Oxabicyclo[3.2.1]oct-6-enes as Templates for the Stereoselective Synthesis of Polypropionates: Total Synthesis of Callystatin A and C19-*epi*-Callystatin A

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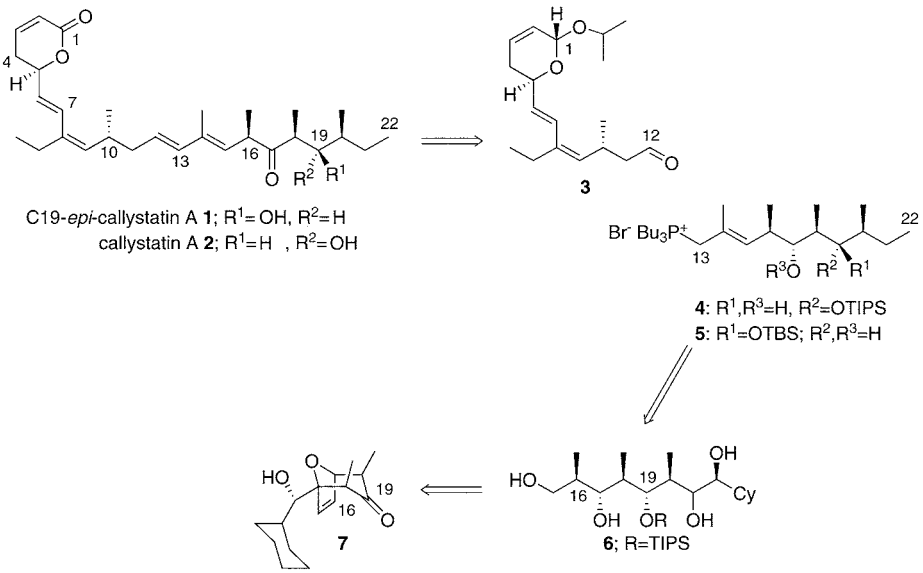
Dedicated to Professor D. Seebach in recognition of his diverse contributions to organic chemistry.

Abstract: The total synthesis of the polyketide natural product callystatin A and its novel analog C19-*epi*-callystatin A is described. Our strategy features the use of an enantiomerically pure oxabicyclo[3.2.1]oct-6-ene as a template for the stereocontrolled preparation of the C15–C21 polypropionate region.

Key words: total synthesis, natural products, asymmetric synthesis, ring opening, stereoselectivity

The structure of the marine polyketide callystatin A (**1**) was reported by Kobayashi and co-workers in 1997[1] and was followed shortly thereafter by the confirmation of its relative and absolute configuration.[2] Callystatin A is one of several structurally related polyketide natural products that display potent and diverse biological activities that include the anguinomycins,[3] kazusamycin,[4] leptofuranins,[5] leptomycins[6] and leptolstatin.[7] Callystatin A has been the target of significant synthetic research interest including total syntheses published by the research groups of Kobayashi,[8] Crimmins,[9] Smith,[10] Kalesse,[11] Marshall,[12] and Enders.[13] Recent efforts from Kobayashi and co-workers have involved the preparation of several structural analogues of callystatin A to develop structure–activity relationships.[14] These studies suggested the pharmacophore of callystatin A is the unsaturated lactone which has been confirmed as the pharmacophore of the related compound leptomycin B.[15] The SAR studies by Kobayashi and co-workers also demonstrated that the remainder of the molecule contributed significantly to activity of callystatin A emphasizing the importance of synthetic analogues of the natural product.

Our retrosynthetic analysis is outlined in Scheme 1 and employed an *E*-selective tributylphosphonium Wittig type reaction[16] to join the known C1–C12 aldehyde **3** and the C13–C22 polypropionate fragments **4** and **5**. This coupling strategy has been shown to be effective in three previous total syntheses.[8,9,13] The work reported in this article primarily focuses on our studies towards the efficient preparation of C13–C22 phosphonium salts **4** and **5**. The structural element of callystatin A **1** which initially attracted our attention to this series of natural products was the C15–C21 polypropionate region containing the 1,3,5-*syn*,*syn*-trimethyl configuration. We anticipated that the C13–C22 fragments would be derived from tetraol intermediate **6**, which contains the desired 1,3,5-*syn*,*syn*-trimethyl configuration, that we had reported in an earlier



Scheme 1 Retrosynthetic analysis of callystatin A

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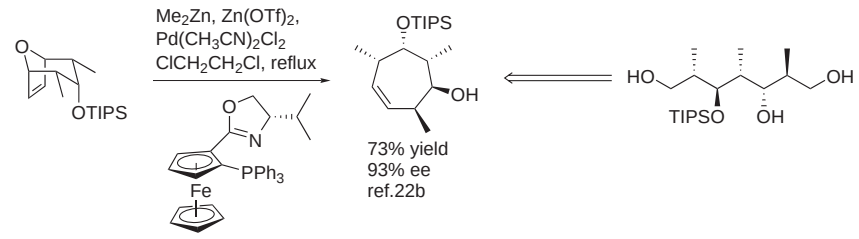
communication.[17] Tetraol **6** had been prepared in four steps (Scheme 4) from enantiomerically pure [3.2.1]oxabicycle **7**.[18]

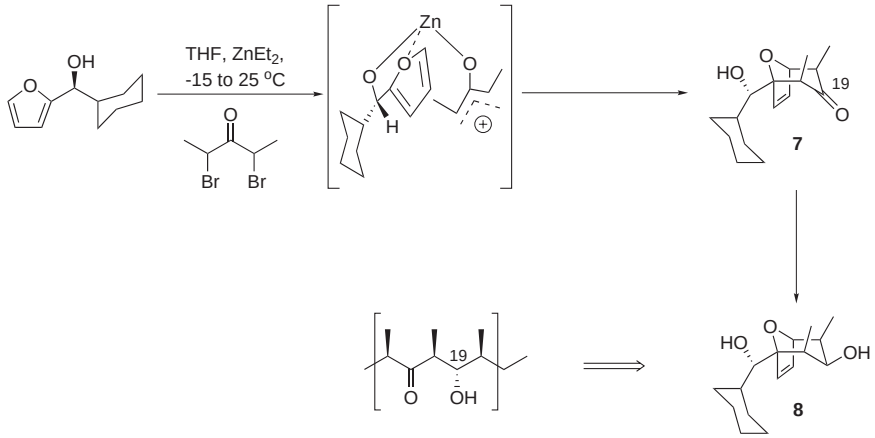
Work in our group and others has focused on the use of [3.2.1]oxabicycles as a templates for the synthesis of acyclic polypropionates.[19–21]One of the key issues relating to the use of [3.2.1]oxabicycles is the need to generate enantiomerically pure intermediates. Strategies reported in the literature include asymmetric hydroboration,[22] asymmetric deprotonation,[23] enzymatic resolution,[24] a tandem catalytic asymmetric cyclopropanation/Cope rearangement[25] and diastereoselective [4 + 3] cycloadditions.[18,26] Recent efforts in our own laboratories have focused on transition metal catalyzed asymmetric methods such as reductive ring opening (RRO)[27] and nucleophilic ring opening (NRO, Scheme 2)[28] reactions of *meso*-[3.2.1]oxabicycles. However, neither of these methodologies are suitable for the preparation of the C15–C21 1,3,5-*syn*,*syn*-trimethyl substituted fragment of callystatin A (**2**). For example, the catalytic asymmetric methyl-NRO of the *meso*-[3.2.1]-oxabicycle shown in Figure 2 results in a functionalized cycloheptene which corresponds to a 1,3,5-*syn*,*anti*-trimethyl relationship.[28b]

We relied upon a previously described diastereoselective [4 + 3] cycloaddition[18] to generate the enantiomerically pure [3.2.1]oxabicycle **7** as illustrated in Scheme 3. Nonracemic (furan-2-yl)cyclohexylmethanol, prepared from a Sharpless asymmetric epoxidation resolution,[29] was treated with diethylzinc and 2,4-dibromopentanone[30] to generate the respective reactive species that undergoes the cycloaddition. The stereoselectivity of the cycloaddition is rationalized by the extended transition state depicted in Scheme 3 where the zinc not only chelates (furan-2-yl)cyclohexylmethoxide, but also the incoming oxyallyl cation providing [3.2.1]oxabicyclooctanone **7** with diaxial methyl groups (relative to the chair conformation drawn for **7** in Scheme 3) in high selectivity, a feature which is unique among [4 + 3] cycloadditions.[31] The key benefit associated with the formation of **7** is that a methyl-NRO reaction will result in the desired 1,3,5-*syn*,*syn*-trimethyl arrangement in contrast to the transition metal catalyzed NRO of *meso*-[3.2.1]oxabicycle illustrated in Scheme 2. Extensive studies on the reduction of the ketone in **7** have allowed selective access to *cis*-alcohol **8**. The consequence of forming this diastereomer is the stereochemistry at what will become C19 of callystatin A is epimeric to the natural product [C19-*epi*-callystatin A (**2**)] necessitating an inversion of the hydroxyl stereochemistry at the C19-position at a later stage in the synthesis in order to access callystatin A (**1**).

