na

(82% yield) at high dilution in vigorously refluxing freshly distilled toluene.[19] The macrolactone **39** was then transformed into the callipeltoside core **3** by removal of the silyl protecting groups by using HF−pyridine in methanol, followed by treatment with PPTS in wet acetonitrile to remove the methyl ketal (91% yield over two steps).

At this stage, we wanted to make sure that the stereochemistry at the C-13 stereocenter was correctly assigned, and, to this end, we synthesized the other C-13 diastereoisomer **40** of the callipeltoside core. The epimeric **24** (i.e. **28)** derives from the Pd AAA reaction using ligand **19** (cf. eq 1). Following the same route as outlined for macrolactone **3** then provided the epimeric one **40** (eq 2). The NMR data show clearly a better match



(2)

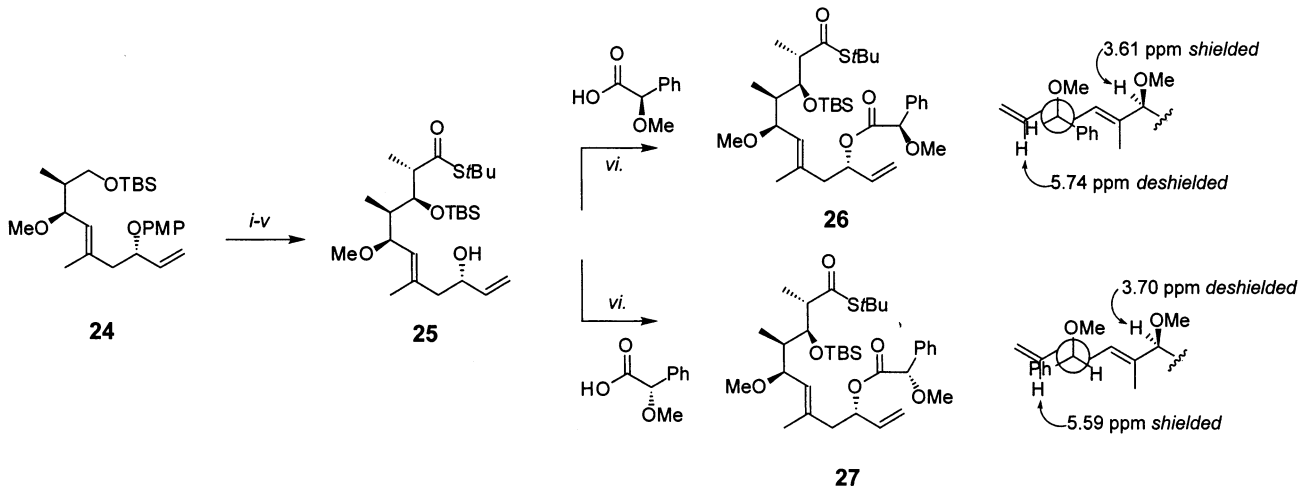
between the diastereoisomer **3** and the natural sample of callipeltoside A than the other diastereoisomer **40**.[20] We also checked the stereochemistry of the two aldol condensations by NMR spectroscopy. For macrolactone **40**, a 10.5 Hz coupling constant was found for H-5 to H-6 and H-6 to H-7, which is indicative of an axial−axial relationship between two protons in a six membered ring. These data together with the 6% nOe observed between H-5 and H-7 establish the diastereoselectivity of the aldol reaction and the correctness of the relative and absolute configuration of both **3** and **40**.

Synthesis of the Callipeltoside Aglycon

Our first synthetic plan used a Wittig type olefination to attach the side chain to the macrolactone. To test this strategy, we first synthesized a deschloro side chain. Scheme 7 shows the straightforward synthesis of phosphonate **45** in five steps from propargyl alcohol and 1-alkynylcyclopropane. The timing for installation of the side chain was dictated by the nature of the two step oxidative cleavage of the terminal alkene and the Emmons−Wadsworth−Horner reaction. Best results for the oxidative cleavage were obtained by performing this transformation at the stage of the macrolide **39** using a sequential dihydroxylation followed by a periodate cleavage of the diol to form aldehyde **46**.[21] Sodium and potassium 1,1,1,3,3,3-hexamethyldisilylamide (HMDS) used as a base in the Emmons−Wadsworth−Horner reaction between phosphonate **45** and aldehyde **46** led to no *E*/*Z* selectivity and poor yields. Best results were obtained with LiHMDS in THF with a temperature gradient between −78 °C and room temperature over 3 h (40% yield, 4/1 *E*/*Z* ratio). The deschlorocallipeltoside aglycon **48** is obtained after deprotection using HF−pyridine in methanol, followed by a transketalization with pyridinium *p*-toluenesulfonate (PPTS) in wet acetonitrile. The deschlorocallipeltoside aglycon **48** is obtained in 60% yield over two steps (Scheme 8)

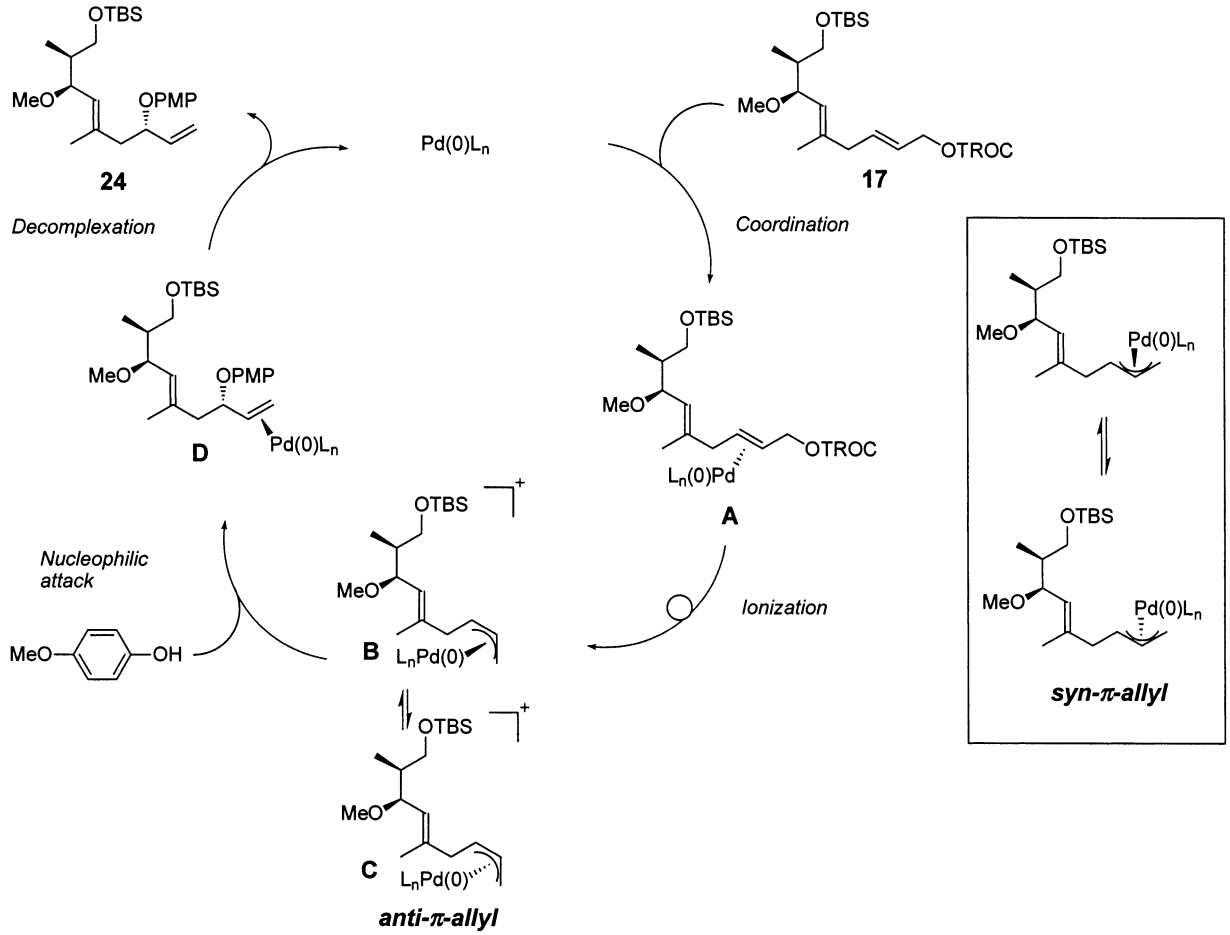
(18) (a) Boeckman, R. K., Jr.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. (b) Chen, C.; Quinn, E. K.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 5011.
(19) When the reaction is carried out at 100 °C, no macrolide is obtained, but instead a mixture of dimer and uncyclized methyl ketone.
(20) Please see Supporting Information for the ^{1}H NMR spectra of **3** and **40**.
(21) If too much osmium tetroxide is used or the reaction is carried out for more than 7 h, a significant amount of double dihydroxylation is observed.

Scheme 4[a]



[a] Reagents and conditions: (i) TBAF, THF, room temperature, 12 h, 91%; (ii) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 5 h, 86%; (iii) *tert*-butylthiopropionate, LDA, THF, −108 °C, 3 h, 5/1 dr, 85%; (iv) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 85%; (v) CAN, MeCN, H_2O, 0 °C, 10 min, 69%; (vi) DCC, DMAP, CH_2Cl_2, room temperature, 12 h, 99%.

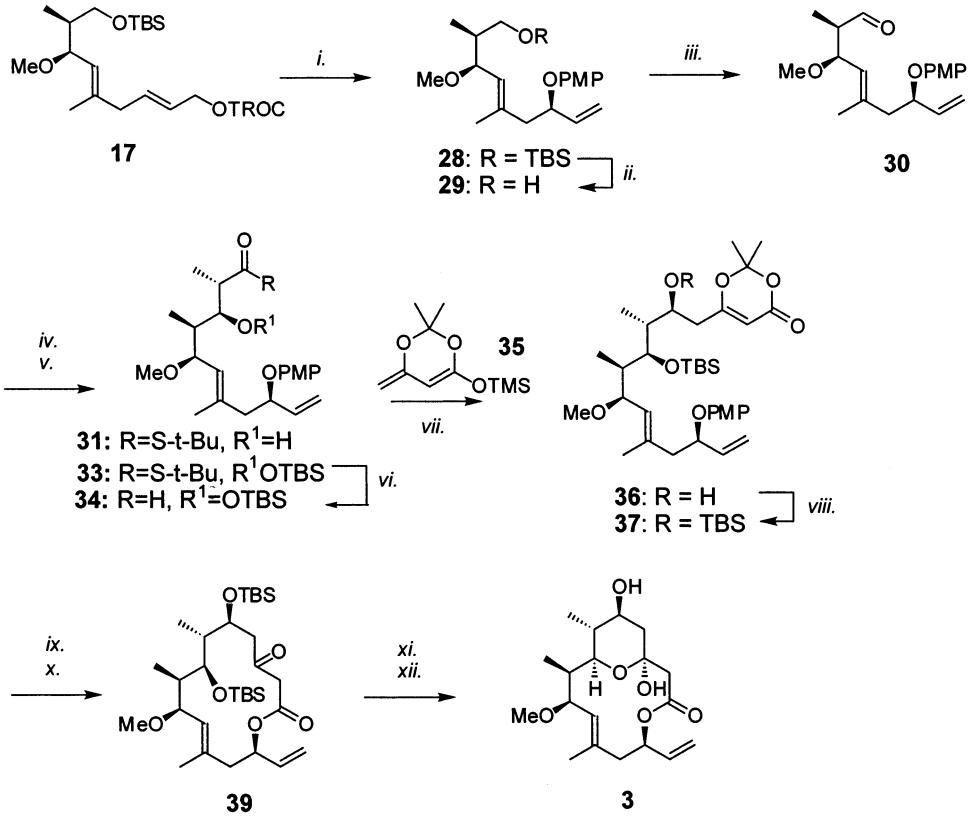
Scheme 5. Proposed Mechanism of the Palladium-Catalyzed Asymmetric Allylic Alkylation Reaction



We then tried to improve the olefination step using the deschlorocyclopropyl side chain and a simple model aldehyde bearing a β-ketoester (see eq 3 and Table 2).[22] The methyl phosphonate **45** gives an excellent yield with this model aldehyde **52** and about the same *E*/*Z* selectivity as with the real aldehyde **46**. The more bulky isopropyl phosphonate **49** is very selective but not reactive enough. The arsonium ylide gave a good selectivity but mediocre yield.[23] The trimethyl phosphonium ylide gave excellent yields and very poor selectivity with the four lithiated bases we tried.[24] However, we thought that a very reactive ylide could be beneficial in our system which suffers from both poor yield and average selectivity. We therefore tried to favor the required equilibration at the transition state to obtain the thermodynamically favored *E* isomer by em-

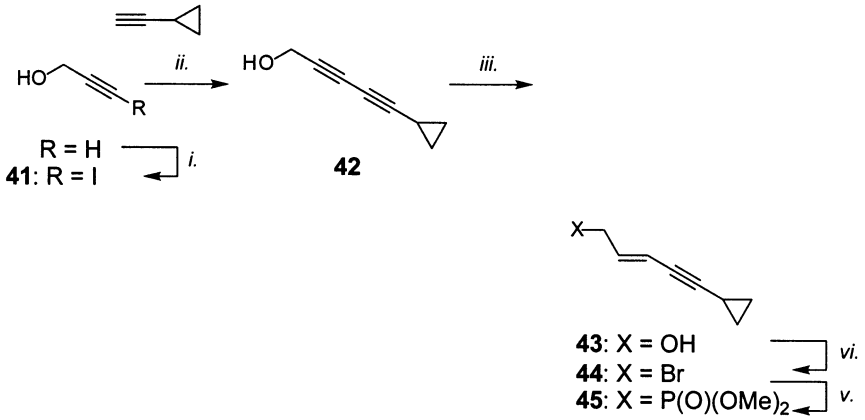
(22) Please see Experimental Section and Supporting Information for the preparation of **49**−**51** and aldehyde **52**.
(23) His, J. D.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 3229.
(24) Waterson, A. G.; Kruger, A. W. Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305.

Scheme 6.[a] Synthesis of the Macrolactone Core



[a] Reagents and conditions: (i) *p*-methoxyphenol, *ent*-**19** (7.5 mol %), Pd_2dba_3·$CHCl_3$ (2.5 mol %), tetrabutylammonium chloride, CH_2Cl_2, room temperature, 20 h, 20/1 dr, 2/1 regioselectivity (2°/1°), 79%; (ii) TBAF, THF, room temperature, 12 h, 96%; (iii) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 5 h, 84%; (iv) *tert*-butylthiopropionate, LDA, THF, −108 °C, 3 h, 5/1 dr, 82%; (v) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 86%; (vi) DIBAL-H, toluene, −78 °C, 3 h, 79%; (vii) BF_3·OEt_2, CH_2Cl_2, −78 °C, 45 min, 94%; (viii) TBDMSOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C, 1 h, 95%; (ix) CAN, acetone/H_2O (4/1), 0 °C, 5 min, 82%; (x) 0.5 mM in toluene, 110 °C, 1 h, 82%; (xi) HF·pyridine, MeOH, 0 °C, 5 h; (xii) PPTS, MeCN, H_2O, room temperature, 3 h, 91% (2 steps).

Scheme 7.[a] Synthesis of Olefination Agent for Deschlorocallipeltoside A



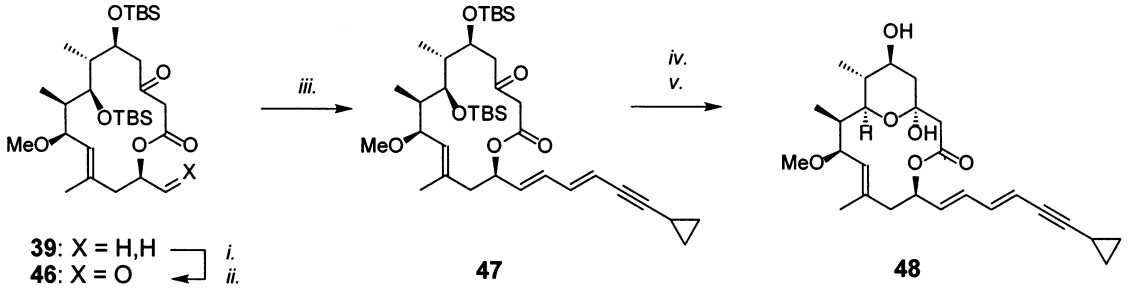
[a] Reagents and conditions: (i) *n*-BuLi, I_2, THF, 0 °C, 2 h, 80%; (ii) CuI, pyrrolidine, THF, 0 °C to room temperature, 2 h, 38%; (iii) Red-Al, THF, 0 °C, 1 h, 96%; (iv) PPh_3, CBr_4, CH_2Cl_2, −40 °C, 1 h, 95%; (v) $P(OMe)_3$, 100 °C, 6 h, 97%.

ploying some additives. All the reactions carried out were nearly quantitative. Alkoxides have no effect on the selectivity, but addition of HMPA (optimum 6 equiv) gives rise to a satisfactory 10/1 *E*/*Z* ratio using *n*-butyllithium as the preferred base. This ratio can be further improved by replacing THF by 1,2-dimethoxyethane (DME), but this combination seemed too risky to try on our sensitive aldehyde. With these new conditions in hand, we carried out the synthesis of the optically active side chain.