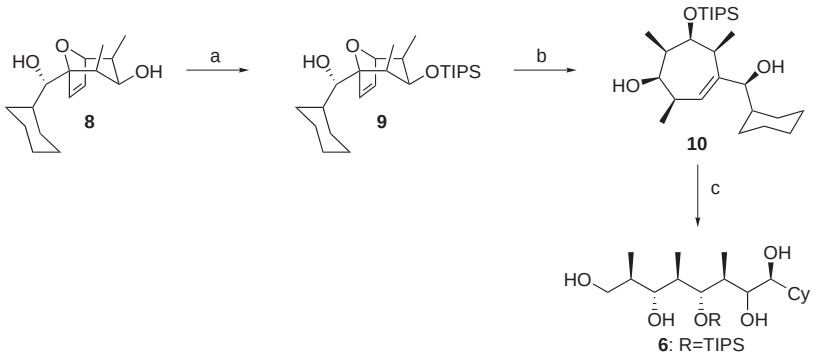
The methyl-NRO reaction of **9**, which secured the desired 1,3,5-*syn*,*syn*-trimethyl arrangement, was studied in detail.[17] Silyl ether **9** was prepared selectively from diol **8** in 90% yield in the presence of triisopropylsilyl triflate and 2,6-lutidine as shown in Scheme 4. Cerium(III) chloride was found to be crucial for the NRO reaction to proceed with methyllithium and further optimization of temperature effects has led to a slightly improved yield of cycloheptene **10**.[17] Oxidative rupture of cycloheptene **10** with ozone followed by reductive work-up with sodium boro-



Scheme 2 Catalytic enantioselective NRO of a *meso*-[3.2.1]oxabicycle



Scheme 3 Diastereoselective [4 + 3] cycloaddition and ketone reduction



Scheme 4 a) TIPSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C, 90%; b) MeLi, $CeCl_3$,THF–Et_2O, –78 to –15 °C, 85%; c) O_3, CH_2Cl_2–MeOH, –78 °C; then $NaBH_4$, 69 h, 20 °C, 91%

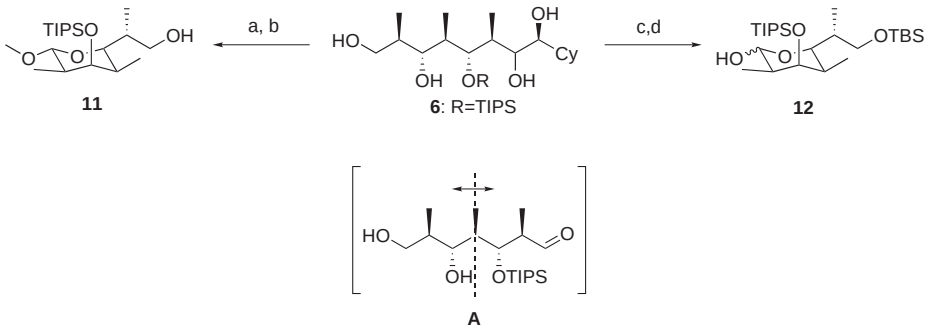
hydride afforded tetraol **6** as a single diasteriomer in 91% yield.

A key challenge in our synthesis was developing a protecting group strategy for the multiple hydroxyls of tetraol **6** that allowed for an efficient route to the C13–C22 fragments for C19-*epi*-callystatin A **4** and callystatin A **5**. A number of strategies were explored and are discussed below. In our initial report,[17] the vicinal diol in tetraol **6** was oxidatively cleaved in the presence of periodic acid resulting in a lactol that could be masked efficiently as methyl lactol **11**, Scheme 5. While the primary hydroxyl of **11** was readily manipulated, the methyl lactol proved highly resistent to hydrolysis without concomitant removal of the triisopropylsilyl ether. Instead we sought to utilize the lactol directly after its formation. To this end we selectivily silylated the primary hydroxyl of **6** then treated the resulting diol with lead(IV) acetate to afford lactol **12** in 98% yield over the two steps. Unfortunately, the lactol proved unreactive towards olefination with a variety of reagents under various conditions.

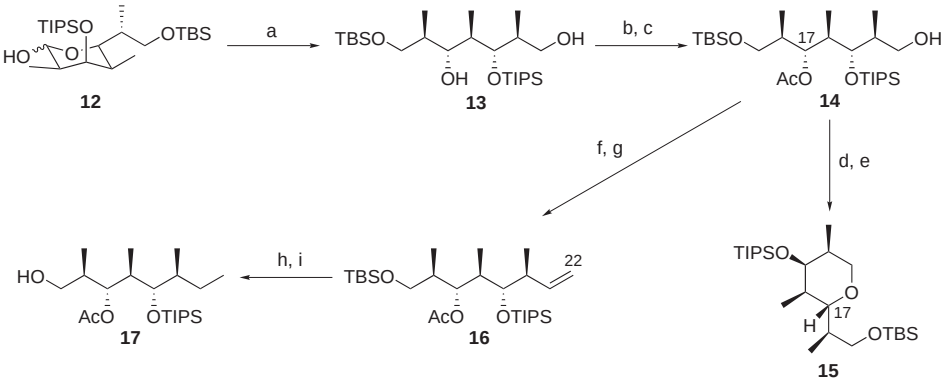
It is interesting to note that the acyclic polypropionate intermediate **A**, the open conformation of lactol **11**, is pseudo-symmetric, diffentiated only by protecting groups and oxidation state. Thus, depending on the absolute configuration of oxabicycle **7**, the polypropionate fragment could be extended in either direction.

While lactol **12** was unreactive towards olefination it could be reduced to acyclic diol **13** in the presence of $LiBH_4$ at 50 °C in a servicable yield of 71% (Scheme 6). The hydroxyls of diol **13** were differentiated through acetylation then a selective saponification of the less hindered acetate to yield alcohol **14**. Installation of the C22 methyl moiety was first attempted by activating the primary hydroxyl as a tosylate (95% yield) then treating the intermediate with $Me_2CuCNLi_2$. There was no observed reaction with the tosylate until warming to 0 °C where pyran **15** was obtained as the major product in 38% yield. Presumably, upon decomposition of the cuprate reagent the acetate at C17 was cleaved and the resulting alkoxide underwent the intramolecular cyclization. The one carbon homologation could be accomplished by oxidation of **14** followed by Wittig olefination to afford alkene **16** in 61% yield. Hydrogenation of the alkene and the subsequent selective hydrolysis of the primary *tert*-butyldimethylsilyl group provided the advanced intermediate **17** in 71% yield over two steps. While this route was successful, we were discouraged by the number of protecting group manipulations. In addition, the route did not present an appealing opportunity to invert the stereochemistry at C19.

The complications associated with the lactol intermediates prompted us to pursue a strategy, which completely circumvented lactol formation. Selective formation of a cyclic carbonate was investigated and our results are



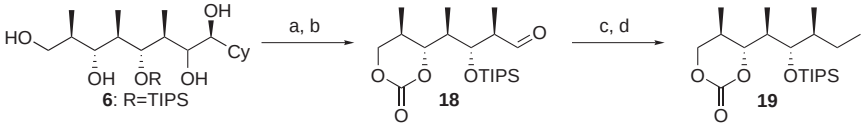
Scheme 5 a) H_5IO_6, $NaHCO_3$, THF–H_2O, 24 °C, 0.25 h, 94%; b) MeOH, TsOH, 24 °C, 8 h, 84%; c) TBSCl, CH_2Cl_2, Im, 0 to 20 °C, 1 h, 98%; d) $Pb(OAc)_4$, PhH–MeOH, 0 °C, 0.5 h, >99%



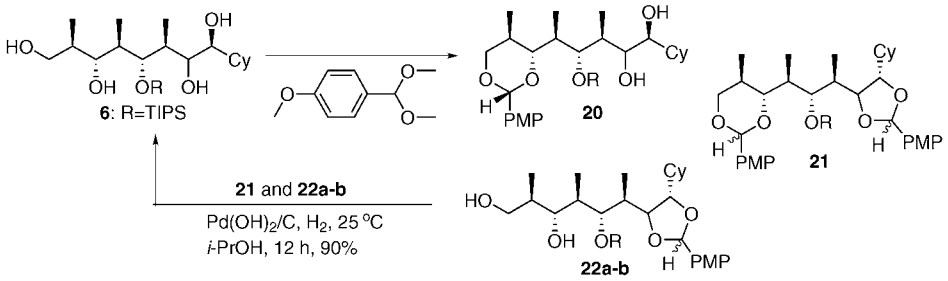
Scheme 6 a) $LiBH_4$, THF, 50 °C, 3 h, 71%; b) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 20 °C, 1.5 h, 96%; c) K_2CO_3, MeOH, 1 h, 20 °C, 92%; d) TsCl, cat. DMAP, Et_3N, CH_2Cl_2, 20 °C, 17 h, 95%; e) $Me_2CuCNLi_2$, Et_2O, –15 to 0 °C, 1 h, 38%; f) TPAP, NMO, CH_2Cl_2, 20 °C, 0.75 h, 95%; g) $Ph_3C{=}CH_2$, THF, –15 °C, 0.33 h, 64%; h) H_2, 10% Pd/C, EtOAc, 20 °C, 0.33 h, >99%; i) PPTS, EtOH, 50 °C, 24 h, 71%

shown in Scheme 7. Acylation of the primary hydroxyl of **6** with (4-nitrophenyl)chloroformate proceeded selectively at 0 °C and upon consumption of the starting material, dimethylaminopyridine was added and the mixture was allowed to warm to ambient temperature to form the cyclic carbonate. Oxidative cleavage of the vicinal diol provided aldehyde **18** in 86% yield over the two steps. The C22 methyl terminus was introduced through Wittig olefination and hydrogenation to afford **19**. Though this strategy significantly reduced the number of steps compared to the previous route described in Scheme 6, intrinsic problems were identified with the carbonate. The leading issues were the selective opening of the carbonate, the low yield of the Wittig olefination and the questionable compatibility of the cyclic carbonate with an oxidation/reduction sequence necessary for the correction of the C19 hydroxyl stereochemistry.

As an alternative to the cyclic carbonate, we investigated the use of a 4-methoxybenzylidene to selectively protect the 1,3-diol of tetraol **6**. The benzylidene was predicted to be stable to the conditions for the oxidation/reduction sequence required for the inversion of the C19-hydroxyl as well as the other anticipated transformations. In addition, benzylidenes have been shown to be versatile in terms of their removal or opening to the corresponding benzyl ethers. The selective formation of acetals and ketals on acyclic polyhydroxylated compounds does appear in the literature.[32] Generally, it has been established that acetonides and pentanolides will selectively protect 1,2-diols but examples exist where a benzylidene was selectively formed on a 1,3-diol in the presence of a 1,2-diol.[32f] With these examples in mind we investigated the reaction shown in Scheme 8. We found the desired reactivity by employing 4-methoxybenzaldehyde dimethylacetal[33] and catalytic acid. Initial attempts, Entry 1, Table 1, demonstrated that the reaction in DMF was partially selective towards the formation of 6-membered benzylidene **20** (49% yield) but bis-benzylidene **21**, 5-membered benzylidenes **22a**–**b**, as well as recovered starting material **6** were also observed. Unfortunately, in DMF, **20** was formed as a mixture of diasteriomers at the benzylidene carbon. The product distribution was essentially unaffected by changing solvent but less polar solvents such as toluene and dichloromethane (Entry 2) favored the formation of a single diasteriomer of **20**. We have tentatively assigned the relative stereochemistry of **20** such that the substituents are disposed equatorially on the six-membered ring. We hypothesized that the 5-membered benzylidene would be favored under kinetic conditions and we observed this to be true at –35 °C based on thin layer chromatography analysis. It then followed that the 6-membered benzylidene may be favored under equilibrating conditions. However, heating the reaction mixture in toluene at 90 °C over a prolonged period resulted in the unfavorable distribution of the observed products reported in Entry 3. We were dismayed to find that when the reaction was performed on a larger scale (4.1 mmol of **6**, Entry 4) the product distribution differed substantially from that shown in Entry 2 (0.4 mmol). Acceptable and reproducible yields were observed at ambient temperature (Entry 5). Further experimentation demonstrated improved reaction performance at higher concentration (Entries 6 and 7). The modest overall yield of **20** necessitated the recycling of the unwanted benzylidenes **21** and **22**, which was done effi-



Scheme 7 a) (4-NO_2PhO)COCl, CH_2Cl_2, Et_3N, 0 °C, 1 h; then DMAP, 24 °C, 60 h, 92%; b) $Pb(OAc)_4$, PhH, MeOH, 0 °C, 10 min, 94% c) $Ph_3C{=}CH_2$, THF, –78 °C, 0.33 h, 49%; d) H_2, 10% Pd/C, Et_2O, 20 °C, 0.5 h, 90%



Scheme 8

Table 1 Optimization for the Formation of the 1,3-Benzylidene **20**

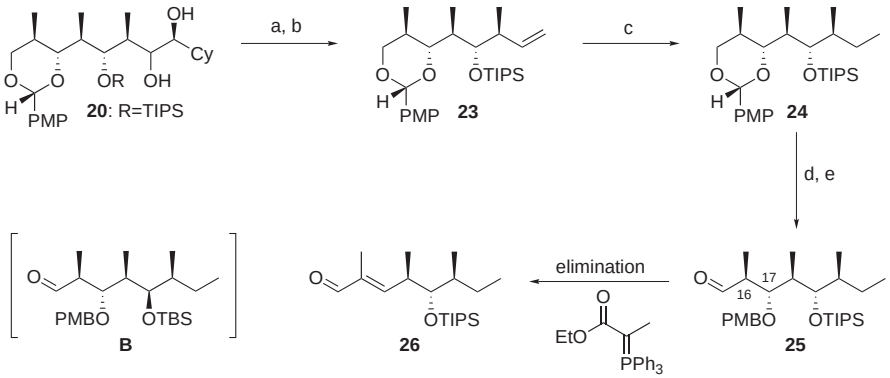
Entry	Conditions	**20**[a]	**21**[a]	**22**[a]	**6**[a]
1	DMF, 0 °C, CSA (10 mol%), acetal (1.2 equiv)	49[b]	19	3	19
2	CH_2Cl_2, 0 °C, CSA (5 mol%, 0.4 mmol)	52	11	11	20
3	PhMe, 90 °C, PPTS (5 mol%), acetal (1.1 equiv)	22	26	23	22
4	CH_2Cl_2, 0 °C, CSA (3 mol%, 4.1 mmol)	21	38	17	12
5	CH_2Cl_2 (0.093 M), 20 °C, CSA (3 mol%, 1.9 mmol)	47	27	19	6
6	CH_2Cl_2 (0.7 M), 20 °C, CSA (3 mol%, 2.1 mmol)	52	27	13	9
7	CH_2Cl_2 (0.01 M), 20 °C, CSA (3 mol%, 2.1 mmol)	18	37	28	27

[a] Isolated yields (%).
[b] Mixture of benzylidene isomers.

ciently through hydrogenolysis with Pearlman's catalyst and H_2 (1 atm) in 2-propanol allowing a 90% recovery of tetraol **6**.

With the appropriately protected intermediate **20** in hand we could address the synthesis of the polypropionate fragments **4** and **5**. Our initial foray is described in Scheme 9. Oxidative cleavage of the vicinal diol of **20** with lead(IV) acetate and subsequent Wittig homologation of the aldehyde produced alkene **23** in excellent yield. After considerable experimentation it was found that selective hydrogenation of the terminal alkene of **23** could be carried out with 10% Pd/C in ethyl acetate without any observable reduction of the benzylidene to cleanly afford **24**. Selective reductive opening of the benzylidene with DIBAL-H[34] in CH_2Cl_2 released the primary hydroxyl, which was then oxidized in the presence of PCC resulting in aldehyde **25** in 80% yield after chromatography. Attempts to homologate aldehyde **25** to the desired (*E*)-unsaturated ester were frustrated by elimination of the C17 4-methoxybenzylalkoxide to form enal **26** or epimerization of the C16-methyl group employing either Horner–Wadsworth–Emmons protocols or stabilized ylides. Marshall[12a] and Dias[35] reported a lack of reactivity with a similar intermediate in their synthesis of the polypropionate region of callystatin A (intermediate **B**, Scheme 9).

Leaving the C17 hydroxyl unprotected provided a direct solution to the elimination problem with the homologation of aldehyde **25**. Elimination of hydroxide under basic conditions should be less facile compared to the 4-methoxybenzylalkoxide and the lack of the protecting group may perturb the conformation of the molecule to make the elimination less favorable.[36] Thus, the desired 1,3-diol **27** was synthesized from intermediate **23** employing Pearlman's catalyst in *i*-PrOH under one atmosphere of H_2 which simultaneously hydrogenated the alkene as well as



Scheme 9 a) $Pb(OAc)_4$, PhH–MeOH, 0 °C, 0.5 h, 97%; b) $Ph_3P{=}CH_2$, THF, –15 to 25 °C, 18 h, 95%; c) 10% Pd/C, EtOAc, H_2, 0.5 h, 25 °C, 99%; d) DIBALH, CH_2Cl_2, –78 °C, 98%; e) PCC, CH_2Cl_2, 25 °C, 3 h, 80%

reductively removed the benzylidene in 97% yield as shown in Scheme 10.[37] It was then necessary to selectively oxidize the 1,3-diol **27**. After experimenting with various oxidizing agents it was found that Swern conditions[38] cleanly provided the β-hydroxy aldehyde **28** contaminated with ~5% of the starting diol.[13,39,40]Aldehyde **28** eliminated to enal **26** during silica gel chromatography but could be used directly after an aqueous work up without further purification. Fortunately, **28** underwent successful olefination with (1-ethoxycarbonyl)ethylidenetriphenylphosphorane to form unsaturated ester **29** as the only observed geometrical isomer. The C13–C22 phosphonium salt **4** was obtained in essentially quantitative yield following DIBAL-H reduction of **29** to the allylic alcohol, conversion to the allylic bromide and treatment of the allylic bromide with tributylphosphine.

Having established access to the C19-*epi*-C13–C22 fragment **4**, we turned our attention to the inversion of the C19 stereochemistry. Ketone **30** was readily prepared through fluoride induced removal of the silyl protecting group of intermediate **24** followed by tetrapropylammonium perruthenate (TPAP) oxidation[41] of the resulting alcohol as shown in Scheme 11. Our hypothesis for the selectivity of the C19-ketone reduction was based on Lewis acid chelation of the C17 ether and C19 carbonyl of **30**, which would allow the C18 methyl to influence the facial selectivity of the hydride delivery towards the *Si*-face as illustrated in Scheme 11. Reduction of **30** was carried out with a variety of reagents and the results are shown in Table 2. We found the selectivity of the reduction was highly dependent on the nature of the reducing agent. Lithium aluminum hydride reduction favored the original stereochemistry **31**-(*S*) almost exclusively (Entry 1). Reducing agents including Red-Al, $LiBH_4$, DIBAL-H and $NaBH_4$ provided discouraging results (Entries 2–5). L-Selectride was shown to be an ideal reagent for the selective reduction but was observed to be sluggish and did not proceed until the mixture was allowed to warm to ambient temperature. Analysis of the products showed that the reduction proceeded with the desired selectivity to **31**-(*R*) but was contaminated with a major byproduct presumed to be the diol **32** arising from reductive opening of the benzylidene. Further experimentation demonstrated that the reductive ring opening could be suppressed by performing the reaction in less polar solvents (Entries 7 and 8). Under the optimized conditions, **31**-(*R*) can be isolated cleanly in 68% under the conditions described in Entry 8.