To be able to assign unambiguously the relative configuration of the *trans*-chlorocyclopropane with regard to the macrolactone, both enantiomers of the side chain had to be synthesized and attached to the macrolactone. Indeed, the isolation of the chlorocyclopropane from the rest of the stereocenters provides no detectable bias by NMR spectroscopy, as shown by the synthesis of two diastereoisomers of the callipeltoside aglycon by Paterson et al.[2c] We therefore performed the synthesis of the side chain for both enantiomers, which starts from the commercially available dimenthyl succinate **54**[25] to form known cyclopropane **55** (see Scheme 9).[26] The diastereomeric ratio is greater than 99/1 when 0.5 equiv of electrophile are used;

(25) $3.1/mmol for both enantiomers (Aldrich), but easily accessible from the inexpensive menthol and succinyl chloride.

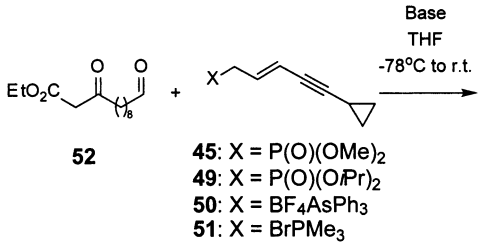
Scheme 8.[a] Attachment of Side Chain for Deschlorocallipeltoside A via Olefination Protocol

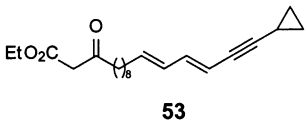


[a] Reagents and conditions: (i) OsO_4, NMO, THF/H_2O (4/1), 0 °C, 4 h; (ii) $NaIO_4$, THF/H_2O, room temperature, 3 h, 80% (2 steps); (iii) **45**, LiHMDS, THF, −78 °C, 3 h, 4/1 (*E*/*Z*), 40%; (iv) HF·pyridine, MeOH, 0 °C, 2 h; (v) PPTS, MeCN, H_2O, room temperature, 3 h, 60% (2 steps).

Table 2. New *E* Selective Olefination Conditions for Unbiased Substrates

entry	X	base	additive	yield (%)	*E*/*Z*
A	$P(O)(OMe)_2$	LiHMDS		100	4.7/1
B	$P(O)(OiPr)_2$	LiHMDS		15	19/1
C	BF_4AsPh_3	KHMDS		31	6.5/1
D	$BrPMe_3$	*n*BuLi		100	2.5/1
E	$BrPMe_3$	*sec*BuLi		100	2.2/1
F	$BrPMe_3$	LiTMP		100	2.7/1
G	$BrPMe_3$	LiHMDS		100	2.5/1
H	$BrPMe_3$	LiHMDS	H_2O	100	2.8/1
I	$BrPMe_3$	*n*BuLi	3 equiv of HMPA	100	5.3/1
J	$BrPMe_3$	*n*BuLi	6 equiv of HMPA	100	10/1
K	$BrPMe_3$	*n*BuLi	10 equiv of HMPA	100	9/1





(3)

however, this leads to a lot of unreacted starting material which is difficult to remove from the product by column chromatography. The dr is lowered to 12/1 if 1 equiv of electrophile is used, but is easily amplified to 99/1 by a single recrystallization in methanol.[27] This stoichiometry reduces the amount of unreacted starting material and therefore is preferred on large scale. One of the menthyl esters was transformed into the known acid chloride **57** in excellent yield using a literature procedure.[28] To place the chloride atom onto the cyclopropane, we first envisioned a palladium mediated decarbonylation of **57**. This reaction would proceeded by insertion of the palladium into the carbon−chloride bond, migration of CO, elimination of CO, and reductive elimination. This process has some literature precedents, but all our attempts using various palladium sources, ligands, additives, and solvents remained unsuccessful.[29]

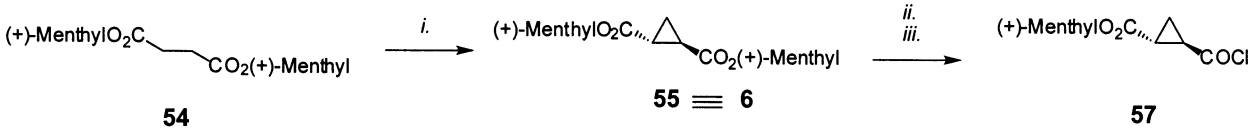
Acid chloride **57** was successfully transformed into chloride **58** using the Barton−Crich−Motherwell decarboxylation in carbon tetrachloride.[30] We first applied the original conditions for this reaction (2-mercaptopyridine-1-oxide sodium salt, DMAP, in refluxing carbon tetrachloride), and obtained unreproduceable yields ranging from 32 to 74%. We therefore embarked on a careful study of this reaction. To this end, we prepared in a separate step the Barton ester **59** starting from the acid **56** using tributyl phosphine and 2,2′-dithiobis(pyridine-*N*-oxide) (eq 4).[31] This esterification is essentially quantitative; however, the Barton ester **59** is very sensitive to any purification technique and was isolated pure in 48% yield. The direct radical chain reaction of the pure Barton ester **59** yielded the chlorocyclopropane **58** in a disappointing 62% yield at $c = 0.02$ M after 6 h at reflux (eq 5). The reaction time can be reduced to 45 min with no loss in the yield by adding a radical initiator (5 mol % azobis(isobutyronitrile) (AIBN)), but the concentration cannot be increased, as no product was detected at $c = 0.2$ M. To our surprise, when the crude esterification mixture was just evaporated in vacuo and subjected to the radical reaction, no product was detected. With those results in hand, we optimized the two step, one pot process starting from acid chloride **57**.

The best conditions were mixing the acid chloride **57**, the Barton salt, DMAP (20 mol %), and a phase-transfer catalyst (nBu_4NI, 20 mol %) in carbon tetrachloride (0.02 M), and stirring that mixture in the absence of light at room temperature for 1 h. Thin-layer chromatography shows very clean formation of the Barton ester **59**. A radical initiator (AIBN, 5 mol %) is then added, and the mixture is heated at reflux in the presence of light for 5 h. This procedure allowed the obtention of desired chlorocyclopropane **58** in a reproducible 60% yield on scales up to 10 mmol with 33/1 diastereomeric ratio (eq 6). This reaction can be performed in 10 min (instead of 6 h) under microwave irradiation (150 °C) in 52% yield but needs to be performed under the same dilute conditions (0.02 M), therefore limiting the scale of each batch.[32]

As shown in Scheme 10, chloride **58** was converted in three steps into known dibromoolefin **62** via Weinreb amide **60** in excellent yield.[33] We used a Weinreb amide because it allowed an easy separation of the menthol and has no volatility issue.[34] The dibromoolefin **62** has been synthesized in seven steps from commercially available starting materials and reagents in 38% overall yield. By using the enantiomeric starting succinate ester,

(26) Misumi, A.; Iwanaga, K.; Furuta, K. Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343.
(27) Furuta, K.; Iwanga, K.; Yamamoto, H. *Org. Synth.* **1988**, *67*, 76.
(28) Ornstein, P. L.; Bleisch, T. J.; Arnold, M. B.; Kennedy, J. H.; Wright, R. A.; Johnson, B. G.; Tizzano, J. P.; Helton, D. R.; Kallman, M. J.; Schoepp, D. D.; Herin, M. *J. Med. Chem.* **1998**, *41*, 358.
(29) (a) Verbicky, J. W., Jr.; Dellacoletta, B. A.; Williams, L. *Tetrahedron Lett.* **1982**, *23*, 371. (b) Hori, K.; Ando, M.; Takaishi, N.; Inamoto, Y. *Tetrahedron Lett.* **1986**, *27*, 4615.
(30) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.
(31) (a) Barton, D. H. R.; Chen, C.; Wall, G. M. *Tetrahedron* **1991**, *47*, 6127. (b) Barton, D. H. R.; Samadi, M. *Tetrahedron* **1992**, *48*, 7083.
(32) Microwave heating was carried out in a Smith Workstation US manufactured by Personal Chemistry AB.

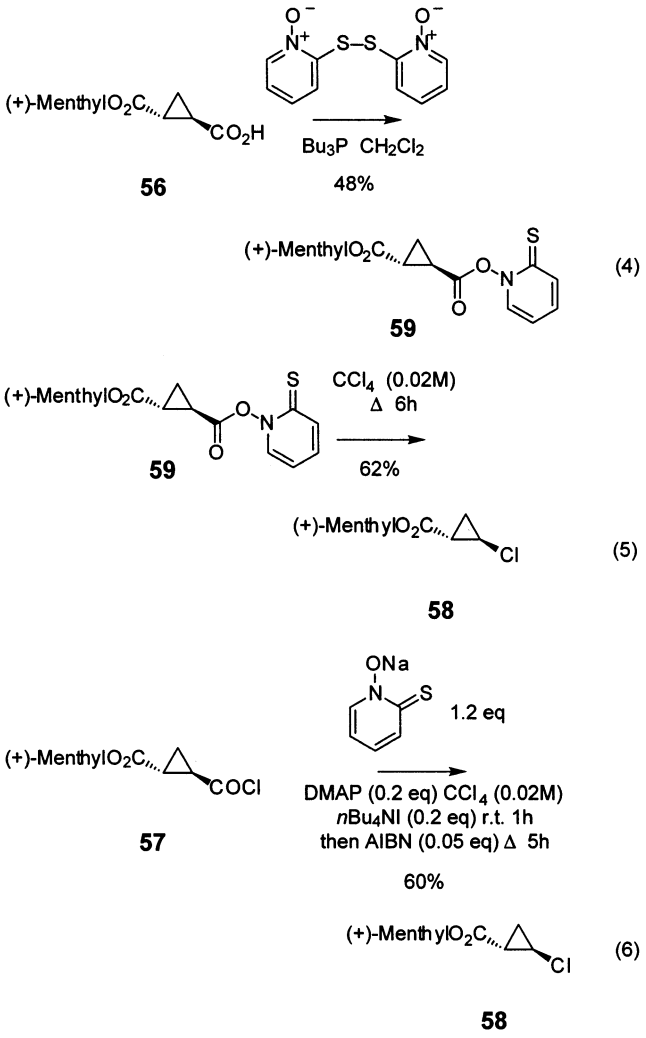
Scheme 9.[a] Asymmetric Synthesis of Chlorocyclopropane



54 **55 ≡ 6** **57**

[a] Reagents and conditions: (i) LiTMP, $BrCH_2Cl$, THF, −78 °C, 4 h, 99/1 dr, 87%; (ii) NaOH (5 M), *i*PrOH, 70 °C, 12 h, 92%; (iii) $SOCl_2$, room temperature, 12 h, 97%.

ent-**62** was obtained in similar yield. We then used the Stille conditions developed by Shen[35] and used by Olivo[2d] for this exact reaction to produce known enyne **63** and its enantiomer in 66% yield.[36] Enyne **63** is easily transformed into phosphonate **65** via the corresponding bromide **64** in good yield. For unknown reasons, we were not able to synthesize the corresponding trimethyl phosphine salt from bromide **64**.[37] The side chain **65** was synthesized over 10 linear steps from the commercially available dimenthyl succinate **54** in an overall yield of 20%.



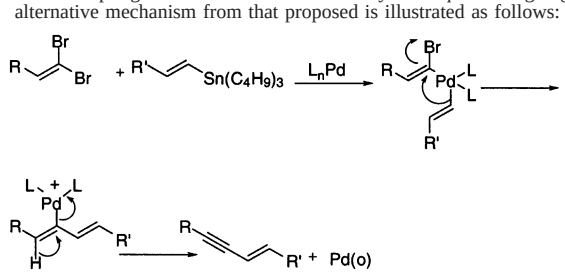
As depicted in Scheme 11, the side chain **65** was coupled to the aldehyde **46** using an Emmons−Wadsworth−Horner reaction and proceeded in similar yield and selectivity as that with the deschloro side chain **45** (52% yield, 4/1 *E*/*Z*). The callipeltoside aglycon **67** was obtained in 96% yield after deprotection with HF−pyridine in methanol.[38] With the synthesis of one of the diastereoisomers of the callipeltoside aglycon achieved, we focused on finding a better reaction for the coupling of the side chain to the macrolactone. Our route to the macrolactone **39** generates a terminal olefin. We therefore sought to use an olefin cross-coupling metathesis reaction to shorten the synthesis.

Scheme 12 outlines our efforts toward this goal. No cross-metathesis attempted between **39** and a terminal alkene proceeded using the first generation of Grubbs' catalyst. While no diene, dienyne, vinylborane, or vinyl silane worked, we were delighted to achieve very clean cross-metathesis using styrene (50% yield) or crotonaldehyde[39] with the second generation of Grubbs' catalyst.[40] α,β-Unsaturated aldehyde **68** obtained after cross-metathesis has not been isolated, but in order to have an estimate of the yield of the reaction, it was trapped by (carbethoxymethylene)triphenylphosphorane to give a stable α,β,γ,δ-unsaturated **69a** ester in nearly quantitative yield. The cross-metathesis reaction between **39** and crotonaldehyde is therefore nearly quantitative. Surprisingly, this reaction does not proceed in benzene at 60 °C. To couple the side chain, we developed a one pot cross-metathesis−Takai olefination to afford vinyl iodide **69b**.[41] This one pot procedure yielded **69b** in 40% yield with a 7/1 *E*/*Z* ratio in straight THF as the Takai

(33) All the spectroscopic data as well as the rotation of **62**/*ent*-**62** are identical to the reported values.[2e] Rotation of **62**, $[\alpha]_D^{27} = -80.3$ ($c = 0.77$, CH_2Cl_2); rotation of *ent*-**62**, $[\alpha]_D^{27} = +80.1$ ($c = 1.40$, CH_2Cl_2); lit. value,[2e] $[\alpha]_D^{25} = -80.5$ ($c = 0.71$, CH_2Cl_2).

(34) Menthyl bromide and dibromoolefin **62** are very difficult to separate.

(35) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. The mechanism of this direct coupling of the dibromide to an enyne is quite intriguing. An alternative mechanism from that proposed is illustrated as follows:



(36) All the spectroscopic data with the exception of the rotation of **63**/*ent*-**63** are identical to the reported values.[2e] Rotation of **63**, $[\alpha]_D^{26} = -222.7$ ($c = 0.70$, CH_2Cl_2); rotation of *ent*-**63**, $[\alpha]_D^{26} = +225.5$ ($c = 0.70$, CH_2Cl_2); lit. value,[2e] $[\alpha]_D^{25} = -78.9$ ($c = 0.705$, CH_2Cl_2).

(37) To exclude any phosphine poisoning in that attempted transformation, bromide **64** was also synthesized by displacing the mesylated analogue of **63** by lithium bromide.

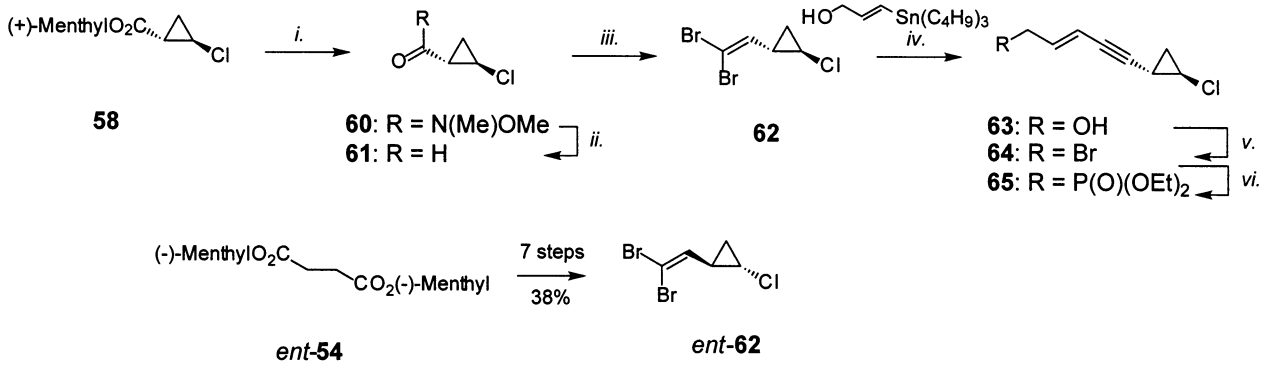
(38) The transketalization (PPTS, MeCN, H_2O) used in the synthesis of **3**, **40**, and **48** was not necessary upon modification of the workup conditions, that is, adding a solution of sodium bicarbonate to the reaction mixture instead of adding the reaction mixture to a solution of sodium carbonate. This modification cannot be used for the synthesis **3** and **40** because the C-5 hydroxyl is susceptible to deshydration in these substrates.

(39) Crotonaldehyde was preferred to acrolein for purity reasons.

(40) For the first report of the second generation catalyst, see: (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. For selected reports of cross-metathesis, see: (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (c) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327.

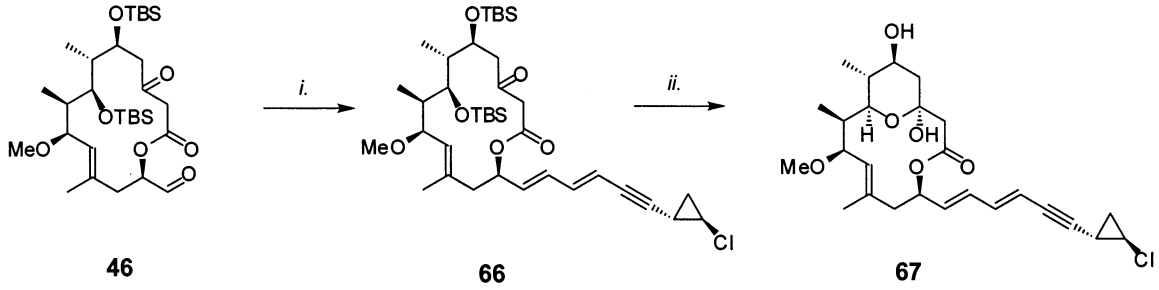
(41) The cross-metathesis reaction is performed in refluxing dichloromethane for 3 h using 10 mol % of the Grubbs' second generation catalyst. The solvent as well as the excess of crotonaldehyde are then removed by evaporation in vacuo. The Takai olefination is then carried out on the black crude residue for 3 h at 0 °C.