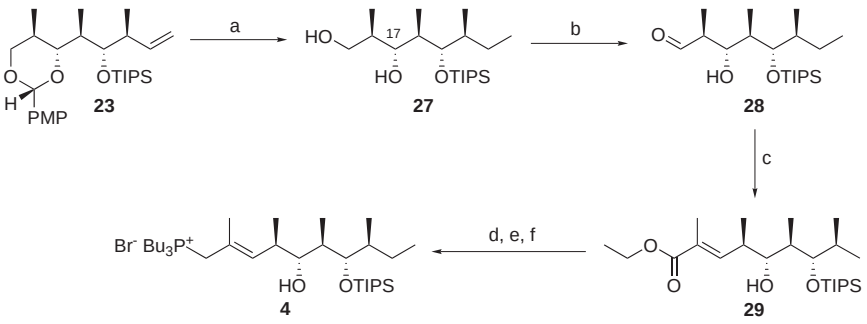
Table 2 Selective Reduction of Ketone **30**

Entry	Conditions	**31**-(*R*/*S*)[a]	**32** (%)
1	$LiAlH_4$, THF, –78 °C	~1:10	
2	Red-Al, PhMe, –78 to 0 °C	~1:4[b]	
3	$LiBH_4$, THF, 0 °C	~1:4[b]	
4	DIBAL-H, CH_2Cl_2, –78 °C	~1:2	
5	$NaBH_4$, MeOH, reflux	decomp.	
6	L-Selectride, THF, 20 °C	>10:1	~60
7	L-Selectride, Et_2O, 20 °C	>10:1	5–10
8	L-Selectride, PhMe, 20 °C	>10:1[c]	0

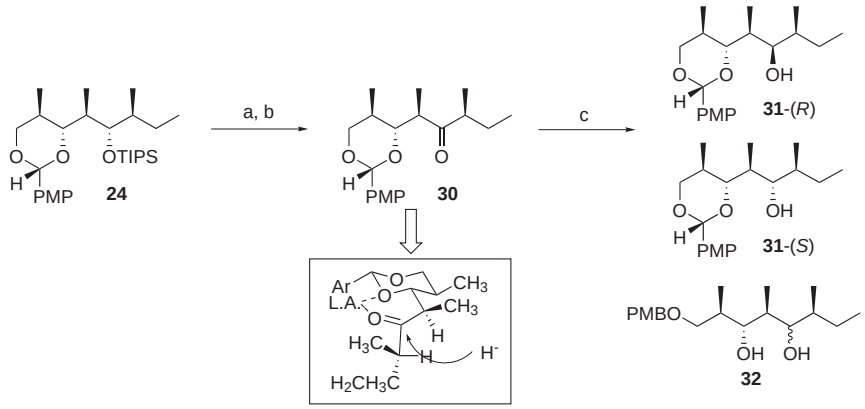
[a] Ratios determined crude ^1H NMR.
[b] Reaction did not go to completion.
[c] 68% isolated yield.

The same series of transformations used to prepare **4** (Scheme 10) could be applied to prepare phosphonium salt **5** epimeric at C19 as outlined in Scheme 12. Silylation of the free alcohol **31**-(*R*) with *tert*-butyldimethylsilyl triflate and 2,6-lutidine was followed by hydrogenolysis of the benzylidene providing diol **33** in 88% and 97% yield, respectively. The diol was selectively oxidized under Swern conditions and the resulting β-hydroxy aldehyde was homologated to unsaturated ester **34** in yields similar to those with the epimeric intermediate **29**. From the unsaturated ester **34**, the same series of manipulations shown in Scheme 10 were used to synthesize phosphonium salt **5**.

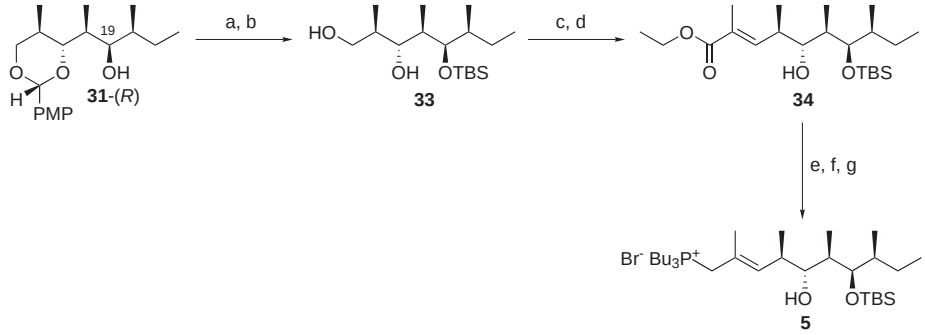
The synthesis of the C1–C12 aldehyde fragment **3** began with the assembly of a C1–C6 lactone precursor. Our approach, shown in Scheme 13, was inspired by a preparation of the compactin lactone reported in the literature,[42] and is similar to that recently reported by Marshall and



Scheme 10 a) $Pd(OH)_2/C$, H_2 (1 atm), 20 °C, *i*-PrOH, 12 h, 97%; b) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, Et_3N, 95%; c) $(Me)(Ph_3P{=})CCO_2Et$, CH_2Cl_2, reflux, 16 h, 81%; d) DIBAL-H, CH_2Cl_2, –78 °C, 99%; e) Ph_3P, CBr_4, MeCN, 2,6-lutidine, 25 °C, 10 min., >99%; f) Bu_3P, MeCN, 24 °C, 3 h



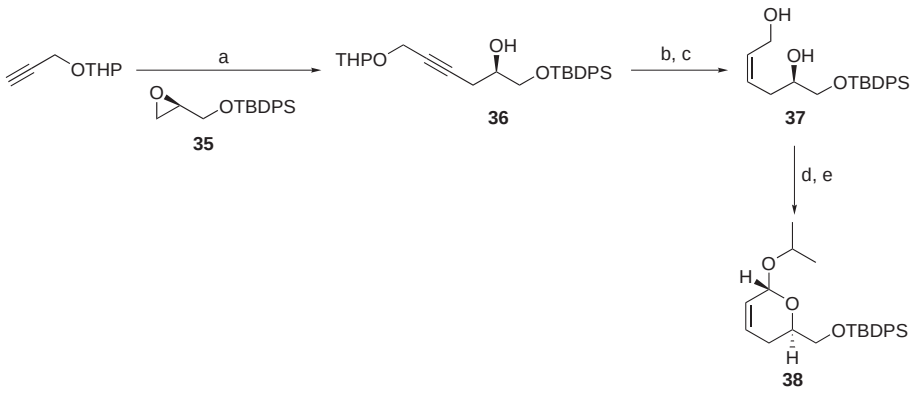
Scheme 11 a) TBAF, THF, 25 °C, 66 h, 99%; b) TPAP, NMO, CH_2Cl_2, 2.5 h, 97%; c) Table 2



Scheme 12 a) TBSOTf, CH_2Cl_2, 2,6-lutidine, –15 °C, 2 h, 88%; b) $Pd(OH)_2$/C, H_2 (1 atm), *i*-PrOH, 20 °C, 1 h, 97%; c) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, Et_3N, ~95%; d) $(Me)(Ph_3P{=})CCO_2Et$, CH_2Cl_2, reflux, 13.5 h, 78%; e) DIBAL-H, CH_2Cl_2, –78 °C, 10 min., 96%; f) Ph_3P, CBr_4, MeCN, 2,6-lutidine, 25 °C, 5 min., 79%; g) Bu_3P, MeCN, 24 °C, 1 h

Bourbeau in their synthesis of callystatin A.[12a] The C5 stereogenic center was derived from (*S*)-glycidol which was utilized as its silyl ether **35**. The tetrahydropyranyl ether of propargylic alcohol was treated with butyllithium followed by boron trifluoride etherate to generate a boryl nucleophile,[43] which was used to open epoxide **35** and form homoalkynyl alcohol **36** in 78% yield. Selective hydrolysis of the tetrahydropyranyl ether **36** followed by semi-hydrogenation proceeded in essentially quantitative yield to *Z*-alkenyl diol **37**. Selective allylic oxidation of the diol **37** to the desired lactol was more difficult than initially anticipated. Under optimized conditions, oxidation to the lactol proceeded in 75% yield based on 67% conversion in the presence of 15 equivalents of manganese(IV) oxide.[44] Known isopropyl lactol **38**[8,9,45]could be obtained in 93% yield by stirring the lactol with catalytic acid and 2-propanol. The relative stereochemistry of the dihydropyran **38** was in agreement with that presented in the literature.[46]

Lastly, we turned our attention to the synthesis of the C7–C12 fragment of callystatin A. The key intermediate is the

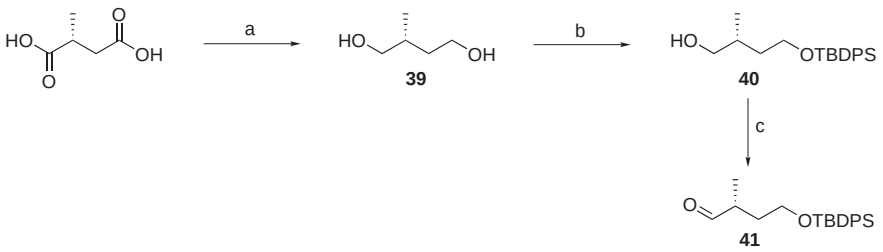


Scheme 13 a) BuLi, THF, –78 °C; then $BF_3{\cdot}Et_2O$; then **35**, 78%; b) PPTS, EtOH, 50 °C, 3 h, 99%; c) Lindlar cat., PhMe, H_2 (1 atm), 20 °C, 3 h, 99%; d) MnO_2, CH_2Cl_2, 20 °C, 13 h, 75% (based on converstion); e) *i*-PrOH, PPTS, 20 °C, 0.75 h, 93%