Scheme 10.[a] Synthesis of Olefination Agent for Callipeltoside A



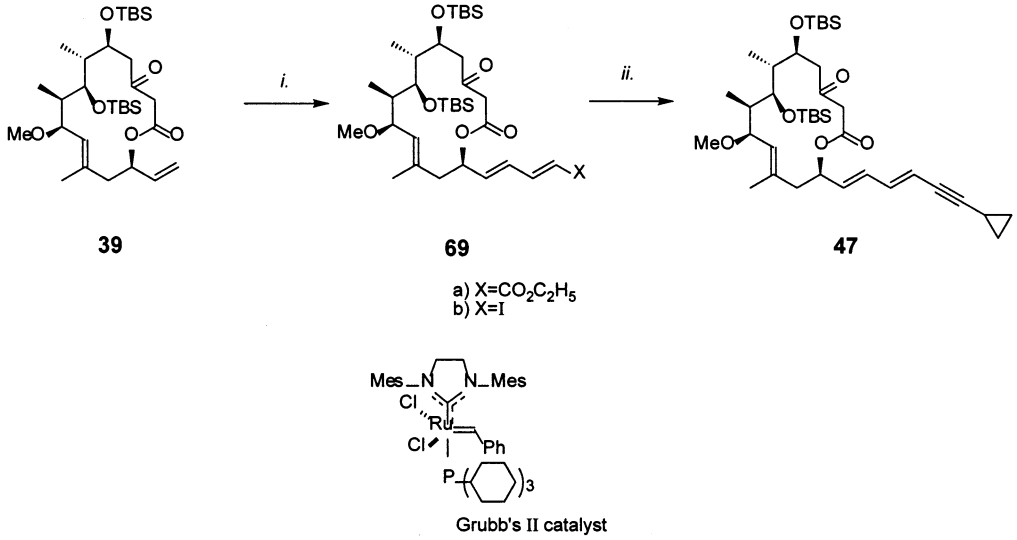
[a] Reagents and conditions: (i.) MeNHOMe·HCl, *i*PrMgCl, THF, −20 °C, 1 h, 99%; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; (iii) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 4 h, 80% (2 steps); (iv) Pd_2dba_3·$CHCl_3$, tris(4-methoxyphenyl)phosphine, DIPEA, DMF, 80 °C, 12 h, 66%; (v) PPh_3, CBr_4, CH_2Cl_2, −40 °C, 1 h, 90%; (vi) $P(OEt)_3$, 100 °C, 4 h, 93%.

Scheme 11.[a] Synthesis of Callipeltoside A Aglycone via Olefination Protocol



[a] Reagents and conditions: (i) **65**, LiHMDS, THF, −78 °C, 3 h, 4/1 (*E*/*Z*), 52%; (ii) HF·pyridine, MeOH, 0 °C, 5 h, 96%.

Scheme 12.[a] Attachment of Side Chain A via Olefination Metathesis−Deschlorocallipeltoside A Aglycone



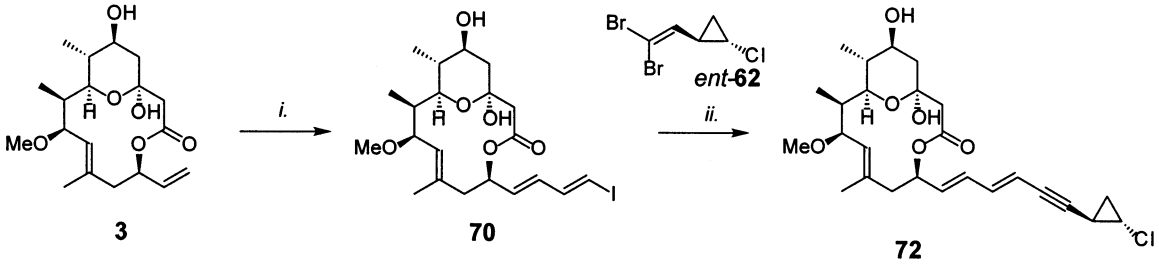
[a] Reagents and conditions: (i) crotonaldehyde, Grubb's II catalyst, CH_2Cl_2, 40 °C, 4 h; then $CrCl_2$, CHI_3, dioxane/THF (4/1), 0 °C, 3 h, 10/1 (*E*/*Z*), 40%; (ii) 1-alkynylcyclopropane, $Cl_2Pd(PhCN)_2$, PPh_3, CuI, DIPA, THF, −20 °C to room temperature, 1 h, 70%.

reaction solvent.[42] This ratio can be improved to 10/1 by use of a 4/1 mixture of dioxane/THF as the solvent.[43] We achieved a formal synthesis of the deschlorocallipeltoside aglycon **48** by synthesizing its direct precursor **47** by a Sonogashira coupling with 1-alkynylcyclopropane (70% yield).[44] This three step, two pot sequence shortens by five steps the previous synthesis of the deschlorocallipeltoside aglycon **48** using the Emmons−Wadsworth−Horner approach and is much more stereoselective and efficient.

However, we were still not satisfied with the yield of the one pot cross-metathesis−Takai olefination process. We anticipated chemoselectivity issues associated with the β-ketoester moiety induced by the chromium species present in the Takai reaction. Accordingly, as illustrated in Scheme 13, this process was performed on the bicyclic macrolide **3**, and we were rewarded with an excellent 84% yield along with 8/1 *E*/*Z* ratio. Paterson et al. achieved a very efficient Sonogashira coupling to form the callipeltoside aglycon on a protected version of **70**.[2c]

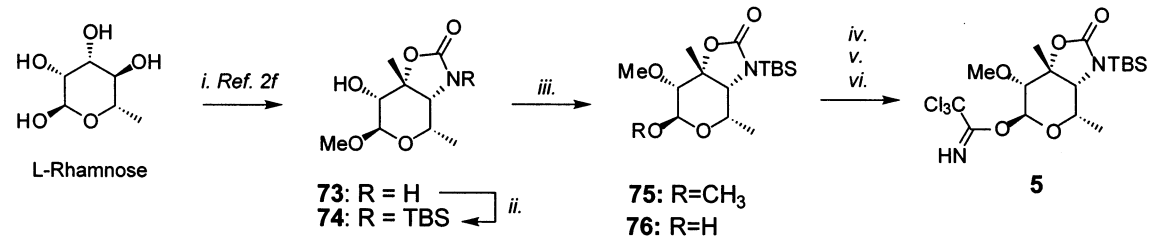
(42) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(43) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.
(44) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.

Scheme 13.[a] Attachment of Side Chain via Olefin Metathesis−20,21-Diepicallipeltoside A Aglycone



[a] Reagents and conditions: (i) crotonaldehyde, Grubb's II catalyst, CH_2Cl_2, 40 °C, 5 h; then $CrCl_2$, CHI_3, dioxane/THF (4/1), 0 °C, 3 h, 8/1 (*E*/*Z*), 84%; 9ii) *n*BuLi, Me_3SnCl, Et_2O, −78 °C to room temperature, 1 h; then **70**, $Cl_2Pd(MeCN)_2$, DMF, room temperature, 45 min, 70%.

Scheme 14.[a] Synthesis of Callipeltoside Glycosylating Agent



[a] Reagents and conditions: (i) ref 2f; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, 2 h, 55%; (iii) MeI, Ag_2O, DMF, room temperature, 12 h, 69%; (iv) H_2SO_4, PPTS, Ac_2O, room temperature, 2 h, 81%; (v) K_2CO_3, MeOH, room temperature, 5 min, 89%; (vi) Cl_3CCN, NaH, CH_2Cl_2, room temperature, 10 min, 86%.

However, volatility and isolation problems for the alkynylchlorocyclopropane used in this reaction are reported by Olivo and Paterson.[2c,d] Since we wanted to achieve a practical synthesis of callipeltoside A, we decided to stay away from this compound and developed a one pot procedure from the dibromoolefin *ent*-**62** to perform a Stille coupling with vinyl iodide **70**. Indeed, the byproducts of the elimination reaction used to form the alkynyl stanane **71** from *ent*-**62** are LiBr, LiCl, *n*-butyl bromide, and butane, none of which in principle is harmful to the Stille coupling reaction. After screening several palladium sources ($Pd_2dba_3{\cdot}CHCl_3$, $(PhCN)_2PdCl_2$, and $(MeCN)_2PdCl_2$), ligands ($AsPh_3$, PPh_3), and solvents (dimethylformamide (DMF), THF, AcOEt, and NMP), we developed a one pot process using the ligandless conditions for the Stille coupling ($(MeCN)_2PdCl_2$ in DMF) and the one pot sequence of formation of the stannane−Stille coupling to afford a second diastereoisomer of the callipeltoside aglycon **72** in 70% yield.[45,46] Indeed, the ligandless conditions gave exclusively the desired product; whereas, other conditions gave significant amounts of reduced vinyl iodide. As we obtained one diastereoisomer **67** of the callipeltoside A aglycon using the Emmons−Wadsworth−Horner route, we synthesized the other diastereoisomer **72** using this one pot cross-metathesis−Takai olefination, one pot formation of the alkynyl stanane−Stille coupling route. Comparison of the analytical data of our synthetic aglycons with those of the enantiomeric aglycons reported by Paterson et al. shows a perfect match.[2c,47] This new approach for the coupling of the side chain is shorter, more stereoselective, and more efficient than the Emmons−Wadsworth−Horner route.

Synthesis of Callipeltose

Scheme 14 outlines the synthesis of the trichloroacetimidate of the *N*-silyl derivative of callipeltose **5**. The intermediate **73** was synthesized from L-rhamnose as previously reported.[2f] In our hands, the *O*-methylation was best accomplished on the silylated oxazolidin-2-one **74** to give **75**. The anomeric position was freed using a mild two step protocol to yield lactol **76**. The sugar was then transformed into the trichloroacetimidate **5** in preparation for the Schmidt glycosidation conditions.[48]

While this route proved productive and allowed generation of sufficient amounts to complete the synthesis, we sought a shorter route that might also provide easy access to either enantiomer. All the other routes begin with the chiral pool, typically a carbohydrate[2f−h] except for the Evans[2i] approach which utilizes threonine. Based upon the Du Bois reaction,[49] we envisaged the strategy depicted in Scheme 15. The ability to form the target oxazolidin-2-one by the oxidative cyclization of the carbamate **78** by the method of Du Bois potentially simplifies the synthesis to the Danishefsky diene and acetaldehyde[50] requiring a diastereoselective epoxidation of glycal **79**[51] and methyl anion addition to ketone **80**. The diastereoselective addition of methyllithium or methylmagnesium bromide to 5-methylcyclohexenone in an axial fashion[52] bodes well for the requisite diastereoselectivity in this addition to ketone **80**. Asymmetric versions of the hetero-Diels−Alder reaction have

(45) Dibromoolefin *ent*-**62** in diethyl ether is treated with 2 equiv of *n*BuLi. The resulting anion is trapped by trimethyltin chloride, and the solvents are evaporated in vacuo (note: the alkynyl stanane **71** is not very volatile; therefore no product is lost during this operation). To this residue is added vinyl iodide **70**, $(MeCN)_2PdCl_2$ (three times 10 mol %), and DMF. The callipeltoside aglycon **72** is obtained after 45 min of reaction at room temperature.

(46) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc*. **1987**, *109*, 2138.

(47) See Supporting Information for ^1H and ^{13}C NMR spectras of **67** and **72**. Rotation of **67**, $[\alpha]_D^{23} = -39.4$ ($c = 1.00$, $CHCl_3$), to be compared with the reported value for *ent*-**67**,[2c] $[\alpha]_D^{20} = +45.8$ ($c = 0.28$, $CHCl_3$). Rotation of **72**, $[\alpha]_D^{25} = +125.0$ ($c = 1.00$, $CHCl_3$), to be compared with the reported value for *ent*-**72**, [2c] $[\alpha]_D^{20} = -97.8$ ($c = 0.19$, $CHCl_3$).

(48) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl*. **1980**, *19*, 731.

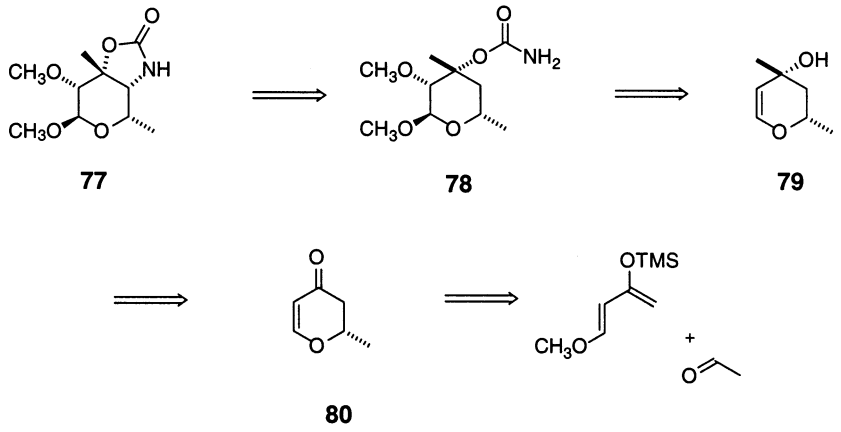
(49) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

(50) For comprehensive reviews for this reaction, see: (a) Danishefsky, S. J.; De Ninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (b) Jörgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

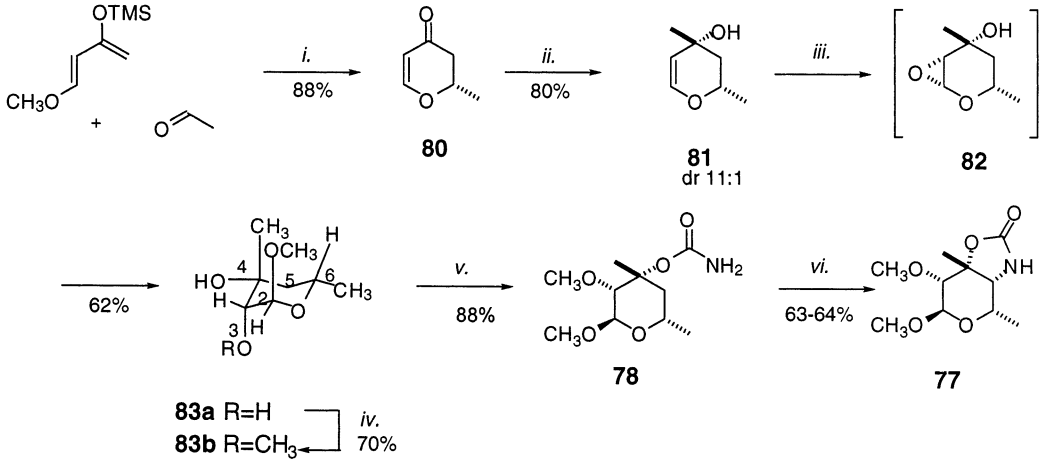
(51) This reaction has been used on a different glycal in an expedient synthesis of D-callipeltose; see ref 2h. Also see: (a) Rainier, J. D.; Allwein, S. P.; Cox, J. *J. Org. Chem.* **2001**, *66*, 1380. (b) Saleh, T.; Rousseau, G. *Synlett* **1999**, *617*. (c) Belluci, G.; Catelani, G.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433.

(52) House, H. O.; Fischer, W. F., Jr. *J. Org. Chem.* **1968**, *33*, 949.

Scheme 15. Retrosynthetic Analysis of Methyl Callipeltose **77**



Scheme 16.[a] Synthesis of Racemic Methyl Callipeltose



[a] Reagents and conditions: (i.) BF_3; ether, −78 °C, 2h; (ii) CH_3Li, THF, −100 °C, 2 h; (iii) *m*-CPBA, $NaHCO_3$, CH_3OH, 0 °C, 2 h; (iv) NaH, CH_3I, THF, 0 °C, 6h; (v) CCl_3CONCO, CH_2Cl_2, room temperature, 1 h and then K_2CO_3, H_2O, CH_3OH, room temperature, 18 h; (vi) see text.

been developed.[53] In fact, an asymmetric version for the exact reaction required has already been reported.[54] Thus, this strategy may provide either enantiomer in a comparatively very short sequence.

Scheme 16 summarizes our new route to racemic methyl callipeltose. The known pyranone **80** was prepared as previously described.[55] Addition of methylithium at −100 °C gave an 11:1 diastereomeric ratio as determined by ^{1}H NMR spectroscopy using the signals for the vinyl proton at δ 6.28 (major) vs δ 6.38 (minor). The assignment of the relative stereochemistry shown for **81** rests on the previously stated analogy and torsional strain considerations at this point.[56] Support for this assignment also derives from an nOe study of a subsequent product. The identity of our final target with that previously reported for methyl callipeltose[2h] ultimately confirmed the correctness of this assignment.

Epoxidation in methanol effected simultaneous solvolysis to the desired product **83a** as a single diastereomer presumably via the epoxide **82**. ^{1}H NMR spectroscopy is in full accord with the assigned structure, and the molecule adopting a chair conformation as depicted. For example, the signal for H-6 shows a dqd, J = 11.0, 6.4, 2.7 Hz, which is fully consistent with this proton being axial and having typical ax−ax and ax−eq coupling with the adjacent methylene group. The 1.6 Hz coupling between H-2 and H-3 is consistent with eq−eq coupling. A significant nOe between the methyl group at C-4 and H-6 confirms both of these groups being axial and supports the diastereoselectivity assigned for formation of **81**.