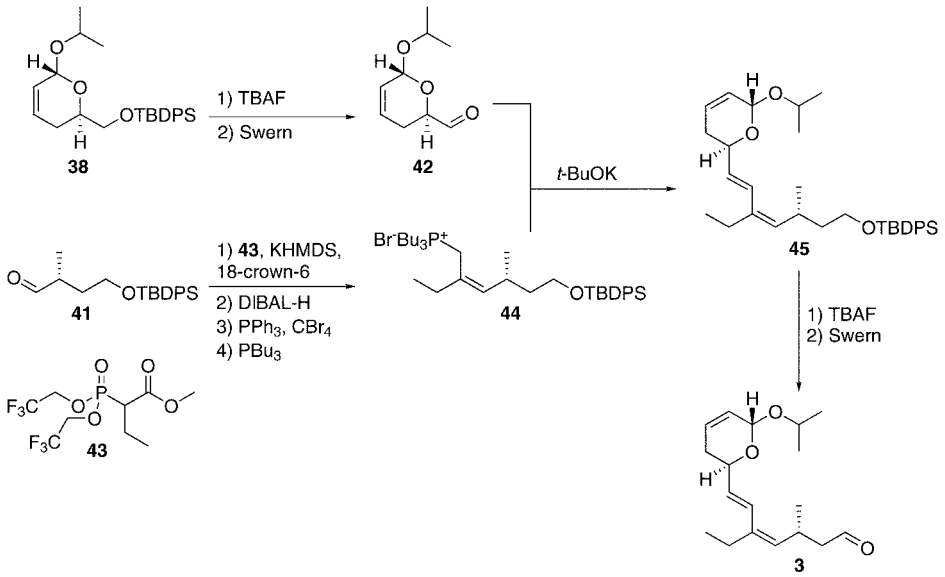
C9–C12 chiral synthon **41** which had been utilized in previous synthesis of this fragment of callystatin A.[8,9,13] We sought to find a more efficient route than those reported in the literature and found the functional, direct approach shown in Scheme 14. The C10 stereochemistry arises from the commercially available (*R*)-α-methylsuccinic acid. The diacid was reduced with lithium aluminum hydride to diol **39** in 87% yield. Selective protection of the less hindered of the two hydroxy groups of **39** was examined with *tert*-butylchlorodiphenylsilane (TBDPSCl) since the TBDPS group would be compatible with the subsequent steps, we could employ it stoichiometrically and the chlorosilane is reactive at low temperatures. Most importantly, the two mono-silylated isomers were separable by flash chromatography, a feature lacking with other protecting groups investigated. Under the optimized conditions with 5 mmol of **39**, we were able to isolate 61% of purified alcohol **40** as well as 14% of bis-silylated material and an additional 6% of a mixture of two mono-silylated alcohols. A 16:1 selectivity was observed for the silylation of the less hindered alcohol.[47] The two mono-silylated alcohols were observed to have nearly overlapping ^{1}H NMR spectra and could not be conclusively identified until oxidation to aldehyde **41**. Overall this route required six fewer steps and resulted in a 23% higher overall yield of **41** compared to the literature route.[48]

Completion of the synthesis of the C1–C12 fragment of callystatin A **3** is illustrated in Scheme 15 and was performed analogously to protocols described in the literature.[2,8,9,11,12a,13,49] Silyl ether **38** was converted to C1–C6 aldehyde **42** by removal to the *tert*-butyldiphenylsilyl group and oxidation of the resulting alcohol under Swern conditions.[38] The C9–C12 aldehyde **41** was homologated with butyrophosphonate **43**. The use of the Still protocol[50] for securing the *Z*-geometry of the C8–C9 alkene is ubiquitous among syntheses of this class of natural products. The C7–C12 phosphonium salt **44** was then prepared using conventional transformations. The *E*-selective tributylphosphonium Wittig type coupling[16] between aldehyde **42** and phosphonium salt **44** was carried out under the conditions reported by Crimmins and King[9] to provide the C1–C12 portion of callystatin A **45** as a single isomer in 82% yield. Cleavage of the *tert*-butyldiphenylsilyl ether in the presence of TBAF followed by Swern oxidation provided aldehyde **3** in high yield.

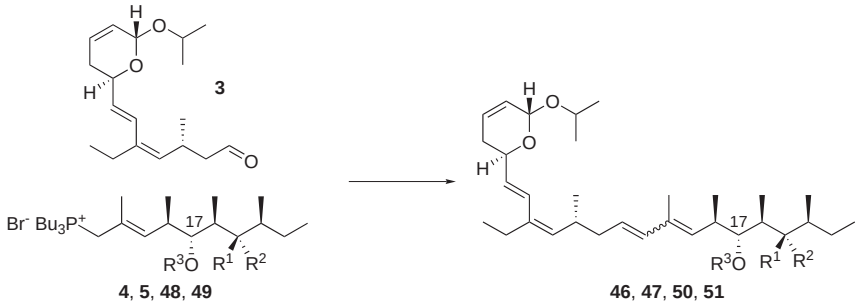
We sought to employ the *E*-selective tributylphosphonium Wittig type reaction[16] that had been shown to be effective for the coupling of the C1–C12 and C13–C22 fragments in previous total syntheses of callystatin A.[8,9,13] The coupling reaction is shown in Scheme 16 and our observations, which are in contrast to those reported in the literature, are shown in Table 3. Our initial attempt to cou-



Scheme 14 a) $LiAlH_4$, THF, 0 °C to 24 °C, 17.5 h, 87%; b) TBDPSCl, DBU, DMF, –50 °C, 0.5 h, 61%; c) DMSO, CH_2Cl_2, $(COCl)_2$, –78 °C, Et_3N, 99%



Scheme 15 Preparation of the C1–C12 aldehyde **3**



Scheme 16

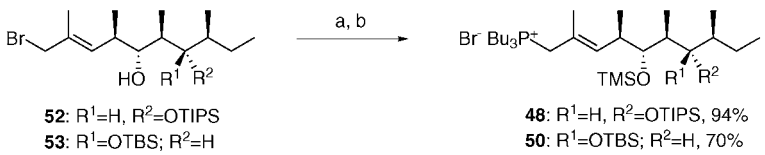
ple C1–C12 aldehyde **3** with the C19-*epi*-C13–C22 phosphonium salt **4** under conditions described by Crimmins and King[8] resulted in the coupled product **46** in a modest yield of 46% and as a 2:1 mixture of inseparable *E*/*Z* isomers, Entry 1. Coupling with the C13–C22 phosphonium salt **5** proceeded in high yield to afford **47** but with essentially no *E*/*Z* selectivity (Entry 2). We were surprised by the poor selectivity of the olefination as Kobayashi and Crimmins had reported obtaining the (*E*)-alkenes exclusively. Interestingly, the C13–C22 phosphonium salt used by Kobayshi and co-workers was identical to **5** expect the stereochemistry of the free hydoxyl at C17. We are unable to account for dramatic effect on *E*/*Z* selectivity from this relatively remote stereochemistry. Experimenting with different bases, solvents and temperatures resulted in reduced yields with essentially no affect on *E*/*Z* selectivity for the coupling reaction as illustrated by examples shown in Entries 3–6 in Table 3. We then investigated the option of protecting the C17 hydroxyl (R^3). The corresponding phosphonium salts **48**,**49** were prepared from allylic bromides **52**,**53** as shown in Scheme 17. We were pleased to find that phosphonium salts **48** and **49** coupled with aldehyde **3** in excellent yields in the presence of potassium *tert*-butoxide with high *E*-selectivity to provide C19-*epi*-C1–C22 intermediate **50** and C1–C22 intermediate **51** as shown in Entries 7 and 8. These observations emphasize the remarkable effect of the C17-substitution on this Wittig coupling.

With the C1–C22 skeletons of C19-*epi*-callystatin **50** and callystatin A **51** assembled, we began to study the final manipulations required to attain the targets shown in Scheme 18. Hydrolysis of the *i*-Pr-lactol proved challenging with the major byproduct of the reaction being isomerization of the lactol to an (*E*)-enal **56**,**57**. Under the optimized conditions, **50** was treated with acetic acid in a

Table 3 Coupling of the C1–C12 and C13–C22 Fragments

Entry	P-Salt	Conditions	R^1	R^2	R^3	Product	Yield (%)	*E*/*Z*[a]
1	**4**	PhMe–THF, 0 °C, *t*-BuOK	H	OTIPS	H	**46**	46	2:1
2	**5**	PhMe–THF, 0 °C, *t*-BuOK	OTBS	H	H	**47**	92	1:1.3
3	**4**	PhMe–THF, 0 °C, LHMDS	H	OTIPS	H	**46**	29	2:1
4	**4**	THF, 0 °C, LHMDS	H	OTIPS	H	**47**	43	1:1
5	**5**	DMF, 0 °C, *t*-BuOK	OTBS	H	H	**49**	27	1:1.3
6	**5**	DMSO, 0 °C, *t*-BuOK	OTBS	H	H	decomp.	n/a	n/a
7	**48**	PhMe–THF, 0 °C, *t*-BuOK	H	OTIPS	TMS	**50**	99	~10:1
8	**49**	PhMe–THF, 0 °C, *t*-BuOK	OTBS	H	TMS	**51**	94	>19:1

[a] Measured by ^{1}H NMR comparison of the C14 methyl integrations.

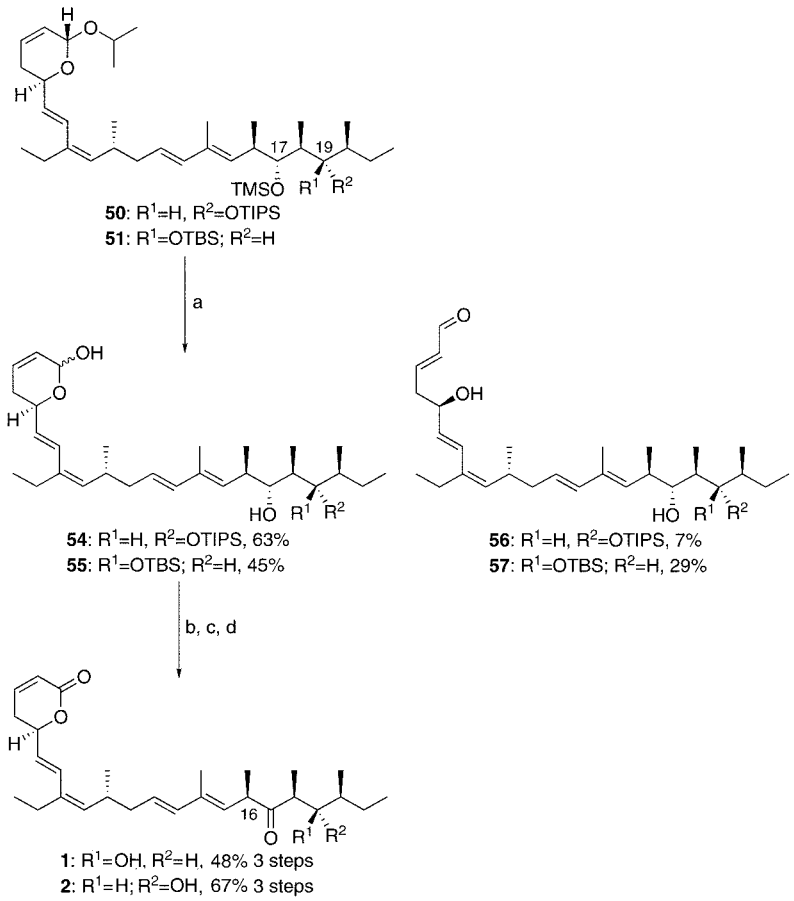


Scheme 17 a) TMSOTf, 2,6-lutidine,CH_2Cl_2, –78 °C; b) Bu_3P, MeCN, 20 °C

mixture of tetrahydrofuran and H_2O to afford lactol **54** in 63% yield along with 7% of enal **56**. The trimethylsilyl ether was concomitantly hydrolyzed under these conditions. Application of the identical conditions to the compound with the correct C19-stereochemistry **51**, led to a disappointing yield of lactol **55** along with 29% of isomerized enal **57**. Attempts to oxidize both the lactol and the C17-hydroxyl simultaneously failed thus the oxidations were carried out sequentially. Optimal yields were obtained when the lactols of **54** and **55** were first oxidized in the presence of manganese(IV) oxide followed by treatment with the Dess–Martin periodinane[51] to provide the corresponding keto-lactone intermediates. Lastly, the silyl protecting groups were cleaved in the presence of hydrogen fluoride pyridine complex to produce C19-*epi*-callystatin A (**1**) and callystatin A (**1**) in good yields over the final three steps. Interestingly, use of HF·pyridine (70:30 mixture, Fluka) has been reported in the literature.[9,10] When we attempted the deprotection leading to callystatin A (**1**) with HF·pyridine (70:30 mixture, Aldrich) and we cleanly obtained what appeared to be the natural product. However, upon closer examination, we determined that two compounds were present with nearly overlapping ^1H and ^{13}C NMR spectra. Although we were unable to separate the compounds we suspect that the C16-methyl group had epimerized under the reaction conditions. Using pyridine as a co-solvent, as reported by Kalesse and co-workers,[11,45] with HF·pyridine (70:30, Aldrich) we were able to cleanly recover C19-*epi*-callystatin A (**1**) and callystatin A (**1**).

In summary we were able efficiently synthesize C19-*epi*-callystatin in 22 steps from furan and the total synthesis of callystatin A was accomplished in 27 steps including a successful inversion of the C19-hydroxyl stereochemistry. Application of the [3.2.1]oxabicycle methodology developed in our laboratories allowed us to generate an acyclic intermediate **6** with the required 1,3,5-*syn*,*syn*-trimethyl arrangement for the C15–C21 polypropionate region. Evaluation of several protecting group strategies for tetraol **6** allowed us to develop a route that required a minimum number of manipulations while also providing the opportunity to selectively invert the C19 stereochemistry.

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. THF, Et_2O and toluene were distilled over sodium in the presence of benzophenone.



Scheme 18 a) HOAc, THF–H_2O, 20 °C; b) MnO_2, CH_2Cl_2, 20 °C; c) Dess–Martin periodinane, CH_2Cl_2, 20 °C; d) HF·pyridine, pyridine–THF, 0 to 20 °C

CH_2Cl_2 was distilled over calcium hydride. Anhyd DMF and DMSO were distilled under reduced pressure over calcium hydride then stored over molecular sieves before use. Cerium(III) chloride heptahydrate (Strem) was crushed into a fine powder then dried at 120 °C under high vacuum for at least 6 h before use in the methyllithium NRO reactions. ^{1}H NMR spectra were referenced from an internal standard of tetramethylsilane (δ = 0.00) and ^{13}C signals were referenced from $CDCl_3$ (δ = 77.23). Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet, AB, ABX); number of protons; coupling constants (*J*, Hz). IR spectra were obtained on a Perkin–Elmer Spectrum 1000 FT-IR spectrometer using NaCl plates. Optical rotations were measured on a Perkin–Elmer 243B polarimeter equiped with a sodium lamp (D-line, ν = 589 nm) and are reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent).

[1*S*,1(1*S*),2*R*,3*R*,4*S*,5*R*]-1-(Cyclohexylhydroxymethyl)-2,4-dimethyl-3-(triisopropylsilanyloxy)-8-oxabicyclo[3.2.1]oct-6-ene (9)

Diol **8** (1.082 g, 4.1 mmol) was dissolved in freshly distilled CH_2Cl_2 (20 mL). The solution was chilled to 0 °C and triisopropylsilyl trifluoromethanesulfonate (2.18 mL, 8.1 mmol) was added followed by the slow addition of 2,6-lutidine (1.18 mL, 10.2 mmol). The reaction was stirred for 1 h at 0 °C before being diluted in EtOAc (125 mL) and washed with sat. aq NH_4Cl (75 mL) and brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:19, 1:9; 1:4; 1:3) afforded [3.2.1]oxabicycle **9**.

Yield: 1.532 g (89%); colorless oil; R_f 0.29 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +29.5 (*c* 1.4, $CHCl_3$).

IR (neat): 3479, 2911, 1652, 1458, 1386, 1111 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.14 (ddd, 1 H, *J* = 6.2, 1.6, 0.9 Hz), 6.08 (d, 1 H, *J* = 6.2 Hz), 4.54, (s, 1 H), 4.15 (t, 1 H, *J* = 6.5 Hz), 3.69 (d, 1 H, *J* = 1.8 Hz), 2.13 (br, 1 H), 1.88–0.94 (m, 13 H), 1.14 (3 H, d, *J* = 7.1 Hz), 1.08 (d, 3 H, *J* = 7.0 Hz), 1.04 (s, 21 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.7, 131.3, 92.2, 82.6, 75.4, 68.0, 38.5, 37.4, 35.1, 32.1, 27.1, 26.8, 26.3, 26.1, 18.0, 13.7, 12.3, 10.1.

HRMS (EI$^+$, M$^+$): *m*/*z* calcd for $C_{25}H_{46}O_3Si$: 422.3216; found: 422.3230.

Anal. Calcd for $C_{25}H_{46}O_3Si$: C, 71.03; H, 10.97. Found: C, 71.00; H, 11.05.

(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*,7*R*)-1-Cyclohexyl-1,2,6,8-tetrahydroxy-4-(triispropylsilanyloxy)-3,5,7-trimethyloctane (6)

Cycloheptene **10** (4.06 g, 9.3 mmol) was dissolved in CH_2Cl_2–MeOH (1:1, 50 mL) with stirring. The solution was cooled to –78 °C and ozone was bubbled through until the characteristic blue color persisted. The solution was purged with nitrogen for 1 h before $NaBH_4$ (0.346 g, 93 mmol) was added. The mixture was allowed to warm r.t. and stirred for 69 h. The reaction was quenched by pouring into sat. aq NH_4Cl (250 mL). The aq phase was extracted with CH_2Cl_2 (3 × 100 mL) and combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:3, 1:2, 1:1) afforded tetraol **6**.

Yield: 4.013 g (91%); white foam which could be crystallized from hexanes; mp. 116.5–118.5 °C (hexanes); R_f 0.16 (EtOAc–hexanes, 1:2); $[\alpha]_D^{20}$ –7.2 (*c* 1.5, $CHCl_3$).

IR (neat): 3391, 2879, 1459, 1265, 1068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (t, 1 H, *J* = 4.3 Hz), 4.23 (br, 1 H), 4.01 (dd, 1 H, *J* = 10.8, 2.8 Hz), 3.70 (dd, 1 H, *J* = 10.6, 2.8 Hz), 3.63–3.55 (m, 2 H), 3.49 (s, 1 H), 3.29 (br, 1 H), 3.16 (br, 1 H), 2.38 (br, 1 H), 2.17–2.10 (1 H, m), 2.09–2.05 (m, 1 H), 1.96 (d, 1 H, *J* = 7.2 Hz), 1.83–1.73 (m, 4 H), 1.65 (d, 1 H, *J* = 10.1 Hz), 1.56 (d, 2 H, *J* = 11.4 Hz), 1.60–1.48 (m, 2 H), 1.39 (dq, 1 H, *J* = 12.4, 3.1), 1.32–1.24 (m, 1 H), 1.22 (d, 3 H, *J* = 7.1 Hz), 1.20–1.06 (m, 21 H), 0.94 (d, 3 H, *J* = 7.0 Hz), 0.93 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.0, 76.5, 75.8, 75.5, 64.0, 41.1, 40.1, 38.4, 34.6, 31.2, 27.0, 26.8, 26.24, 26.21, 18.1, 15.9, 14.7, 12.6, 11.8.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{26}H_{55}O_5Si$: 475.3819; found: 475.3796.