O-Methylation (to **83b**) and carbamate formation (to **78**) proceeded uneventfully. Reaction of the carbamate with 10 mol % rhodium acetate, 2.3 equiv of diacetoxyiodobenzene, and 1.4 equiv of base in refluxing methylene chloride gave 79−80% conversion. Using MgO as base then led to a 57% yield of the target **77** which increased to 63% using 2,6-di-*tert*-butylpyridine as base. No significant improvement occurred by switching to rhodium triphenylacetate as catalyst. In this case, a higher yield (64%) was obtained with MgO as base compared to 2,6-di-*tert*-butylpyridine (54%). Comparison of the spectral data with those previously reported for methyl callipeltose[2h] demonstrated their identity. Thus, racemic methyl callipeltose is available in six steps and 17% overall yield. Since the asymmetric synthesis of enone **80** is already known, this route is the shortest reported synthesis to either enantiomer of this sugar moiety.

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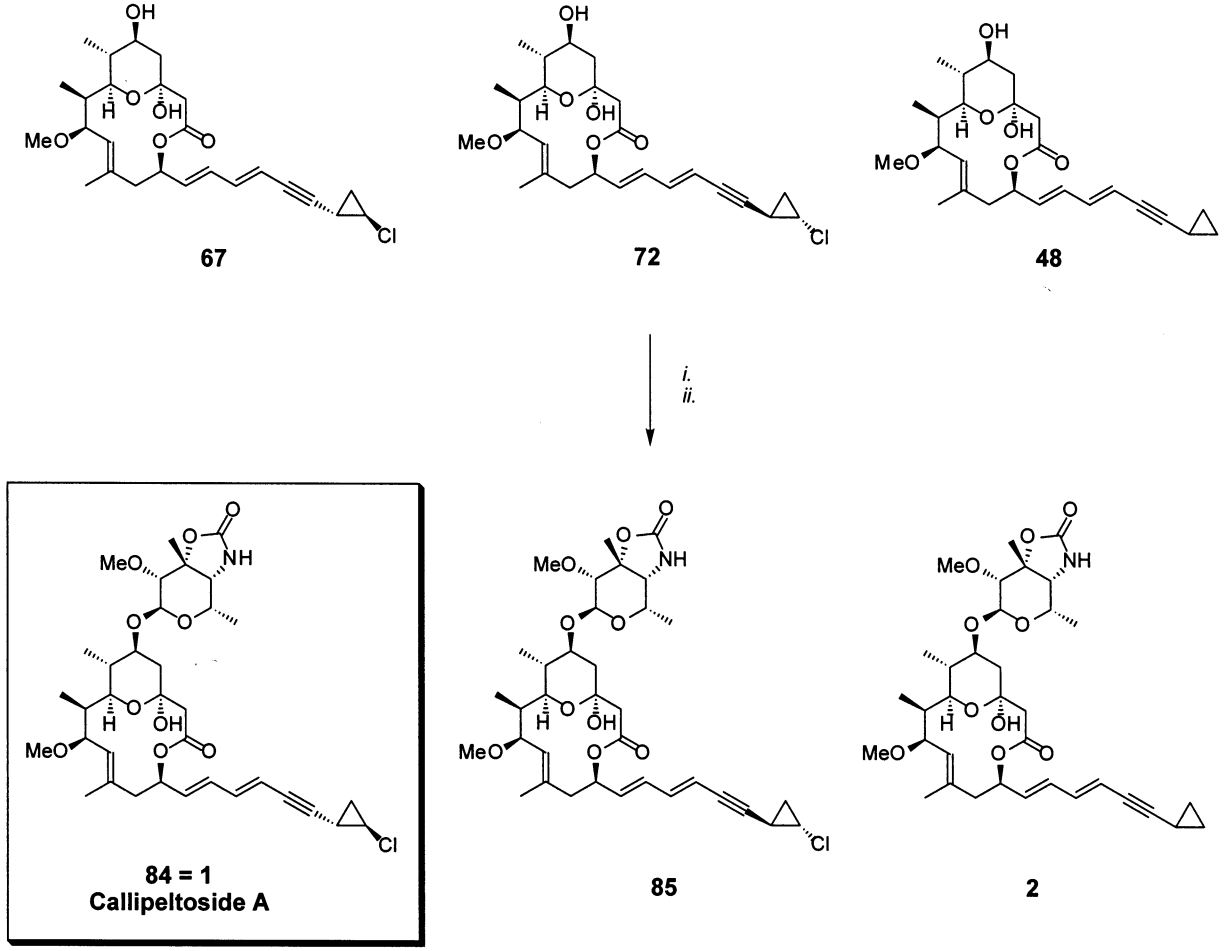
(54) Mituda, M.; Hasegawa, J. U.K. Pat. Appl. 1997, 33; *Chem. Abstr.* **1997**, *127*, 34124

(55) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982**, *47*, 1597.

(56) Wu, Y. D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656.

Scheme 17.[a] Synthesis of Callipeltoside A, Its C-20, C-21 Epimers, and Deschloro Analogue



[a] Reagents and conditions: (i.) **5**, TMSOTf, dichloroethane, 4 Å MS, −30 °C, 10 min, 73%; (ii) TBAF, AcOH, THF, room temperature, 5 min, 95%.

Completion of the Synthesis

The total synthesis of deschlorocallipeltoside A (2) and two diastereoisomers of callipeltoside A **84** and **85** was then completed after a Schmidt glycosidation using a catalytic amount of TMSOTf in dichloroethane at −30 °C, followed by a buffered TBAF deprotection of the only protecting group (see Scheme 17). These reactions proceeded excellently and gave single diastereoisomers **2**, **84**, and **85** in high yield. The ^{1}H and ^{13}C NMR spectroscopic data as summarized in Tables 3−5 (provided in the Supporting Information) show, as expected, no difference between **84**, **85**, and the natural sample.[57] The unambiguous assignment of the absolute and relative configuration comes from the rotation values. Indeed, **84** has a rotation of $[\alpha]_D^{22} = -19.2$ ($c = 1.0$, CH_3OH), very close in the absolute value and the same sign as the natural sample $[\alpha]_D = -17.6$ ($c = 0.04$, CH_3OH), whereas **85** has a rotation of $[\alpha]_D^{22} = +156.3$ ($c = 0.55$, CH_3OH). This significant difference allows us to assign the absolute and relative configuration of callipeltoside A **(1)** as **84**.

Biological Activity

The cytotoxicity of **1**, its diastereoisomer **78**, **2**, and callipeltoside A aglycon **67** has been measured using a different cell line (A2780 human ovarian carcinoma cells after a 48 h incubation) than the one used by Minale et al. Table 6 shows

Table 6. Biological Data

entry	compd	IC_{50} (μM)
A	**67**	>100
B	**1**	20.2
C	**78**	7.0
D	**2**	17.4

that the sugar is essential for the biological activity and that the chloride atom is not essential to the biological activity.

Conclusion

The macrolactone part of callipeltoside A, **3**, has been synthesized in 16 linear steps from methyl-3-hydroxy-2-methyl propionate. The C-13 epi analogue was also readily available by the same route but just by employing a different catalyst in the AAA reaction. This route highlights a new synthesis of geometrically defined trisubstituted alkenes using ruthenium catalysis and regio- as well as diastereoselective synthesis of an allyl ether via palladium catalyzed AAA reaction that could not be easily accomplished otherwise. This route also highlights the utility of the Boeckman macrocyclization method since the dioxolenone serves two purposes—an efficient diastereoselective aldol reaction of acetoacetate at the methyl group as the donor and a convenient source of a reactive acylating agent.

Overall, **84 (**i.e. **1)** was synthesized in 22 steps for the longest linear sequence (3.8% overall yield) and 46 total steps in 0.05% overall yield using the olefination protocol for attachment of

(57) See supporting material for ^{1}H and ^{13}C NMR spectras of **77** and **78**.

the dienyne side chain from all commercially available starting materials. The diepi **85** was also synthesized in 22 steps for the longest linear sequence (5.1% overall yield) and 46 total steps in 0.14% overall yield, all starting with commercially available materials. In the case of the synthesis of callipeltoside A, its synthesis would also be shortened by three to 43 total steps using the olefin metathesis strategy for attaching the side chain. This sequence is also noteworthy for the development of a convenient one pot olefin metathesis−Takai olefination protocol. It highlights the efficiency of the Yamamoto protocol which provides easy access to either enantiomeric chlorocyclopropane using the Barton version of a Hunsdiecker reaction. The deschloro analogue required only 36 total steps via the metathesis route. All of these syntheses will be reduced by four total steps by employing the new synthesis of methyl callipeltose described herein.

This strategy is highly convergent as the three main pieces of the molecule, i.e., the macrolactone, the aglycone side chain, and the sugar, are assembled within the last four steps of the synthesis. This convergent approach is perfectly suited to pursue structure−activity studies and enabled us to synthesize the C-13 epimeric macrolactone core and two isomers of **1** as well as deschlorocallipeltoside A **2**.

Experimental Section

(2*S*,3*S*)-*tert*-Butyldimethylsilyloxy-2-methylhex-4-yn-3-ol (11). Ketone **10** (0.05 g, 0.2 mmol) was dissolved in THF (1 mL, 0.2 M) and cooled to −30 °C. To this solution was added 2-methyl (*S*)-CBS oxazaborolidine (0.42 mL of 1 M in toluene, 0.42 mmol), and borane−dimethyl sulfide (0.5 mL of a 2 M in THF, 1.0 mmol) was added dropwise over 2 min. After the resulting reaction mixture was stirred for 1 h at −30 °C, the reaction was quenched by addition of ethanol (0.8 mL), warmed to room temperature, and diluted with water (10 mL) and diethyl ether (10 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (SiO_2, 1/9 to 1/2 ether:PE) to afford a 10/1 dr of predominately **11** (48 mg, 99%): $[\alpha]_D = +16.7$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 3418, 2958, 2930, 2859, 2229, 1472, 1390, 1362, 1255, 1092, 1019, 838, 777, 668$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43−4.28 (m, 1 H), 3.86 (dd, J = 10.0, 4.0 Hz, 1 H), 3.53 (dd, J = 9.5, 7.0 Hz, 1 H), 3.49 (br s, 1 H), 1.90−1.82 (m, 1 H), 1.83 (d, J = 2.0 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.3, 79.2, 67.2, 67.0, 40.8, 25.8, 18.1, 13.0, 3.6, −5.6, −5.7 ppm. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.60; H, 10.65.

Undesired Diastereomer 12. $[\alpha]_D = +23.4$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 3436, 2958, 2930, 2859, 1472, 1256, 1090, 1022, 837, 777$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40−4.35 (m, 1 H), 3.81 (d, J = 7.5 Hz, 1 H), 3.80 (dd, J = 9.5, 9.5 Hz, 1 H), 3.63 (dd, J = 10.0, 4.5 Hz, 1 H), 2.11−2.02 (m, 1 H), 1.83 (d, J = 2.0 Hz, 3 H), 0.87 (s, 9 H), 0.84 (d, J = 7.0 Hz, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.6, 78.3, 67.3, 66.8, 39.9, 25.8, 18.1, 12.4, 3.6, −5.6, −5.7 ppm. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.36; H, 10.78.

(2*E*,5*E*)(7*S*,8*S*)-9-(*tert*-Butyldimethylsilyloxy)-7-methoxy-5,8-dimethylnona-2,5-dienoxycarbonyloxy-2,2,2-trichloroethyl (17). Alkyne **13** (900 mg, 3.5 mmol) and 3-butenyloxycarbonyloxy-2,2,2-trichloroethane (**16**) (2.6 g, 10.5 mmol) were dissolved in acetone (7.0 mL, 0.5 M) and treated wtih $CpRu(NCMe)_3PF_6$ (76 mg, 0.18 mmol) for 20 min at room temperature. The reaction mixture was concentrated and purified by flash column chromatography (SiO_2, 1/9 to 1/3, ether:PE) to afford **17** (1.49 g, 85%): $[\alpha]_D = +3.3$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 2930, 2858, 2818, 1761, 1667, 1463, 1389, 1237, 1082, 1029, 969, 914, 837, 778, 729, 670$ cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86−5.79 (m, 1 H), 5.68−5.60 (m, 1 H), 5.02 (ddd, J = 9.5, 2.5, 1.0 Hz, 1 H), 4.74 (s, 2 H), 4.66 (dd, J = 6.5, 1.0 Hz, 2 H), 3.85 (dd, J = 9.5, 2.5 Hz, 1 H), 3.55 (dd, J = 10.0, 6.0 Hz, 1 H), 3.49 (dd, J = 10.0, 5.5 Hz, 1 H), 3.18 (s, 3 H), 2.79 (d, J = 6.5 Hz, 2 H), 1.79−1.71 (m, 1 H), 1.64 (d, J = 1.5 Hz, 3 H), 0.87 (s, 9 H) 0.79 (d, J = 7.0 Hz, 3 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 138.1, 135.6, 125.3, 124.3, 94.4, 77.9, 76.7, 69.4, 64.5, 55.9, 42.0, 40.5, 25.9, 18.3, 16.9, 12.5, −5.4, −5.5 ppm. Anal. Calcd for $C_{21}H_{37}O_5Si$: C, 50.05; H, 7.40. Found: C, 50.17; H, 7.35.

(*E*)-(2*R*,3*R*,7*S*)-*tert*-Butyl[3-methoxy-7-(4-methoxyphenoxy)-2,5-dimethylnona-4,8-dienyloxy]dimethylsilane (24). To a degassed flask containing Pd_2dba_3·$CHCl_3$ (40 mg, 0.039 mmol), (−)-(1*R*,2*R*)-bis(2′-diphenylphosphinobenzamido)-1,2-diphenylethane (**19**) (92 mg, 0.12 mmol), 4-methoxylphenol (192 mg, 1.55 mmol), and tetrabutylammonium chloride (108 mg, 0.39 mmol) was added degassed CH_2Cl_2 (15 mL). After the purple reaction mixture was stirred for 15 min, the solution became yellow, and allyl carbonate **17** (650 mg, 1.29 mmol) was added as a solution in CH_2Cl_2 (10 mL). The resulting reaction mixture was stirred at ambient temperature for 12 h, concentrated, and purified by flash column chromatography (SiO_2, 1/3 to 1/1, ether/PE) to afford a 3.0/1.0 mixture of 2°/1° substitution (443 mg, 79%).

(a) 2° Substituted Aryl Ether 24. $[\alpha]_D = -2.3$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 2956, 2930, 2858, 1506, 1471, 1387, 1361, 1229, 1083, 1041, 925, 836, 776, 671$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84−6.75 (m, 4 H), 5.83 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.23 (d, J = 17.0 Hz, 1 H), 5.17 (d, J = 10.5 Hz, 1 H), 5.11 (d, J = 9.5 Hz, 1 H), 4.63 (ddd, J = 7.0, 6.5, 6.0 Hz, 1 H), 3.88 (dd, J = 9.5, 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.55 (dd, J = 9.5, 5.5 Hz, 1 H), 3.50 (dd, J = 9.5, 5.0 Hz, 1 H), 3.19 (s, 3 H), 2.56 (dd, J = 14.0, 7.0 Hz, 1 H), 2.39 (dd, J = 14.0, 6.0 Hz, 1 H), 1.80−1.72 (m, 1 H), 1.74 (s, 3 H), 0.89 (s, 9 H) 0.80 (d, J = 6.5 Hz, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.1, 137.9, 136.2, 127.2, 117.1, 116.5, 114.4, 78.4, 77.7, 64.5, 55.8, 55.5, 46.0, 40.6, 25.8, 18.2, 17.4, 12.5, −5.5, −5.5 ppm. Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.88; H, 9.53.

(b) 1° Substituted Aryl Ether. $[\alpha]_D = +2.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 2956, 2930, 2858, 1667, 1592, 1464, 1386, 1230, 1181, 1107, 1082, 1040, 970, 836, 776, 669$ cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85−6.76 (m, 4 H), 5.82−5.66 (m, 2 H), 5.03 (d, J = 9.5 Hz, 1 H), 4.43 (d, J = 5.5 Hz, 2 H), 3.85 (dd, J = 10.0, 7.0 Hz, 1 H), 3.74 (s, 3 H), 3.55 (dd, J = 9.5, 5.5 Hz, 1 H), 3.50 (dd, J = 9.5, 5.0 Hz, 1 H), 3.19 (s, 3 H), 2.79 (d, J = 6.5 Hz, 2 H), 1.79−1.71 (m, 1 H), 1.65 (s, 3 H), 0.88 (s, 9 H) 0.80 (d, J = 7.0 Hz, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 138.7, 132.6, 126.9, 124.9, 115.7, 114.5, 77.9, 69.2, 64.5, 55.9, 55.7, 42.7, 40.5, 25.9, 18.3, 16.9, 12.6, −5.4, −5.5 ppm. Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.83; H, 9.90.