[1*S*,2*R*,3*R*,4*R*,5*R*,5(4*R*),5(5*R*)]-1-Cyclohexyl-5-{2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl}-3-methyl-4-(triisopropylsilanyloxy)hexan-1,2-diol (20)

Tetraol **6** (0.991 g, 2.1 mmol) was combined with *p*-anisaldehyde dimethylacetal (0.456 g, 2.5 mmol) in freshly distilled CH_2Cl_2 (3 mL) under an N_2 atmosphere. Camphorsulfonic acid (0.015 g, 0.1 mmol) was added and the solution was stirred 10 min before being quenched by pouring into sat. aq $NaHCO_3$ (75 mL). The mixture was partitioned with Et_2O (100 mL) and the organic phase was washed with brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography (EtOAc–hexanes; 1:19, 1:9, 1:4, 1:3, 1:2, 1:1, 2:1). Recovered bis-benzylidene **21** (0.399 g, 27%), the high R_f 5-memebered benzylidene **22a** (0.053 g, 4%) and the low R_f 5-membered benzylidene **22b** (0.105 g, 7%), starting tetraol **6** (0.084 g, 9%) as well and the desired 6-membered benzylidene **20** were obtained.

Yield: 0.644 g (52%); R_f 0.51 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ –36.3 (*c* 1.4, $CHCl_3$).

IR (neat): 3492, 2939, 2847, 1739, 1614, 1589, 1714, 1468, 1390, 1248, 1172, 1124 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39 (d, 2 H, *J* = 8.8 Hz), 6.90 (d, 2 H, *J* = 8.8 Hz), 5.37 (s, 1 H), 4.33 (t, 1 H, *J* = 3.6 Hz), 4.13 (dd, 1 H, *J* = 11.3, 4.7 Hz), 3.89–3.84 (m, 1 H), 3.82 (s, 3 H), 3.55–3.51 (m, 1 H), 3.49–3.42 (m, 1 H), 3.40–3.33 (m, 1 H), 2.78 (d, 1 H, *J* = 8.5 Hz), 2.31–2.23 (m, 1 H), 2.22–2.14 (m, 1 H), 2.13–2.02 (m, 1 H), 1.94–1.85 (m, 1 H), 1.78–1.56 (m, 3 H), 1.50–1.38 (m, 3 H), 1.22 (d, 3 H, *J* = 7.2 Hz), 1.15–1.05 (m, 21 H), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.88 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 131.3, 127.4, 113.8, 101.7, 68.3, 78.3, 76.0, 75.4, 73.5, 55.4, 42.8, 39.0, 37.7, 32.1, 31.3, 27.0, 26.9, 26.6, 26.4, 18.5, 18.4, 16.8, 13.5, 13.1, 12.8.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{34}H_{61}O_6Si$: 593.4237; found: 593.4209.

[3*S*,4*S*,5*R*,5(2*R*),5(4*R*),5(5*R*)]-5-{2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl}-3-methyl-4-(triisopropylsilanyloxy)hex-1-ene (23)

Diol **20** (0.856 g, 1.4 mmol) was dissolved in benzene and MeOH (9:1, 20 mL). The solution was chilled to 0 °C and lead(IV) acetate (0.960 g, 2.2 mmol) was added. The heterogeneous mixture was stirred for 1 h at 0 °C before being diluted in Et_2O (20 mL). The suspension was filtered through silica gel (Et_2O) and the filtrate was concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:19, 1:9, 1:4) afforded the aldehyde.

Yield: 0.667 g (97%); colorless oil; R_f 0.54 (EtOAc–hexanes, 1:4); $[\alpha]_D^{20}$ –45.9 (*c* 1.5, $CHCl_3$).

IR (neat): 2838, 2718, 1726, 1711, 1612, 1513, 1468, 1382, 1302, 1249 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.89 (d, 1 H, *J* = 2.2 Hz), 7.35 (d, 2 H, *J* = 8.4 Hz), 6.88 (d, 2 H, *J* = 8.1 Hz), 5.35 (s, 1 H), 4.42–4.39 (m, 1 H), 4.08 (dd, 1 H, *J* = 11.2, 4.4 Hz), 3.80 (s, 3 H), 3.50–3.41 (m, 2 H), 3.01–2.93 (m, 1 H), 2.28–2.20 (m, 1 H), 2.04–1.94 (m, 1

H), 1.20 (d, 3 H, *J* = 7.1 Hz), 1.17 (d, 3 H, *J* = 7.1 Hz), 1.10–1.07 (m, 21 H), 0.86 (d, 3 H, *J* = 6.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.8, 160.1, 131.2, 127.4, 113.8, 101.8, 86.0, 75.7, 73.4, 55.5, 49.4, 42.4, 32.6, 18.5, 18.4, 14.2, 13.2, 13.1, 13.0.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{27}H_{45}O_5Si$: 477.3036; found: 477.3030.

Freshly dried methyltriphenylphosphonium bromide (0.157 g, 0.4 mmol) was suspended in freshly distilled THF (2 mL). The mixture was chilled to –15 °C and butyllithium (1.27 M in hexanes; 0.347 mL, 0.4 mmol) was added. The solution was stirred for 10 min at –15 °C before the aldehyde (0.141 g, 0.3 mmol) was added to the yellow solution via cannula as a solution in freshly distilled THF (2 mL plus a 2 mL wash). The heterogeneous mixture was stirred for 2 h between –15 °C and –10 °C then allowed to warm to r.t. for an additional 14 h. The mixture was diluted in Et_2O (25 mL) and washed with H_2O (15 mL) and brine (15 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:19, 1:9) afforded alkene **23**.

Yield: 0.1322 (95%); colorless oil; R_f 0.66 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –26.5 (*c* 1.5, $CDCl_3$).

IR (neat): 2962, 2855, 1614, 1514, 1462, 1384, 1302, 1250, 1119, 1039, 883 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41 (d, 2 H, *J* = 8.6 Hz), 6.88 (d, 2 H, *J* = 8.6 Hz), 6.18–6.08 (m, 1 H), 5.37 (s, 1 H), 4.93–4.85 (m, 2 H), 4.16–4.13 (m, 1 H), 4.07 (dd, 1 H, *J* = 11.4, 4.8 Hz), 3.81 (s, 3 H), 3.49–3.43 (m, 2 H), 2.85–2.75 (m, 1 H), 2.18–2.08 (m, 1 H), 2.06–1.95 (m, 1 H), 1.12–1.03 (m, 27 H), 0.84 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 142.7, 131.6, 127.5, 113.6, 113.2, 101.5, 86.0, 75.8, 73.6, 55.5, 43.2, 41.4, 32.5, 21.3, 18.6, 13.3, 12.8.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{28}H_{48}O_4Si$: 476.3322; found: 476.3298.

[3*S*,4*S*,5*R*,5(2*R*),5(4*R*),5(5*R*)]-5-{2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl}-3-methyl-4-(triisopropylsilanyloxy)hexane (24)

Alkene **23** (0.334 g, 0.7 mmol) was dissolved in EtOAc (5 mL) under an N_2 atmosphere before palladium on carbon (10% by weight, ~50 mg) was added. Hydrogen was bubbled through the mixture for 45 min after which the solution was purged with N_2 for 15 min. The catalyst was removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo to afford **24** cleanly.

Yield: 0.333 g (>99%); colorless oil; R_f 0.66 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –23.5 (*c* 1.4, $CHCl_3$).

IR (neat): 2961, 2863, 1614, 1514, 1462, 1384, 1302, 1250, 1117, 883 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.39 (d, 2 H, *J* = 8.6 Hz), 6.87 (d, 2 H, *J* = 8.2 Hz), 5.35 (s, 1 H), 4.09–4.02 (m, 2 H), 3.80 (s, 3 H), 3.50–3.42 (m, 2 H), 2.18–2.09 (m, 1 H), 2.06–1.95 (m, 1 H), 1.88–1.79 (m, 1 H), 1.78–1.57 (m, 2 H), 1.12 (d, 3 H, *J* = 7.3 Hz), 1.11–1.03 (m, 21 H), 0.95 (d, 3 H, *J* = 6.8 Hz), 0.85 (t, 3 H, *J* = 7.1 Hz), 0.84 (d, 3 H, *J* = 6.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 131.7, 127.5, 113.8, 101.5, 85.7, 76.6, 73.6, 55.5, 43.5, 38.7, 32.6, 24.8, 18.7, 18.61, 18.57, 18.2, 13.4, 13.2, 12.7, 12.6.

HRMS [EI$^+$, (M – C_3H_7)$^+$]: *m*/*z* calcd for $C_{25}H_{43}O_4Si$: 435.2931; found: 435.2930.

(2*S*,3*S*,4*S*,5*S*,6*S*)-3-(4-Methoxybenzyloxy)-5-(triisopropylsilanyloxy)-2,4,6-trimethyloctanal (25)

In an oven-dried flask under an N_2 atmosphere, benzylidene **24** (0.333 g, 0.7 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL). The solution was chilled to 0 °C and DIBAL-H (1.0 M in heptanes; 2.78 mL, 2.8 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 2 h. The reaction was quenched by pouring into H_2O (30 mL) and the aluminum salts were solubilized by acidification with 10% aq HCl (2 mL). The aq phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to cleanly afford the alcohol.