(*E*)-(2*R*,3*R*,7*R*)-*tert*-Butyl[3-methoxy-7-(4-methoxyphenoxy)-2,5-dimethylnona-4,8-dienyloxy]dimethylsilane (28). Allyl carbonate **17** (10.5 g, 20.8 mmol) and 4-methoxyphenol (3.1 g, 25.0 mmol) were dissolved in degassed CH_2Cl_2 (350 mL) and treated with a solution of tetrabutylammonium chloride (1.73 g, 6.24 mmol) in CH_2Cl_2 (25 mL) and a solution of Pd_2dba_3·$CHCl_3$ (0.538 g, 0.52 mmol) and (−)-(1*S*,2*S*)-bis(2′-diphenylphosphinobenzamido)-1,2-diphenylethane (*ent*-**19**) (1.23 g, 1.56 mmol) in CH_2Cl_2 (40 mL). The resulting reaction mixture was stirred at room temperature for 20 h and concentrated, and the crude ^{1}H NMR showed a 2.0/1.0 mixture of 2°/1° substitution and a 20/1 dr. The residue was purified by flash column chromatography (SiO_2, 1/3 to 1/1, ether/PE) to afford the 1° substitution product (2.4 g, 26%) and desired **28** (4.6 g, 51%): $[\alpha]_D = 5.5$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 2929, 2857, 1850, 1729, 1667, 1644, 1592, 1506, 1464, 1443, 1387, 1361, 1228, 1182, 1082, 1040, 990, 925, 836, 776, 739, 670$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84−6.74 (m, 4 H, ArH), 5.84 (ddd, J = 17.5, 10.5, 6.5 Hz, 1 H, H-8), 5.22 (dt, J = 17.5, 1.0 Hz, 1 H, H-9a), 5.17 (dt, J = 10.5, 1.0 Hz, 1 H, H-9b), 5.11 (d, J = 10.0, 1.0

Hz, 1 H, H-4), 4.62 (ddd, J = 7.0, 6.5, 6.5 Hz, 1 H, H-7), 3.87 (dd, J = 9.5, 7.5 Hz, 1 H, H-3), 3.73 (s, 3 H, MeOAr), 3.54 (dd, J = 9.5, 6.0 Hz, 1 H, H-1a), 3.49 (dd, J = 9.5, 5.5 Hz, 1 H, H-1b), 3.18 (s, 3 H, MeO), 2.55 (dd, J = 14.0, 7.5 Hz, 1 H, H-6a), 2.37 (dd, J = 14.0, 6.0 Hz, 1 H, H-6b), 1.78−1.70 (m, 1 H, H-2), 1.72 (s, 3 H, MeS), 0.86 (s, 9 H, *t*-BuSi), 0.80 (d, J = 7.0 Hz, 3 H, Me-2), 0.01 (s, 3 H, MeSi), −0.02 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.2, 138.0, 136.2, 127.3, 117.1, 116.6, 114.4, 78.5, 77.8, 64.5, 55.9, 55.6, 46.1, 40.6, 25.9, 18.2, 17.3, 12.5, −5.5, −5.5 ppm. Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.82; H, 9.86.

(*E*)-(2*R*,3*S*,4*R*,5*R*,9*R*)-3-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-9-(4-methoxyphenoxy)-2,4,7-trimethylundeca-6,10-dienethioic Acid S-tert-Butyl Ester (33). Diisopropylamine (5.7 mL, 41 mmol) was placed in a flame-dried flask and dissolved in THF (45 mL), cooled to −78 °C, and treated with *n*-butyllithium (23 mL, 36.7 mmol). The reaction was stirred at −78 °C for 30 min, then warmed to 0 °C, and then back to −78 °C before addition of *tert*-butyl thiopropionate (6.0 g, 40.8 mmol) as a solution in THF (50 mL). The resulting reaction mixture was stirred at −78 °C for 30 min and then cooled to −107 °C (liquid N_2 in ether), and the aldehyde **30** (2.6 g, 8.2 mmol) was added as a solution in THF (50 mL). The reaction was stirred at −107 °C for 3 h before quenching by addition of acetic acid (3.5 mL, 61.2 mmol) as a solution in THF (20 mL). The reaction was then warmed to 0 °C, diluted with ether (50 mL), and washed with a solution of saturated aqueous sodium bicarbonate (50 mL). The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (SiO_2, 1:9 to 1/1, ether/PE) to afford the aldol product **31** (3.1 g, 82%): $[\alpha]_D$ = 0.4 (c = 1.0, CH_2Cl_2); IR (thin film, KBr) ν = 3514, 2967, 2936, 2055, 1853, 1682, 1505, 1455, 1364, 1289, 1228, 1182, 1084, 1039, 987, 958, 825, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83−6.73 (m, 4 H, ArH), 5.81 (ddd, J = 17.0, 9.5, 6.5 Hz, 1 H, H-10), 5.24 (d, J = 9.5 Hz, 1 H, H-6), 5.21 (dd, J = 17.0, 1.0 Hz, 1 H, H-11), 5.16 (dd, J = 10.5, 1.0 Hz, 1 H, H-11′), 4.61 (ddd, J = 6.5, 6.5, 6.5 Hz, 1 H, H-9), 4.20−4.15 (m, 1 H, H-3), 3.90 (dd, J = 9.5, 6.0 Hz, 1 H, H-5), 3.72 (s, 3 H, MeOAr), 3.15 (s, 3 H, MeO), 2.90 (d, J = 4.0 Hz, 1 H, OH), 2.65−2.58 (m, 1 H, H-2), 2.52 (dd, J = 14.0, 7.5 Hz, 1 H, H-8), 2.37 (dd, J = 14.0, 6.0 Hz, 1 H, H-8′), 1.71 (s, 3 H, Me-6), 1.62−1.55 (m, 1 H, H-4), 1.44 (s, 9 H, *t*-BuS), 1.00 (d, J = 7.0 Hz, 3 H, Me-2), 0.84 (d, J = 7.0 Hz, 3 H, Me-4) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 153.8, 152.0, 137.8, 136.6, 127.7, 117.1, 116.7, 114.3, 80.1, 78.3, 72.3, 56.1, 55.6, 52.1, 47.9, 45.9, 39.4, 29.7, 17.3, 14.8, 9.3 ppm. HRMS. Calcd for $C_{26}H_{40}O_5S$: 464.2596. Found: 464.2598.

The alcohol (1.5 g, 3.23 mmol) was dissolved in CH_2Cl_2 (32 mL, 0.1 M), cooled to 0 °C, and treated with 2,6-lutidine (1.13 mL, 9.7 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.48 mL, 6.46 mmol). The reaction was stirred at 0 °C for 1 h and quenched by addition of a solution of saturated aqueous sodium bicarbonate (50 mL), and the product was extracted into ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (SiO_2, 1/19 to 1/3, ether/PE) to afford **33** (1.6 g, 86%): $[\alpha]_D$ = +31.3 (c = 1.0, CH_2Cl_2); IR (thin film, KBr) ν = 2929, 2857, 1851, 1682, 1592, 1506, 1463, 1364, 1228, 1152, 1082, 1041, 955, 834, 776, 738, 672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84−6.74 (m, 4 H, ArH), 5.83 (ddd, J = 17.5, 10.5, 6.5 Hz, 1 H, H-10), 5.21 (d, J = 17.5 Hz, 1 H, H-11a), 5.16 (d, J = 10.5 Hz, 1 H, H-11b), 4.99 (d, J = 10.0 Hz, 1 H, H-6), 4.61 (ddd, J = 7.0, 6.5, 6.5 Hz, 1 H, H-9), 4.51 (d, J = 8.0 Hz, 1 H, H-3), 3.74 (dd, overlapped, 1 H, H-5), 3.73 (s, 3 H, MeOAr), 3.13 (s, 3 H, MeO), 2.69−2.62 (m, 1 H, H-2), 2.54 (dd, J = 14.0, 7.5 Hz, 1 H, H-8a), 2.37 (dd, J = 14.0, 6.0 Hz, 1 H, H-8b), 1.70 (d, J = 1.5 Hz, 3 H, Me-7), 1.56−1.50 (m, 1 H, H-4), 1.43 (s, 9 H, *t*-BuSi), 1.05 (d, J = 7.0 Hz, 3 H, Me-2), 0.86 (s, 9 H, *t*-BuSi), 0.68 (d, J = 6.5 Hz, 3 H, Me-4), 0.08 (s, 3 H, MeSi), 0.04 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 153.8, 152.1, 138.0, 136.5, 128.8, 117.1, 116.7, 114.4, 78.5, 76.9, 70.5, 55.6, 55.0, 54.6, 47.8, 46.1, 40.2, 29.9, 26.3, 18.5, 17.5, 15.5, 8.9, −4.0, −4.4 ppm. Anal. Calcd for $C_{32}H_{54}O_5SSi$: C, 66.39; H, 9.40; S, 5.54. Found: C, 66.37; H, 9.51; S, 5.31.

(*E*)-(2*S*,3*R*,4*S*,5*R*,6*R*,10*R*)-6-[4-(*tert*-Butyldimethylsilanyloxy)-2-hydroxy-6-methoxy-10-(4-methoxyphenoxy)-3,5,8-trimethyldodeca-7,11-dienyl]-2,2-dimethyl[1,3]dioxin-4-one (36). A solution of thioester **33** (900 mg, 1.55 mmol) in toluene (10 mL, 0.3 M) was cooled to −78 °C and treated with diisobutylaluminum hydride (6.22 mL of a 1 M solution in toluene, 6.22 mmol). The resulting reaction was stirred at −78 °C for 4 h and was quenched by addition of a solution of acetic acid (886 μL, 15.5 mmol) in THF (5 mL), then warmed to 0 °C, and diluted with water (50 mL) and ether (50 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (SiO_2, 1/20 to 1/3, ether/PE) to afford **34** (600 mg, 79%): $[\alpha]_D$ = +16.0 (c = 1.0, CH_2Cl_2); IR (thin film, KBr) ν = 2933, 2858, 2710, 2045, 1850, 1728, 1669, 1644, 1592, 1505, 1464, 1384, 1228, 1182, 1150, 1107, 1084, 1038, 927, 835, 775, 676 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, J = 3.0 Hz, 1 H, CHO), 6.73−6.83 (m, 4 H, ArH), 5.83 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H, H-10), 5.23 (d, J = 17.0 Hz, 1 H, H-11a), 5.17 (d, J = 10.5 Hz, 1 H, H-11b), 5.01 (dd, J = 9.5, 1.0 Hz, 1 H, H-6), 4.62 (ddd, J = 7.0, 6.5, 6.0 Hz, 1 H, H-9), 4.41 (dd, J = 7.0, 1.5 Hz, 1 H, H-3), 3.75 (dd, overlapped, 1 H, H-5), 3.73 (s, 3 H, MeOAr), 3.14 (s, 3 H, MeO), 2.55 (dd, J = 13.5, 6.5 Hz, 1 H, H-8a), 2.49 (m, 1 H, H-2), 2.39 (dd, J = 13.5, 5.0 Hz, 1 H, H-8b), 1.71 (d, J = 1.5 Hz, 3 H, Me-7), 1.58−1.53 (m, 1 H, H-4), 1.01 (d, J = 7.0 Hz, 3 H, Me-2), 0.86 (s, 9 H, *t*-BuSi), 0.75 (d, J = 7.0 Hz, 3 H, Me-4), 0.09 (s, 3 H, MeSi), 0.04 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 153.9, 152.1, 137.9, 136.9, 128.3, 117.1, 116.7, 114.4, 78.4, 77.1, 71.6, 55.6, 55.1, 51.8, 46.0, 41.7, 26.0, 18.4, 17.5, 11.5, 9.6, −4.0, −4.1 ppm.

A solution of aldehyde **34** (600 mg, 1.22 mmol) in CH_2Cl_2 (25 mL, 0.05 M) was cooled to −78 °C and treated with freshly prepared 2,2-dimethyl-6-methylene-4-(trimethylsiloxy)-1,3-diox-4-ene (**35**) (1.3 g, 6.1 mmol) and boron trifluoride diethyl etherate (450 μL, 3.66 mmol). The reaction was stirred at −78 °C for 45 min before quenching with aqueous phosphate buffer (pH 7.0, 25 mL). The product was extracted into ether (3 × 20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (SiO_2, 1/2 to 3/1, ether/PE) to afford **36** (725 mg, 94%): $[\alpha]_D$ = +1.5 (c = 1.0, CH_2Cl_2); IR (thin film, KBr) ν = 3479, 2933, 2857, 2248, 1732, 1634, 1505, 1464, 1392, 1228, 1080, 1015, 905, 834, 774, 735, 674 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82−6.72 (m, 4 H, ArH), 5.82 (ddd, J = 17.5, 10.5, 6.5 Hz, 1 H, H-14), 5.32 (s, 1 H, H-2), 5.21 (d, J = 17.5 Hz, 1 H, H-15a), 5.16 (d, J = 10.5 Hz, 1 H, H-15b), 4.99 (d, J = 9.5 Hz, 1 H, H-10), 4.61 (ddd, J = 7.0, 6.5, 6.5 Hz, 1 H, H-5), 4.30−4.25 (m, 1 H, H-13), 4.09 (dd, J = 4.0, 2.0 Hz, 1 H, H-7), 3.72 (s, 3 H, MeOAr), 3.67 (dd, J = 9.5, 9.5 Hz, 1 H, H-9), 3.15 (s, 3 H, MeO), 3.02 (d, J = 2.5 Hz, 1 H, OH), 2.54 (dd, J = 14.0, 7.5 Hz, 1 H, H-4a), 2.42 (dd, J = 14.5, 9.5 Hz, 1 H, H-12a), 2.38 (dd, J = 14.0, 5.5 Hz, 1 H, H-4b), 2.20 (dd, J = 14.5, 4.5 Hz, 1 H, H-12b), 1.74−1.66 (m, 1 H, H-8), 1.71 (d, J = 1.0 Hz, 3 H, Me-11), 1.66 (2s, 6 H), 1.50−1.44 (m, 1 H, H-6), 0.94 (d, J = 7.0 Hz, 3 H, Me-6), 0.88 (s, 9 H, *t*-BuSi), 0.78 (d, J = 7.5 Hz, 3 H, Me-8), 0.09 (s, 3 H, MeSi), 0.09 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 161.1, 153.8, 152.0, 137.9, 136.9, 127.8, 117.1, 116.7, 114.3, 106.4, 94.7, 79.0, 78.3, 75.3, 68.1, 55.5, 55.4, 46.0, 43.2, 41.6, 39.6, 26.1, 25.3, 24.7, 18.3, 17.4, 11.1, 10.2, −3.9, −4.3 ppm. Anal. Calcd for $C_{35}H_{56}O_8Si$: C, 66.42; H, 8.92. Found: C, 66.23; H, 8.85.

(*E*)-(2*S*,3*R*,4*S*,5*R*,6*R*,10*R*)-6-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-10-hydroxy-6-methoxy-3,5,8-trimethyldodeca-7,11-dienyl]-2,2-dimethyl[1,3]dioxin-4-one (38). Aryl ether **37** (530 mg, 0.71 mmol) was dissolved in acetone (12 mL) and treated with a solution of ceric ammonium nitrate (973 mg, 1.78 mmol) in water (2.8 mL) at 0 °C over 5 min. The product was extracted into ether (2 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column

chromatography (SiO_2, 1/2 to 2/1, ether/PE) to afford **38** (374 mg, 82%): $[\alpha]_D = +3.84$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 3454$, 2930, 2895, 2857, 1732, 1634, 1476, 1391, 1273, 1254, 1205, 1082, 1016, 920, 903, 836, 810, 774, 734, 679 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.86 (ddd, $J = 16.5$, 10.5, 6.0 Hz, 1 H, H-14), 5.33 (s, 1 H, H-2), 5.25 (dt, $J = 16.0$, 1.5 Hz, 1 H, H-15a), 5.10 (dt, $J = 10.5$, 1.5 Hz, 1 H, H-15b), 4.95 (dd, $J = 10.0$, 1.0 Hz, 1 H, H-10), 4.26−4.20 (m, 1 H, H-13), 4.21 (d, $J = 6.5$ Hz, 1 H, H-7), 3.92 (dd, $J = 11.0$, 6.0 Hz, 1 H, H-5), 3.66 (dd, $J = 10.0$, 10.0 Hz, 1 H, H-9), 3.16 (s, 3 H, MeO), 2.55 (dd, $J = 15.0$, 5.0 Hz, 1 H, H-4a), 2.41 (dd, $J = 15.0$, 6.0 Hz, 1 H, H-4b), 2.29 (dd, $J = 13.0$, 5.5 Hz, 1 H, H-12a), 2.25 (dd, $J = 13.0$, 8.0 Hz, 1 H, H-12b), 1.80−1.72 (m, 1 H, H-6), 1.69 (d, $J = 1.5$ Hz, 3 H, Me-11), 1.67 (s, 3 H, Me), 1.66 (s, 3 H, Me), 1.55−1.47 (m, 1 H, H-8), 0.88 (s, 9 H, *t*-BuSi), 0.87 (d, overlapped, 3 H, Me-6), 0.86 (s, 9 H, *t*-BuSi), 0.70 (d, $J = 7.0$ Hz, 3 H, Me-8), 0.08 (s, 3 H, MeSi), 0.06 (s, 3 H, MeSi), 0.06 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 161.1, 140.4, 136.9, 128.8, 114.9, 106.3, 95.6, 78.2, 70.9, 70.7, 70.5, 55.3, 47.9, 44.0, 39.8, 39.7, 26.1, 25.9, 25.3, 24.9, 18.4, 18.2, 17.2, 11.0, 10.5, −3.4, −3.7, −4.1, −4.5 ppm. Anal. Calcd for $C_{34}H_{62}O_7Si_2$: C, 63.91; H, 9.78. Found: C, 63.76; H, 9.70.

(*E*)-(6*S*,7*R*,8*S*,9*R*,10*R*,14*R*)-6,8-Bis(*tert*-butyldimethylsilanyloxy)-10-methoxy-7,9,12-trimethyl-14-vinyloxacyclotetradec-11-ene-2,4-dione (39). A solution of alcohol **38** (200 mg, 0.313 mmol) in freshly distilled toluene (100 mL) was added via cannula to toluene (500 mL, 0.5 mM) at reflux over 45 min. The reaction was stirred at reflux for 1.5 h, cooled, and concentrated. The residue was purified by flash column chromatography (SiO_2, 1/19 to 1/4, ether/PE) to afford cyclized product **39** (150 mg, 82%): $[\alpha]_D = -28.6$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 2957$, 2888, 2857, 1748, 1722, 1472, 1387, 1360, 1256, 1186, 1105, 1005, 939, 838, 776, 676 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 50 °C) δ 5.66−5.60 (m, 2 H, H-13 & H-14), 5.57 (br d, $J = 9.5$ Hz, 1 H, H-10), 5.14 (dd, $J = 16.0$, 1.0 Hz, 1 H, H-15a), 4.96 (dd, $J = 9.0$, 1.0 Hz, 1 H, H-15b), 4.49 (dd, $J = 3.0$, 1.5 Hz, 1 H, H-7), 4.23 (ddd, $J = 9.0$, 6.5, 2.5 Hz, 1 H, H-5), 3.72 (dd, $J = 9.5$, 2.0 Hz, 1 H, H-9), 3.21 (d, $J = 16.0$ Hz, 1 H, H-2a), 3.05 (dd, $J = 17.0$, 9.0 Hz, 1 H, H-4a), 3.04 (s, 3 H, MeO), 2.99 (d, $J = 16.0$ Hz, 1 H, H-2b), 2.43 (dd, $J = 14.0$, 11.5 Hz, 1 H, H-12a), 2.26 (dd, $J = 17.0$, 2.0 Hz, 1 H, H-4b), 2.19−2.12 (m, 1 H, H-6), 2.09 (d, $J = 14.0$ Hz, 1 H, H-12b), 1.69−1.60 (m, 1 H, H-8), 1.57 (s, 3 H, Me-11), 1.19 (d, $J = 7.0$ Hz, 3 H, Me-8), 1.08 (s, 9 H, *t*-BuSi), 1.00 (s, 9 H, *t*-BuSi), 0.93 (d, $J = 7.0$ Hz, 3 H, Me-6), 0.29 (s, 3 H, MeSi), 0.24 (s, 3 H, MeSi), 0.22 (s, 3 H, MeSi), 0.18 (s, 3 H, MeSi) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 191.4, 157.5, 128.0, 126.3, 121.1, 107.8, 73.8, 63.7, 63.0, 60.2, 47.0, 41.9, 39.2, 37.5, 37.0, 31.3, 17.8, 17.8, 10.2, 9.8, 7.0, 6.7, 3.5, −12.3, −12.7, −12.8 ppm. Anal. Calcd for $C_{31}H_{58}O_6Si_2$: C, 63.87; H, 10.03. Found: C, 64.01; H, 9.86.

(*E*)-(1*S*,5*R*,9*R*,10*R*,11*R*,12*R*,13*S*)-1,13-Dihydroxy-9-methoxy-7,10,12-trimethyl-5-vinyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (3). To a solution of **39** (20 mg, 34.3 μmol) in methanol (1.5 mL) at 0 °C, is added in 4 portions over 4 h a premixed solution of HF−pyridine (3 mL) in methanol (4 mL). After 5 h, the mixture is added to a saturated solution of sodium bicarbonate (200 mL). This solution is extracted 5 times by ethyl acetate, and the combined organic fractions are washed with brine, dried over magnesium sulfate, filtrated, and evaporated in vacuo. The residue was redissolved in benzene (5 mL) and evaporated in vacuo. This residue is dissolved in a 3/1 mixture of acetonitrile and water (2 mL), and PPTS (10 mg) is added. After 3 h at room temperature, a saturated solution of sodium bicarbonate is added and the mixture is extracted 3 times by dichloromethane. The organic phases are washed with brine, dried over magnesium sulfate, filtrated, and evaporated in vacuo. The tetrahydropyran **3** (11 mg, 31.1 μmol) is obtained pure after column chromatography (PE/ether 1/1) with 91% yield: $R_f = 0.46$ (PE/EtOAc 1/1); $[\alpha]_D^{25} = -40.2$ ($c = 0.5$, CH_2Cl_2); IR (neat) 3450, 2969, 2927, 1704, 1416, 1352, 1319, 1229, 1178, 1081, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddd, $J = 17.0$, 10.5 Hz, 6.0, 1 H), 5.76 (m, 1 H), 5.29 (d, $J = 9.0$ Hz, 1 H), 5.28 (dt, $J = 17.0$, 1.5 Hz, 1 H), 5.17 (dt, $J = 10.5$, 1.0 Hz, 1 H), 5.07 (d, $J = 2.5$ Hz, 1 H), 3.79 (dd, $J = 9.5$, 2.5 Hz, 1 H), 3.77 (ddd, $J = 12.0$, 12.0, 4.5 Hz, 1 H), 3.60 (dd, $J = 10.0$, 2.5 Hz, 1 H), 3.22 (s, 3 H), 2.53 (d, $J = 13.0$ Hz, 1 H), 2.43 (d, $J = 13.0$ Hz, 1 H), 2.26 (m, 2 H), 2.19 (m, 1 H), 2.09 (dd, $J = 4.5$, 12.0 Hz, 1 H), 1.73 (d, $J = 1.0$ Hz, 3 H), 1.56 (s, 1 H), 1.38 (m, 1 H), 1.29 (ddd, $J = 2.5$, 12.0, 12.0 Hz, 1 H), 0.97 (d, $J = 7.0$ Hz, 3 H), 0.95 (d, $J = 6.5$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.1, 132.6, 127.6, 116.5, 95.3, 79.8, 74.9, 72.2, 69.5, 55.2, 46.8, 44.7, 43.8, 40.1, 36.8, 16.1, 12.0, 6.5 ppm. HRMS (ESI). Calcd for $C_{19}H_{30}O_6Na$: 377.1940. Found: 377.1927.

(*E*)-(1*S*,5*S*,9*R*,10*R*,11*R*,12*R*,13*S*)-1,13-Dihydroxy-9-methoxy-7,10,12-trimethyl-5-vinyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (40). $[\alpha]_D = -29.3$ ($c = 1.0$, CH_2Cl_2); IR (thin film, KBr) $\nu = 3460$, 2920, 1706, 1435, 1383, 1297, 1232, 1165, 1087, 1050, 1025, 986, 931, 901, 866, 724 cm^{-1}; ^{1}H NMR (500 MHz, pyridine-d_5) δ 5.97 (ddd, $J = 17.0$, 10.5, 5.0 Hz, 1 H, H-14), 5.82−5.76 (m, 1 H, H-13), 5.50 (d, $J = 10.0$ Hz, 1 H, H-10), 5.35 (dd, $J = 17.0$, 1.5 Hz, 1 H, H-15a), 5.15 (d, $J = 10.5$ Hz, 1 H, H-15b), 4.57 (d, $J = 2.0$ Hz, 1 H, OH), 4.18 (dd, $J = 10.0$, 4.5 Hz, 1 H, H-9), 4.10 (ddd, $J = 10.5$, 10.5, 4.5 Hz, 1 H, H-5), 3.72 (d, $J = 10.5$ Hz, 1 H, H-7), 3.25 (s, 3 H, OMe), 2.97 (d, $J = 13.5$ Hz, 1 H, H-2a), 2.88 (d, $J = 13.5$ Hz, 1 H, H-2b), 2.72 (dd, $J = 16.0$, 4.0 Hz, 1 H, H-12), 2.61−2.55 (m, 1 H, H-8), 2.53 (dd, $J = 12.5$, 5.0 Hz, 1 H, H-4a), 2.27 (dd, $J = 16.0$, 8.0 Hz, 1 H, H-2b), 1.80−1.78 (m, 1 H, H-6), 1.78 (s, 3 H, Me-11), 1.75 (dd, $J = 11.0$, 11.0 Hz, 1 H, H-4b), 1.21 (d, $J = 6.5$ Hz, 3 H), 1.20 (d, $J = 7.0$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, pyridine-d_5) δ 168.8, 137.7, 132.9, 124.4, 115.7, 96.0, 79.8, 74.3, 72.9, 69.6, 55.1, 48.5, 45.3, 42.2, 41.2, 37.4, 18.9, 13.1, 6.4 ppm; ^{1}H NMR (500 MHz, CD_3OD) δ 5.99 (ddd, $J = 17.0$, 10.5, 5.0 Hz, 1 H, H-14), 5.63−5.57 (m, 1 H, H-13), 5.30 (d, $J = 17.0$ Hz, 1 H, H-15a), 5.19 (d, overlapped, 1 H, H-10), 5.19 (d, $J = 10.5$ Hz, 1 H, H-15a), 4.60 (br s, 1 H, OH), 4.03 (dd, $J = 10.0$, 5.0 Hz, 1 H, H-9), 3.52 (ddd, $J = 11.0$, 11.0, 4.5 Hz, 1 H, H-5), 3.35 (d, $J = 10.5$ Hz, 1 H, H-7), 3.21 (s, 3 H, OMe), 2.80 (d, $J = 14.0$ Hz, 1 H, H-2a), 2.73 (dd, $J = 16.0$, 4.5 Hz, 1 H, H-12a), 2.56 (d, $J = 14.5$ Hz, 1 H, H-2b), 2.38−2.30 (m, 2 H, H-8 & H-4a), 2.09 (dd, $J = 12.5$, 5.0 Hz, 1 H, H-12b), 1.77 (s, 3 H, Me-11), 1.40−1.32 (m, 1 H, H-6), 1.31 (dd, $J = 12.0$, 12.0 Hz, 1 H, H-4b), 0.96 (d, $J = 6.5$ Hz, 3 H), 0.87 (d, $J = 7.0$ Hz, 3 H) ppm. HRMS. Calcd for $C_{19}H_{30}H_{30}O_6Na$ ($M^+ + Na$): 377.1940. Found: 377.1927.

(1*S*,2*R*)-2-Chlorocyclopropanecarboxylic Acid (1*S*,2*R*,5*S*)-5-Isopropyl-2-methylcyclohexyl Ester (58). To a solution of acid chloride **57** (2.5 g, 8.75 mmol) in carbon tetrachloride (430 mL, 0.02 M) is added, at room temperature and in the dark, 2-mercaptopyridine-1-oxide sodium salt (1.57 g, 10.5 mmol), DMAP (0.214 g, 1.75 mmol), and tetrabutylammonium iodide (0.650 g, 1.75 mmol). This mixture is stirred in the dark at room temperature for 1 h. At this time, thin layer chromatography (TLC) shows clean formation of the Barton ester **59** [$R_f = 0.66$ (ether)]. 2,2′-Azobis(isobutyronitrile) (0.072 g, 0.44 mmol) is then added, and the mixture is placed under reflux in the presence of light for 5 h. At this time, TLC shows disappearance of the Barton ester. The mixture is then evaporated in vacuo and the trans chloride **58** (1.328 g, 5.25 mmol, 60% yield) is isolated as pure white crystals after column chromatography (petroleum ether/ether 100/3). The cis isomer of the chloride **58** (0.04 g, 0.16 mmol) is isolated as well as a white solid. The diastereomeric ratio is 33/1 in favor of the trans **58**: $R_f = 0.75$ (PE/ether 9/1); mp 60 °C; $[\alpha]_D^{24} = -29.8$ ($c = 1.1$, CH_2Cl_2); IR (neat) 2954, 2920, 2860, 1720, 1430, 1390, 1180 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (dt, $J = 4.4$, 11.0 Hz, 1 H), 3.34 (ddd, $J = 2.7$, 4.6, 7.0 Hz, 1 H), 1.95 (ddd, $J = 2.7$, 5.9, 9.3 Hz, 2 H), 1.82 (dquintuplet, $J = 2.4$, 6.8 Hz, 1 H), 1.66 (m, 2 H), 1.52 (m, 2 H), 1.34 (m, 2 H), 1.04 (m, 3 H), 0.88 (d, $J = 6.6$, 3 H), 0.87 (d, $J = 6.8$, 3 H), 0.72 (d, $J = 6.8$, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ (in italics are the carbons belonging to the cyclopropane ring) 171.0, 75.0, 47.0, 40.8, 34.2, *33.2*, 31.4, 26.2, *24.0*, 23.4, 22.0, 20.7, *18.3*, 16.3.

Anal. Calcd for $C_{14}H_{23}O_2Cl$: C, 64.98 H, 8.96; Cl, 13.70. Found: C, 65.12; H, 8.99; Cl, 13.99.

(1*R*,2*S*)-2-Chlorocyclopropanecarboxylic Acid (1*R*,2*S*,5*R*)-5-Isopropyl-2-methylcyclohexyl Ester (*ent*-58). $[\alpha]_D^{24} = +27.0$ (c = 1.00, CH_2Cl_2). **(*E*)-(6*S*,7*R*,8*S*,9*R*,10*R*,14*R*)-6,8-Bis(*tert*-butyldimethylsilanyloxy)-14-[(1*E*,3*E*)-6-((1*S*,2*R*)-2-chlorocyclopropyl)hexa-1,3-dien-5-ynyl]-10-methoxy-7,9,12-trimethyloxacyclotetradec-11-ene-2,4-dione (66).** To a solution of phosphonate **65** (29 mg, 0.10 mmol) in THF (1 mL) at −78 °C is added dropwise lithium bis(trimethylsilyl) amide (1 M in THF) (100 μL, 0.10 mmol). The mixture is stirred 2 min at −78 °C, warmed to 0 °C over 5 min and recooled to −78 °C. A solution of the aldehyde **46** (23 mg, 39 μmol) in THF (1 mL) is then added dropwise, and the mixture is stirred for 2 h at −78 °C, 30 min at −40 °C, and 15 min at room temperature. Water and ether are then added, and the mixture is extracted by ether. The organic layer is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The cis diene (2.5 mg, 3.5 μmol, 9% yield) [R_f = 0.34 (PE/ether 9/1)] and then the trans diene **66** (12 mg, 17 μmol, 43% yield) (52% yield with 4/1 *E*/*Z* ratio) are obtained pure as clear oils after column chromatography (PE/ether 95/5, then 93/7, then 90/10, and then 85/15): R_f = 0.22 (PE/ether 9/1); $[\alpha]_D^{25} = -67.3$ (*c* = 1.0, CH_2Cl_2); IR (neat) 2930, 2855, 2282, 2215, 1746, 1716, 1470, 1390, 1360, 1250, 1184, 1103 cm^{-1}; ^1H NMR (500 MHz, C_6D_6 50 °C) δ 6.43 (dd, *J* = 15.4, 10.7 Hz, 1 H), 6.13 (dd, *J* = 15.2, 10.7 Hz, 1 H), 5.63 (m, 1 H), 5.57 (d, *J* = 9.5 Hz, 1 H), 5.52 (dd, *J* = 15.6, 1.7 Hz, 1 H), 5.45 (dd, *J* = 15.1, 6.6 Hz, 1 H), 4.48 (s, 1 H), 4.23 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 1 H), 3.73 (d, *J* = 9.5 Hz, 1 H), 3.20 (d, *J* = 15.6 Hz, 1 H), 3.06 (s, 3 H), 3.04 (m, 1 H), 2.97 (d, *J* = 15.6 Hz, 1 H), 2.88 (ddd, *J* = 8.8, 5.6, 3.2 Hz, 1 H), 2.40 (dd, *J* = 12.0, 14.4 Hz, 1 H), 2.26 (dd, *J* = 15.1, 1.7 Hz, 1 H), 2.15 (dquint, *J* = 3.2, 6.8 Hz, 1 H), 2.03 (d, *J* = 14.2 Hz, 1 H), 1.68 (m, 1 H), 1.59 (s, 3 H), 1.38 (m, 1 H), 1.20 (d, *J* = 7.1 Hz, 3 H), 1.08 (s, 9 H), 1.00 (s, 9 H), 0.94 (d, *J* = 7.3 Hz, 3 H), 0.84 (m, 2 H), 0.30 (s, 3 H), 0.25 (s, 3 H), 0.22 (s, 3 H), 0.18 (s, 3 H) ppm; ^{13}C NMR (125 MHz, C_6D_6 50 °C) δ 200.0, 166.2, 140.4, 134.6, 133.1, 131.7, 130.0, 127.5, 125.8, 113.3, 92.8, 82.5, 78.1, 71.7, 71.6, 55.7, 50.5, 47.7, 46.2, 45.8, 40.0, 34.3, 30.5, 30.1, 26.5, 19.2, 18.8, 18.5, 15.6, 15.3, 12.3, −3.6, −4.0, −4.05, −4.1 ppm. HRMS (ESI). Calcd for $C_{38}H_{63}ClO_6Si_2Na$: 729.3749. Found: 729.3762.

(*E*)-(1*S*,5*R*,9*R*,11*R*,12*R*,13*S*)-5-[(1*E*,3*E*)-6-((1*S*,2*R*)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl]-1,13-dihydroxy-9-methoxy-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (67). To a solution of **66** (20 mg, 28.3 μmol) in methanol (1.5 mL) at 0 °C is added in 4 portions over 4 h a premixed solution of HF−pyridine (3 mL) in methanol (4 mL). After 5 h, a saturated solution of sodium bicarbonate (5 mL) is slowly and carefully added to the reaction mixture. The resulting mixture is then carefully added to a saturated solution of sodium bicarbonate (200 mL). This solution is extracted 5 times with ethyl acetate, and the combined organic fractions are washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The tetrahydropyran **67** (13 mg, 27 μmol, 96% yield) is obtained pure after column chromatography (petroleum ether/ether 1/1): R_f = 0.46 (PE/EtOAc 1/1); $[\alpha]_D^{23} = -39.4$ (*c* = 1.0, $CHCl_3$); IR (neat) 3444, 2925, 1704, 1432, 1227, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 15.4, 10.7 Hz, 1 H), 6.24 (dd, *J* = 14.9, 10.7 Hz, 1 H), 5.80 (m, 1 H), 5.74 (dd, *J* = 6.4, 15.1 Hz, 1 H), 5.55 (dd, *J* = 15.6, 2.0 Hz, 1 H), 5.28 (d, *J* = 9.5 Hz, 1 H), 5.01 (d, *J* = 2.4 Hz, 1 H), 3.78 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.77 (m, 1 H), 3.59 (dd, *J* = 10.3, 2.4 Hz, 1 H), 3.21 (s, 3 H), 3.16 (m, 1 H), 2.52 (d, *J* = 12.9 Hz, 1 H), 2.42 (d, *J* = 13.0 Hz, 1 H), 2.26 (m, 2 H), 2.19 (m, 1 H), 2.08 (dd, *J* = 4.6, 11.7 Hz, 1 H), 1.78 (m, 1 H), 1.71 (s, 3 H), 1.56 (s, 1 H), 1.38 (m, 1 H), 1.30 (m, 3 H), 0.95 (d, *J* = 6.8 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 140.1, 132.6, 132.3, 130.9, 127.8, 112.5, 95.3, 92.2, 79.7, 77.4, 74.9, 71.5, 69.5, 55.2, 46.9, 44.7, 43.7, 40.0, 36.8, 34.3, 19.3, 16.1, 12.03, 12.01, 6.5 ppm. HRMS (ESI). Calcd for $C_{26}H_{35}ClO_6Na$: 501.2020. Found: 501.2008.

(*E*)-(6*S*,7*R*,8*S*,9*R*,10*R*,14*R*)-6,8-Bis(*tert*-butyldimethylsilanyloxy)-14-[(1*E*,3*E*)-4-iodobuta-1,3-dienyl]-10-methoxy-7,9,12-trimethyloxacyclotetradec-11-ene-2,4-dione (69b). To a solution of macrolactone **39** (18 mg, 30.9 μmol) and freshly distilled crotonaldehyde (26 μL, 0.3 mmol) in dry degassed dichloromethane (1 mL) at room temperature is added Grubb's II catalyst (2.7 mg, 3 μmol), and the mixture is heated to 40 °C for 4 h. The mixture is then cooled to room temperature, evaporated in vacuo, and dried under high vacuum. Crude NMR (benzene-d_6) shows total conversion. The crude aldehyde **68** is used with no purification in the next step.

Chromium chloride (33 mg, 0.27 mmol) is placed in a flask in a drybox under nitrogen atmosphere. In a separate flask is placed the aldehyde **68** as well as iodoform (53 mg, 0.13 mmol), and the flask is purged with argon. Dry degassed THF (0.3 mL) is added to the chromium chloride flask, and this suspension is cooled to 0 °C. Dry degassed dioxane (1 mL) is added to the other flask, and its content is transferred into the chromium chloride flask. This dark mixture is scealed and stirred at 0 °C for 3 h. Water and ether are then added, and the mixture is extracted with ether. The organic layer is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The vinyl iodide **69b** (9.2 mg, 12.5 μmol, 40% yield) is obtained pure as a clear oil after column chromatography (PE/ether 95/5, then 93/7, and then 90/10) as a 10/1 mixture of *E*/*Z* isomers (determined by ^1H NMR): R_f = 0.24 (PE/ether 9/1); $[\alpha]_D^{27} = -7.9$ (*c* = 0.70, CH_2Cl_2); IR (neat) 3446, 2930, 2855, 1746, 1717, 1472, 1387, 1360, 1250, 1185, 1103 cm^{-1}; ^1H NMR (500 MHz, C_6D_6 50 °C) δ 6.73 (dd, *J* = 14.4, 10.7 Hz, 1 H), 5.99 (d, *J* = 14.4 Hz, 1 H), 5.87 (dd, *J* = 15.4, 10.7 Hz, 1 H), 5.56 (m, 2 H), 5.27 (dd, *J* = 15.2, 6.6 Hz, 1 H), 4.48 (s, 1 H), 4.23 (apparent t, *J* = 6.6 Hz, 1 H), 3.72 (d, *J* = 9.8 Hz, 1 H), 3.23 (d, *J* = 15.9 Hz, 1 H), 3.06 (s, 3 H), 3.00 (m, 2 H), 2.39 (dd, *J* = 14.4, 11.7 Hz, 1 H), 2.27 (dd, *J* = 1.7, 16.6 Hz, 1 H), 2.16 (dt, *J* = 2.9, 6.8 Hz, 1 H), 2.02 (d, *J* = 15.6 Hz, 1 H), 1.67 (m, 1 H), 1.58 (s, 3 H), 1.21 (d, *J* = 6.6 Hz, 3 H), 1.08 (s, 9 H), 1.00 (s, 9 H), 0.95 (d, *J* = 7.1 Hz, 3 H), 0.30 (s, 3 H), 0.25 (s, 3 H), 0.22 (s, 3 H), 0.17 (s, 3 H) ppm; ^{13}C NMR (125 MHz, C_6D_6 50 °C) δ 200.0, 166.2, 144.2, 134.5, 132.2, 131.7, 130.1, 125.8, 82.5, 81.3, 71.5, 55.7, 50.5, 47.7, 46.1, 45.9, 40.0, 30.5, 26.5, 18.8, 18.5, 15.7, 15.3, 12.3, −3.7, −4.0, −4.1, −4.1 ppm. HRMS (ESI). Calcd for $C_{33}H_{59}IO_6Si_2Na$: 757.2793. Found: 757.2773.

(*E*)-(6*S*,7*R*,8*S*,9*R*,10*R*,14*R*)-6,8-Bis(*tert*-butyldimethylsilanyloxy)-14-[(1*E*,3*E*)-6-cyclopropyl)hexa-1,3-dien-5-ynyl]-10-methoxy-7,9,12-trimethyloxacyclotetradec-11-ene-2,4-dione (47). A solution of vinyl iodide **69b** (4 mg, 5.4 μmol), 1-alkynylcyclopropane (4 mg, 54 μmol), triphenylphosphine (0.3 mg, 1.1 μmol), freshly purified copper iodide-(I) (0.3 mg, 1.6 μmol) and (di(benzonitrile))palladium dichloride (0.2 mg, 0.54 μmol) is diluted by a 1/1 mixture of THF and diisopropylamine (1 mL) at −20 °C. After 30 min at this temperature, the mixture is warmed to room temperature. After 30 min, the mixture is evaporated in vacuo and dried with high vacuum. The enyne **47** (2.6 mg, 3.8 μmol, 70% yield) is isolated pure as a clear oil after preparative thin layer chromatography (PE/ether 85/15): R_f = 0.22 (PE/ether 9/1); $[\alpha]_D^{25} = +3.0$ (*c* = 1.2, CH_2Cl_2); IR (neat) 2955, 2929, 2893, 2856, 2205, 1745, 1719, 1472, 1387, 1360, 1249, 1185, 1103, 1006 cm^{-1}; ^1H NMR (500 MHz, C_6D_6 50 °C) δ 6.48 (dd, *J* = 15.0, 11.0 Hz, 1 H), 6.12 (dd, *J* = 15.0, 11.0 Hz, 1 H), 5.65 (m, 1 H), 5.64 (dd, *J* = 15.0, 1.5 Hz, 1 H), 5.58 (br d, *J* = 10.0 Hz, 1 H), 5.39 (dd, *J* = 15.0, 6.5 Hz, 1 H), 4.52 (s, 1 H), 4.23 (br ddd, *J* = 9.5, 7.0, 2.5 Hz, 1 H), 3.71 (br d, *J* = 9.0 Hz, 1 H), 3.15 (br d, *J* = 16.0 Hz, 1 H), 3.07 (m, 1 H), 3.03 (s, 3 H), 2.91 (d, *J* = 16.0 Hz, 1 H), 2.40 (dd, *J* = 14.0, 12.0 Hz, 1 H), 2.16 (m, 1 H), 2.15 (br d, *J* = 16.0 Hz, 1 H), 1.99 (d, *J* = 14.5 Hz, 1 H), 1.64 (m, 1 H), 1.58 (s, 3 H), 1.20 (d, *J* = 7.0 Hz, 3 H), 1.13 (m, 1 H), 1.09 (s, 9 H), 1.01 (s, 9 H), 0.90 (d, *J* = 7.5 Hz, 3 H), 0.61 (m, 2 H), 0.39 (m, 2 H), 0.32 (s, 3 H), 0.26 (s, 3 H), 0.24 (s, 3 H), 0.20 (s, 3 H) ppm; ^{13}C NMR (125 MHz, C_6D_6 50 °C) δ 200.0, 166.2, 139.3, 134.8, 132.1, 132.1, 129.9, 127.6, 127.4, 114.4, 97.8, 82.5, 75.6, 71.9, 71.7, 55.7, 50.6, 47.7, 46.3, 45.8, 39.9, 26.5, 18.8, 18.5, 15.6, 15.3, 12.3, 8.8, 0.8,

−3.6, −4.0, −4.1, −4.1 ppm. HRMS (ESI). Calcd for $C_{38}H_{64}O_6Si_2Na$: 695.4138. Found: 695.4138.

(*E*)-(1*S*,5*R*,9*R*,11*R*,12*R*,13*S*)-1,13-Dihydroxy-5-((1*E*,3*E*)-4-iodobuta-1,3-dienyl)-9-methoxy-7,10,12-trimethyl-5-vinyl-4,15-dioxabicyclo-[9.3.1]pentadec-7-en-3-one (70). To a solution of macrolactone **3** (10 mg, 28.2 μmol) and freshly distilled crotonaldehyde (23 μL, 0.28 mmol) in dry degassed dichloromethane (1 mL) at room temperature is added Grubb's II catalyst (2.7 mg, 3 μmol), and the mixture is heated to 40 °C for 5 h. The mixture is then cooled to room temperature, evaporated in vacuo, and dried under high vacuum. Crude NMR shows total conversion. The crude aldehyde is used with no purification in the next step.

Chromium chloride (33 mg, 0.27 mmol) is placed in a flask in a drybox under nitrogen atmosphere. In a separate flask is placed the aldehyde as well as iodoform (53 mg, 0.13 mmol), and the flask is purged with argon. Dry degassed THF (0.3 mL) is added to the chromium chloride flask, and this suspension is cooled to 0 °C. Dry degassed dioxane (1 mL) is added to the other flask, and its content is transferred into the chromium chloride flask. This dark mixture is sealed and stirred at 0 °C for 3 h. Water and ether are then added, and the mixture is extracted with ether. The organic layer is washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The vinyl iodide **70** (12 mg, 23.6 μmol, 84% yield) is obtained pure as a clear oil after column chromatography (PE/ether 1/1) as a 8/1 mixture of *E*/*Z* isomers (determined by ^{1}H NMR): R_f = 0.40 (PE/ether 1/1); $[\alpha]_D^{22}$ = +14.1 (*c* = 1.10, CH_2Cl_2); IR (neat) 3451, 2925, 2360, 2055, 1704, 1462, 1226, 1152 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 14.4, 11.0 Hz, 1 H), 6.40 (d, *J* = 14.4 Hz, 1 H), 6.18 (dd, *J* = 14.9, 10.7 Hz, 1 H), 5.74 (m, 2 H), 5.29 (d, *J* = 9.7 Hz, 1 H), 5.00 (d, *J* = 2.4 Hz, 1 H), 3.78 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.75 (m, 1 H), 3.59 (dd, *J* = 10.3, 2.4 Hz, 1 H), 3.21 (s, 3 H), 2.52 (d, *J* = 12.9 Hz, 1 H), 2.42 (d, *J* = 12.9 Hz, 1 H), 2.26 (m, 2 H), 2.20 (m, 1 H), 2.08 (dd, *J* = 4.6, 11.9 Hz, 1 H), 1.71 (d, *J* = 1.0 Hz, 3 H), 1.56 (s, 1 H), 1.38 (m, 1 H), 1.29 (ddd, *J* = 2.4, 11.4, 11.5 Hz, 1 H), 0.96 (d, *J* = 7.1 Hz, 3 H), 0.95 (d, *J* = 5.6 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 144.0, 132.2, 131.4, 127.8, 125.5, 95.3, 81.0, 79.7, 74.9, 71.2, 69.5, 55.2, 46.8, 44.7, 43.7, 40.0, 36.8, 16.1, 12.0, 6.5 ppm. HRMS. Calcd for $C_{21}H_{31}O_6INa$: 529.1063. Found: 529.1059.

(*E*)-(1*S*,5*R*,9*R*,11*R*,12*R*,13*S*)-5-[(1*E*,3*E*)-6-((1*R*,2*S*)-2-Chlorocyclo-propyl)hexa-1,3-dien-5-ynyl]-1,13-dihydroxy-9-methoxy-7,10,12-trimethyl-4,15-dioxabicyclo[9.3.1]pentadec-7-en-3-one (72). To a solution of *ent*-**62** (23 mg, 88.4 μmol) in ether (1 mL) at −78 °C is added *n*BuLi (1.4 M in hexanes) (64 μL, 88 μmol), and the mixture is allowed to warm to room temperature over 15 min. The mixture is then recooled to −78 °C and *n*BuLi (1.4 M in hexanes) (64 μL, 88 μmol) is added, and the mixture is allowed to warm to 0 °C over 20 min. The mixture is recooled to −78 °C, and a solution of trimethyltin chloride (18 mg, 88.4 μmol) in ether (0.5 mL) is added. After 30 min at room temperature, the solvent is removed under vacuum. A solution of iodide **70** (9 mg, 17.7 μmol) in dry degassed DMF (1 mL) as well as $(MeCN)_2PdCl_2$ (0.4 mg, 1.8 μmol) is then added to the same flask at 0 °C. After 15 min at room temperature, the same quantity of palladium catalyst is added. This operation is repeated after another 15 min. After 45 min of reaction, water and l ether are added, and the phases are separated. The aqueous layer is back-extracted twice with ethyl acetate, and the combined organic phases are washed with brine, dried over magnesium sulfate, filtered, and evaporated in vacuo. The tetrahydropyran **72** (6 mg, 12.5 μmol, 70% yield) is obtained pure after column chromatography (PE/ether 1/1): R_f = 0.46 (PE /EtOAc 1/1); $[\alpha]_D^{25}$ = +125.0 (*c* = 1.0, $CHCl_3$); IR (neat) 3444, 2925, 1704, 1432, 1227, 1152 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (dd, *J* = 15.4, 10.7 Hz, 1 H), 6.24 (dd, *J* = 14.9, 10.7 Hz, 1 H), 5.80 (m, 1 H), 5.74 (dd, *J* = 6.4, 15.1 Hz, 1 H), 5.55 (dd, *J* = 15.6, 2.0 Hz, 1 H), 5.28 (d, *J* = 9.5 Hz, 1 H), 5.01 (d, *J* = 2.4 Hz, 1 H), 3.78 (dd, *J* = 9.5, 2.4 Hz, 1 H), 3.77 (m, 1 H), 3.59 (dd, *J* = 10.3, 2.4 Hz, 1 H), 3.21 (s, 3 H), 3.16 (m, 1 H), 2.52 (d, *J* = 12.9 Hz, 1 H), 2.42 (d, *J* = 13.0, 1 H), 2.26 (m, 2 H), 2.19 (m, 1 H), 2.08 (dd, *J* = 4.6, 11.7 Hz, 1 H), 1.78 (m, 1 H), 1.71 (s, 3 H), 1.56 (s, 1 H), 1.38 (m, 1 H), 1.30 (m, 3 H), 0.95 (d, *J* = 6.8 Hz, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 140.1, 132.6, 132.3, 130.9, 127.8, 112.5, 95.3, 92.2, 79.7, 77.4, 74.9, 71.5, 69.5, 55.2, 46.9, 44.7, 43.7, 40.0, 36.8, 34.2, 19.3, 16.1, 12.03, 12.01, 6.5 ppm. HRMS (ESI). Calcd for $C_{26}H_{35}ClO_6Na$: 501.2020. Found: 501.2006.

Deschlorocallipeltoside A (2). A solution of core **48** (11 mg, 0.025 mmol) and sugar **5** (14 mg, 0.030 mmol) in dichloroethane (1.5 mL) was transferred via cannula to a flask containing flame dried 4 Å MS (200 mg). Trimethylsilyltriflate (24 μL of a solution of 50 μL in 1 mL of dichloroethane, 0.006 mmol) was slowly added to the reaction mixture, and it was stirred at room temperature for 30 min before quenching by addition with triethylamine (0.1 mL) and a saturated sodium bicarbonate solution (5 mL). The product was extracted into dichloromethane (3 × 6 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (SiO_2, 1/9 to 2/3, EtOAc/PE) to afford glycosylated product (14.5 mg, 80%): $[\alpha]_D$ = +2.8 (*c* = 0.8, CH_2Cl_2); IR (thin film, KBr) ν = 3453, 2933, 2204, 1738, 1732, 1713, 1463, 1416, 1366, 1325, 1250, 1228, 1201, 1182, 1155, 1138, 1103, 1065, 1025, 983, 893, 839, 806, 785, 737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 15.0, 11.0 Hz, 1 H, H-16), 6.24 (dd, *J* = 15.0, 11.0 Hz, 1 H, H-15), 5.82−5.75 (m, 1 H, H-13), 5.69 (dd, *J* = 15.0, 6.5 Hz, 1 H, H-14), 5.57 (dd, *J* = 15.0, 1.5 Hz, 1 H, H-17), 5.27 (d, *J* = 9.5 Hz, 1 H, H-10), 4.89 (d, *J* = 2.0 Hz, 1 H, OH), 4.81 (d, *J* = 6.0 Hz, 1 H, H-1′), 3.90−3.84 (m, 1 H, H-5′), 3.78 (dd, *J* = 9.5, 2.5 Hz, 1 H, H-9), 3.75 (ddd, *J* = 10.5, 10.5, 4.5 Hz, 1 H, H-5), 3.62 (dd, *J* = 10.5, 2.5 Hz, 1 H, H-7), 3.56 (s, 3 H, OMe), 3.31 (d, *J* = 2.5 Hz, 1 H, H-4′), 3.23−3.18 (m, 1 H, H-2′), 3.21 (s, 3 H, OMe), 2.48 (d, *J* = 13.0 Hz, 1 H, H-2a), 2.39 (d, *J* = 13.0 Hz, 1 H, H-2b), 2.28−2.24 (m, 2 H, H-12), 2.21 (dd, *J* = 12.0, 4.5 Hz, 1 H, H-4a), 2.24−2.17 (m, 1 H, H-8), 1.70 (s, 3 H, Me-11), 1.48 (s, 3 H, Me-3′), 1.50−1.42 (m, 1 H, H-6), 1.38−1.33 (m, 1 H, H-20), 1.34−1.27 (m, 1 H, H-4b), 1.14 (d, *J* = 6.5 Hz, 3 H, Me-6_), 1.00 (s, 9 H, *t*-BuSi), 0.95 (2d, *J* = 7.0 Hz, 6 H, Me-6 & Me-8), 0.83−0.79 (m, 2 H, H-21a), 0.73−0.68 (m, 2 H, H-21b) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 161.0, 139.1, 132.4, 131.8, 131.3, 127.7, 113.4, 101.8, 97.3, 95.1, 82.2, 82.1, 79.8, 77.4, 74.9, 74.8, 71.5, 65.4, 65.3, 61.3, 55.3, 46.9, 44.8, 43.1, 38.5, 36.8, 27.7, 22.4, 20.1, 17.3, 16.1, 12.2, 8.7, 6.5, 0.4, −3.8, −4.0 ppm.

The glycosylated product (10 mg, 0.013 mmol) was dissolved in THF (0.5 mL) and was treated with a solution (16 μL, 0.015 mmol) of TBAF (1 mL of 1 M in THF) and acetic acid (50 μL) for 5 min at room temperature. The reaction was quenched with a solution of saturated sodium bicarbonate (1 mL), and the product was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and purified by pipet column (SiO_2, 1/4 to 4/1, EtOAc/PE) to afford **2** (8 mg, 95%): $[\alpha]_D$ = +45.0 (*c* = 0.5, MeOH); IR (thin film, KBr): ν = 3452, 3285, 2968, 2933, 2204, 1749, 1373, 1324, 1266, 1227, 1182, 1155, 1058, 1027, 980, 897, 822 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 15.0, 11.0 Hz, 1 H, H-16), 6.24 (dd, *J* = 15.0, 11.0 Hz, 1 H, H-15), 5.82−5.76 (m, 1 H, H-13), 5.70 (dd, *J* = 15.0, 6.5 Hz, 1 H, H-14), 5.67 (s, 1 H, NH), 5.58 (dd, *J* = 15.0, 2.0 Hz, 1 H, H-17), 5.27 (d, *J* = 8.5 Hz, 1 H, H-10), 4.93 (d, *J* = 2.5 Hz, 1 H, OH), 4.85 (d, *J* = 6.0 Hz, 1 H, H-1′), 3.88 (ddd, *J* = 6.5, 6.5, 2.0 Hz, 1 H, H-5′), 3.78 (dd, *J* = 9.5, 2.5 Hz, 1 H, H-9), 3.76 (ddd, *J* = 10.5, 10.5, 5.0 Hz, 1 H, H-5), 3.63 (dd, *J* = 10.5, 2.5 Hz, 1 H, H-7), 3.58 (s, 3 H, OMe), 3.32 (d, *J* = 2.0 Hz, 1 H, H-4′), 3.23−3.18 (m, 1 H, H-2′), 3.21 (s, 3 H, OMe), 2.49 (d, *J* = 13.0 Hz, 1 H, H-2a), 2.41 (d, *J* = 13.0 Hz, 1 H, H-2b), 2.28−2.25 (m, 2 H, H-12), 2.21 (dd, *J* = 12.0, 5.0 Hz, 1 H, H-4a), 2.23−2.17 (m, 1 H, H-8), 1.71 (d, *J* = 1.0 Hz, 3 H, Me-11), 1.53 (s, 3 H, Me-3′), 1.50−1.43 (m, 1 H, H-6), 1.38−1.33 (m, 1 H, H-20), 1.35−1.28 (m, 1 H, H-4b), 1.11 (d, *J* = 6.5 Hz, 3 H, Me-6′), 0.95 (d, *J* = 7.0 Hz, 3 H, Me-6), 0.94 (d, *J* = 6.5 Hz, Me-8), 0.83−0.79 (m, 2 H, H-21), 0.72−0.69 (m, 2 H, H-21′) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 158.3, 139.1, 132.4, 131.8, 131.3, 127.6, 113.4, 101.6, 97.3, 95.1, 82.0, 81.8, 79.7, 77.7, 74.9, 74.8,

71.6, 63.4, 61.6, 61.3, 55.2, 46.9, 44.8, 43.0, 38.5, 36.8, 23.2, 16.1, 15.7, 12.2, 8.7, 6.5, 0.4 ppm; ^{1}H NMR (500 MHz, CD_3OD) δ 6.43 (dd, J = 15.5, 11.0 Hz, 1 H, H-16), 6.31 (dd, J = 14.0, 11.0 Hz, 1 H, H-15), 5.82−5.75 (m, 1 H, H-13), 5.81−5.77 (m, 1 H, H-14), 5.63 (dd, J = 15.5, 1.5 Hz, 1 H, H-17), 5.26 (d, J = 9.5 Hz, 1 H, H-10), 4.70 (d, J = 6.0 Hz, 1 H, H-1′), 3.95 (dq, J = 6.5, 2.0 Hz, 1 H, H-5′), 3.88 (dd, J = 9.5, 2.5 Hz, 1 H, H-9), 3.72 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, H-5), 3.65 (dd, J = 10.5, 1.5 Hz, 1 H, H-7), 3.59 (s, 3 H, OMe), 3.43 (d, J = 2.0 Hz, 1 H, H-4′), 3.42 (d, J = 6.5 Hz, 1 H, H-2′), 3.21 (s, 3 H, OMe), 2.52 (d, J = 12.5 Hz, 1 H, H-2a), 2.46 (d, J = 13.0 Hz, 1 H, H-2b), 2.35−2.27 (m, 2 H, H-12), 2.24−2.20 (m, 1 H, H-8), 2.23−2.18 (m, 1 H, H-4a), 1.74 (s, 3 H, Me-11), 1.52−1.46 (m, 1 H, H-6), 1.50 (s, 3 H, Me-3′), 1.42−1.36 (m, 1 H, H-4b), 1.40−1.34 (m, 1 H, H-20), 1.08 (d, J = 6.5 Hz, 3 H, Me-6′), 0.99 (d, J = 6.5 Hz, 3 H, Me-6), 0.96 (d, J = 7.0 Hz, 3 H, Me-8), 0.84−0.79 (m, 2 H, H-21), 0.65−0.60 (m, 2 H, H-21) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 161.1, 140.4, 134.5, 133.3, 132.4, 128.3, 114.5, 103.7, 97.9, 96.6, 83.9, 83.0, 81.4, 78.7, 76.4, 75.7, 72.8, 65.3, 62.7, 62.0, 55.4, 47.9, 46.0, 44.5, 39.9, 38.2, 23.0, 16.3, 15.9, 12.7, 9.0, 6.8, 0.9 ppm. MALDI−FTMS. Calcd for $C_{35}H_{49}NO_{10}$ (M + Na^+): 666.3248. Found: 666.3220.

(3a*R*,4*S*,7*R*,7a*R*)-6-[(1*S*,5*R*,9*R*,10*R*,11*R*,12*R*)-(*E*)-5-[(1*E*,3*E*)-6-((1*R*,2*S*)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl]-1-hydroxy-9-methoxy-7,10,12-trimethyl-3-oxo-4,15-dioxabicyclo[9.3.1]pentadec-7-en-13-yloxy]-7-methoxy-4,7a-dimethyltetrahydropyrano-[3,4-*d*]oxazol-2-one (85). A mixture of alcohol **72** (10 mg, 20.9 μmol) and trichloroacetimidate **5** (13 mg, 27.4 μmol) are dried by benzene azeotrope, diluted with dichloroethane (1 mL), and transferred via cannula into a flask containing freshly flame dried molecular sieves 4 Å (100 mg). This mixture is stirred for 10 min at room temperature and then cooled to −30 °C. TMSOTf (10 μL of a solution containing 50 μL of TMSOTf in 1 mL of dichloroethane, 2.8 μmol) is then added dropwise, and the mixture is stirred for 15 min. Triethylamine (0.5 mL) is then added, and the mixture is warmed to room temperature. A saturated solution of sodium bicarbonate is added, and the mixture is extracted three times with dichloromethane. The combined organic phases are washed with brine, dried over magnesium sulfate, filtrated, and evaporated in vacuo. The glycosilated product (12 mg, 15.2 μmol) is obtained pure after two preparative TLC (petroleum ether/ethyl acetate 1/1 and then 7/3) with 73% yield.

This product (11 mg, 13.9 μmol) is diluted with THF (0.5 mL) and buffered TBAF (17 μL of a solution containing 1 mL of a 1 M solution of TBAF in THF, and 0.1 mL of acetic acid (17 μmol) is added at room temperature. After 5 min, the reaction mixture is directly applied on a preparative TLC (ethyl acetate pure) and then further purified by preparative HPLC (C-18 Dynamax-60A) (methanol/water 60/40 5 mL/min, room temperature = 5.0 min) to yield **85** (9 mg, 13.3 μmol, 95% yield): R_f = 0.55 (EtOAc); $[\alpha]_D^{22}$ = +156.3 (c = 0.55, CH_3OH); IR (neat) 3445, 2926, 1748, 1538, 1417, 1373, 1262, 1150, 1097, 1058 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.39 (dd, J = 15.4, 10.7 Hz, 1 H), 6.22 (dd, J = 14.4, 10.7 Hz, 1 H), 5.71 (m, 2 H), 5.54 (dd, J = 1.9, 15.6 Hz, 1 H), 5.16 (bd, J = 9.5 Hz, 1 H), 4.60 (d, J = 6.1 Hz, 1 H), 3.84 (dq, J = 6.6, 1.7 Hz, 1 H), 3.77 (dd, J = 9.7, 2.4 Hz, 1 H), 3.61 (dt, J = 10.9, 4.8 Hz, 1 H), 3.54 (dd, J = 10.5, 2.4 Hz, 1 H), 3.49 (s, 3 H), 3.34 (d, J = 2.2 Hz, 1 H), 3.32 (d, J = 6.3 Hz, 1 H), 3.14 (m, 1 H), 3.11 (s, 3 H), 2.42 (d, J = 12.7 Hz, 1 H), 2.35 (d, J = 12.9 Hz, 1 H), 2.24 (m, 1 H), 2.16 (m, 1 H), 2.11 (m, 2 H), 1.70 (m, 1 H), 1.64 (s, 3 H), 1.42 (m, 1 H), 1.39 (s, 3 H), 1.29 (t, J = 11.5 Hz, 1 H), 1.16 (m, 2 H), 0.98 (d, J = 6.3 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 161.1, 141.6, 134.4, 134.3, 132.0, 128.3, 113.5, 103.7, 96.5, 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, 46.0, 44.5, 39.8, 38.2, 35.1, 23.0, 19.8, 16.3, 15.9, 12.8, 6.8 ppm. HRMS (ESI). Calcd for $C_{35}H_{48}ClNO_{10}Na$: 700.2864. Found: 700.2852.

(3a*R*,4*S*,7*R*,7a*R*)-6-[(1*S*,5*R*,9*R*,10*R*,11*R*,12*R*)-(*E*)-5-[(1*E*,3*E*)-6-((1*S*,2*R*)-2-Chlorocyclopropyl)hexa-1,3-dien-5-ynyl]-1-hydroxy-9-methoxy-7,10,12-trimethyl-3-oxo-4,15-dioxabicyclo[9.3.1]pentadec-7-en-13-yloxy]-7-methoxy-4,7a-dimethyltetrahydropyrano-[3,4-d]oxazol-2-one (84 = 1, Callipeltoside A). A mixture of alcohol **67** (10 mg, 20.9 μmol) and trichloroacetimidate **5** (13 mg, 27.4 μmol) are dried by benzene azeotrope, diluted with dichloroethane (1 mL), and transferred via cannula into a flask containing freshly flame dried molecular sieves 4 Å (100 mg). This mixture is stirred for 10 min at room temperature and then cooled to −30 °C. TMSOTf (10 μL of a solution containing 50 μL of TMSOTf in 1 mL of dichloroethane, 2.8 μmol) is then added dropwise, and the mixture is stirred for 15 min. Triethylamine (0.5 mL) is then added, and the mixture is warmed to room temperature. A saturated solution of sodium bicarbonate is added, and the mixture is extracted three times with dichloromethane. The combined organic phases are washed with brine, dried over magnesium sulfate, filtrated,and evaporated in vacuo. The glycosilated product (12 mg, 15.2 μmol) is obtained pure after two preparative TLC (PE/EtOAc 1/1 and then 7/3) with 73% yield.

This product (11 mg, 13.9 μmol) is diluted with THF (0.5 mL) and buffered TBAF (17 μL of a solution containing 1 mL of a 1 M solution of TBAF in THF, and 0.1 mL of acetic acid (17 μmol) is added at room temperature. After 5 min, the reaction mixture is directly applied on a preparative TLC (ethyl acetate pure) and then further purified by preparative HPLC (C-18 Dynamax-60A) (methanol/water 60/40 5 mL/min, room temperature = 5.0 min) to yield callipeltoside A **1** (9 mg, 13.3 μmol) with 95% yield: R_f = 0.55 (EtOAc); $[\alpha]_D^{22}$ = −19.2 (c = 1.0, CH_3OH); IR (neat) 3445, 2926, 1748, 1538, 1417, 1373, 1262, 1150, 1097, 1058 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.39 (dd, J = 15.4, 10.7 Hz, 1 H), 6.22 (dd, J = 14.4, 10.7 Hz, 1 H), 5.71 (m, 2 H), 5.54 (dd, J = 1.7, 15.4 Hz, 1 H), 5.15 (bd, J = 9.8 Hz, 1 H), 4.60 (d, J = 6.1 Hz, 1 H), 3.84 (dq, J = 6.6, 1.7 Hz, 1 H), 3.77 (dd, J = 9.5, 2.4 Hz, 1 H), 3.61 (dt, J = 10.7, 4.6 Hz, 1 H), 3.54 (dd, J = 10.5, 2.4 Hz, 1 H), 3.49 (s, 3 H), 3.34 (d, J = 1.9 Hz, 1 H), 3.32 (d, J = 6.1 Hz, 1 H), 3.14 (m, 1 H), 3.11 (s, 3 H), 2.42 (d, J = 13.0 Hz, 1 H), 2.35 (d, J = 13.0 Hz, 1 H), 2.24 (m, 1 H), 2.16 (m, 1 H), 2.11 (m, 2 H), 1.70 (m, 1 H), 1.64 (s, 3 H), 1.42 (m, 1 H), 1.39 (s, 3 H), 1.29 (t, J = 11.5 Hz, 1 H), 1.16 (m, 2 H), 0.98 (d, J = 6.3 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H) ppm; ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.28 (s, 1 H), 6.66 (dd, J = 15.4, 10.7 Hz, 1 H), 6.43 (dd, J = 15.4, 11.0 Hz, 1 H), 6.13 (s, 1 H), 5.99 (m, 1 H), 5.91 (dd, J = 6.1, 15.1 Hz, 1 H), 5.83 (dd, J = 1.7, 15.6 Hz, 1 H), 5.52 (d, J = 9.8 Hz, 1 H), 5.13 (d, J = 6.1 Hz, 1 H), 4.07 (m, 2 H), 4.00 (dd, J = 2.4, 9.8 Hz, 1 H), 3.92 (dd, J = 1.9, 10.3 Hz, 1 H), 3.63 (s, 3 H), 3.57 (d, J = 6.3 Hz, 1 H), 3.52 (d, J = 1.2 Hz, 1 H), 3.41 (m, 1 H), 3.26 (s, 3 H), 2.78 (d, J = 12.4 Hz, 1 H), 2.68 (d, J = 12.7 Hz, 1 H), 2.55 (dd, J = 4.6, 12.0 Hz, 1 H), 2.43 (m, 2 H), 2.36 (m, 1 H), 1.98 (m, 1 H), 1.82 (s, 3 H), 1.76 (m, 1 H), 1.67 (dt, J = 1.5, 11.0 Hz, 1 H), 1.59 (s, 3 H), 1.30 (m, 2 H), 1.26 (d, J = 6.1 Hz, 3 H), 1.21 (d, 3 H), 1.05 (d, J = 6.3 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 172.9, 161.1, 141.6, 134.4, 134.3, 132.0, 128.3, 113.5, 103.7, 96.5, 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, 46.0, 44.5, 39.8, 38.2, 35.1, 23.0, 19.8, 16.3, 15.9, 12.8, 6.8 ppm. HRMS (ESI). Calcd for $C_{35}H_{48}ClNO_{10}Na$: 700.2864. Found: 700.2862.

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Supporting Information Available: Text giving general experimental conditions and preparations of **5**, *ent*-**6**, **8**−**10**, **13**, **16**, **25a**,**b**, **27**, **29**, **30**, **32**, **37**, **45**, **47**, **48**, **51**−**53**, **56**, **57**, **59**, **60**, **62**−**65**, **74**−**76**, Tables 3−5, and figures showing the ^{1}H and ^{13}C NMR spectra of natural and synthetic callipeltoside A (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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