Yield: 0.335 g (>99%); colorless oil; R_f 0.62 (EtOAc–hexanes, 1:2); $[\alpha]_D^{20}$ –9.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3435, 2950, 2868, 1614, 1514, 1462, 1249, 1058 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23 (d, 2 H, *J* = 8.6 Hz), 6.85 (d, 2 H, *J* = 8.6 Hz), 4.54 (A of an ABX, 1 H, *J* = 10.4 Hz), 4.50 (B of an ABX, 1 H, *J* = 10.4 Hz), 4.04 (t, 1 H, *J* = 3.5 Hz), 3.88 (dt, 1 H, *J* = 11.0, 3.7 Hz), 3.79 (s, 3 H), 3.58–3.52 (m, 1 H), 3.47 (dd, 1 H, *J* = 9.2, 2.7 Hz), 2.93 (d, 1 H, *J* = 7.5 Hz), 2.20–2.10 (m, 1 H), 1.98–1.91 (m, 1 H), 1.77–1.67 (m, 1 H), 1.63–1.55 (m, 1 H), 1.21 (d, 3 H, *J* = 7.1 Hz), 1.13–1.03 (m, 22 H), 1.00 (d, 3 H, *J* = 6.8 Hz), 0.96 (d, 3 H, *J* = 7.1 Hz), 0.89 (t, 3 H, *J* = 7.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 130.5, 129.3, 113.9, 87.2, 77.1, 74.9, 64.9, 55.4, 43.5, 38.3, 36.2, 25.4, 18.5, 18.4, 18.3, 16.6, 13.2, 12.6, 12.3.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{28}H_{53}O_4Si$: 481.3713; found: 481.3730.

The alcohol (0.0337 g, 0.1 mmol) was combined with activated molecular sieves (~100 mg, 3 Å) in freshly distilled CH_2Cl_2 (2 mL). PCC (0.030 g, 0.1 mmol, 2 equiv) was added and the mixture was stirred for 3.5 h at r.t. The reaction mixture was concentrated under reduced pressure and the resulting residue was filtered through a plug of silica gel (EtOAc–hexanes, 1:1) to afford aldehyde **25**.

Yield: 0.0304 g (91%); colorless oil; R_f 0.59 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +3.0 (*c* 1.0, $CHCl_3$).

IR (neat): 2960, 2868, 1724, 1614, 1514, 1464, 1384, 1301, 1249, 1175, 1059, 883, 823 cm^{-}-^{1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.81 (d, 1 H, *J* = 1.8 Hz), 7.23 (d, 2 H, *J* = 8.6 Hz), 6.86 (d, 2 H, *J* = 8.8 Hz), 4.49 (A of an AB, 1 H, *J* = 10.8 Hz), 4.45 (B of an AB, 1 H, *J* = 11.0 Hz), 4.01 (t, 1 H, *J* = 4.0 Hz), 3.82–3.78 (m, 4 H), 2.76 (qt, 1 H, *J* = 7.0, 2.2 Hz), 2.17–2.08 (d, 1 H), 1.68-1.48 (m, 3 H), 1.19 (d, 3 H, *J* = 7.1 Hz), 1.11–1.00 (m, 21 H), 0.93 (d, 3 H, *J* = 7.0 Hz), 0.87 (t, 3 H, *J* = 7.5 Hz), 0.86 (d, 3 H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 159.0, 130.5, 128.9, 113.8, 82.4, 77.0, 72.3, 55.6, 48.8, 42.3, 38.9, 25.9, 18.8, 17.8, 13.6, 12.9, 12.3, 11.2.

HRMS [EI$^+$, (M – C_3H_7)$^+$]: *m*/*z* calcd for $C_{25}H_{43}O_4Si$: 435.2931; found: 435.2922.

(2*R*,3*R*,4*R*,5*S*,6*S*)-2,4,6-Trimethyl-5-(triisopropylsilanyloxy)octane-1,3-diol (27)

Alkene **23** (0.369 g, 0.8 mmol) was dissolved in 2-propanol (5 mL) under an N_2 atmosphere. Pearlman's catalyst (0.075 g) was added before H_2 was bubbled through the solution for 10 min. The mixture was then stirred for 14 h under 1 atm of H_2. The mixture was purged with N_2 for 10 min before the catalyst was removed by filtration through Celite. After concentration, the crude product was purified by flash chromatography (EtOAc–hexanes; 1:9, 1:4) to afford diol **27**.

Yield: 0.267 g (96%); colorless oil; R_f 0.22 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +10.6 (*c* 1.0, $CHCl_3$).

IR (neat): 3347, 2962, 2863, 1462, 1383, 1250, 1112, 1059, 975, 883 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 4.29 (s, 1 H), 4.00 (d, 1 H, *J* = 11.2 Hz), 3.90 (t, 1 H, *J* = 4.0 Hz), 3.66 (d, 1 H, *J* = 10.1 Hz), 3.57–3.50 (m, 1 H), 3.35 (d, 1 H, *J* = 8.2 Hz), 2.05–1.95 (m, 1 H), 1.79–1.72 (m, 1 H), 1.71–1.63 (m, 1 H), 1.47–1.36 (m, 1 H), 1.21 (d, 3 H, *J* = 7.1 Hz), 1.10–1.05 (m, 22 H), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.94 (t, 3 H, *J* = 7.0 Hz), 0.86 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.5, 79.4, 64.2, 42.5, 37.3, 35.2, 26.1, 18.4, 18.3, 17.9, 16.0, 13.7, 13.0, 12.6.

HRMS (EI^+, MH^+): *m*/*z* calcd for $C_{20}H_{45}O_3Si$: 361.3138; found: 361.3155.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3-Hydroxy-2,4,6-trimethyl-5-(triisopropylsilanyloxy)octanal (28)

In an oven-dried flask under an N_2 atmosphere, DMSO (0.111 mL, 1.6 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 mL). The solution was cooled to –78 °C and $(COCl)_2$ (0.075 mL, 0.9 mmol) was added dropwise. After 5 min, diol **27** (0.267 g, 0.8 mmol) was added via cannula as a solution in CH_2Cl_2 (2 mL plus 1 mL wash). The white slurry was stirred 10 min at –78 °C before Et_3N (0.433 g, 3.1 mmol) was added dropwise. The solution was allowed to warm to r.t. before being diluted in Et_2O (100 mL) and washed with sat. aq NH_4Cl (75 mL), $NaHCO_3$ (75 mL) and brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to provide β-hydroxy aldehyde **28**.

Yield: 0.261 g (98%); colorless oil; R_f 0.54 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +22.3 (*c* 2.2, $CHCl_3$).

IR (neat): 3506, 2954, 2868, 1721, 1462, 1385, 1116, 1058, 1013, 990, 883 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 9.84 (d, 1 H, *J* = 2.9 Hz), 4.05 (s, 1 H), 3.89 (dd, 1 H, *J* = 4.6 Hz), 3.81 (d, 1 H, *J* = 10.1 Hz), 1.26 (d, 3 H, *J* = 7.0 Hz), 1.14–1.06 (m, 21 H), 0.95–0.88 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.0, 82.3, 76.8, 48.8, 42.5, 37.6, 26.1, 18.4, 18.3, 17.7, 13.7, 13.0, 12.6, 12.0.

HRMS (EI^+, MH^+): *m*/*z* calcd for $C_{20}H_{43}O_3Si$: 359.2981; found: 359.2990.

(*E*)-(4*R*,5*R*,6*R*,7*S*,8*S*)-5-Hydroxy-2,4,6,8-tetramethyl-7-(triisopropylsilanyloxy)dec-2-enoic Acid Ethyl Ester (29)

Aldehyde **28** (0.128 g, 0.4 mmol) and (1-ethoxycarbonylethylidene)triphenylphosphorane (0.324 g, 0.9 mmol) were combined in freshly distilled CH_2Cl_2 (5 mL). The solution was heated to reflux and stirred for 16 h. The reaction mixture was concentrated and the resulting residue was purified by flash chromatography (hexanes, 1:19; EtOAc–hexanes, 1:9, 1:4) to afford unsaturated ester **29** in addition to diol **27** (0.007 g, 5%).

Yield: 0.129 g (81%); waxy white solid; R_f 0.54 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +12.0 (*c* 1.6, $CHCl_3$).

IR (neat): 3519, 2962, 2858, 1720, 1711, 1692, 1462, 1384, 1367, 1242, 1138, 1114, 1087, 1059, 1003, 883 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.01 (d, 1 H, *J* = 10.3 Hz), 4.25–4.14 (m, 2 H), 3.85 (t, 1 H, *J* = 4.0 Hz), 3.80 (s, 1 H), 3.59 (d, 1 H, *J* = 9.9 Hz), 2.73–2.64 (m, 1 H), 1.85 (d, 3 H, *J* = 1.3 Hz), 1.69–1.58 (m, 3 H), 1.44–1.31 (m, 2 H), 1.29 (t, 3 H, *J* = 7.0 Hz), 1.12–1.01 (m, 21 H), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.90 (t, 3 H, *J* = 7.5 Hz), 0.80 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 142.8, 127.7, 82.2, 60.5, 42.3, 38.2, 35.9, 26.2, 18.5, 18.43, 18.38, 18.33, 17.5, 14.5, 13.9, 13.0, 12.6.

HRMS [EI^+, $(M-C_3H_7)^+$]: *m*/*z* calcd for $C_{22}H_{43}O_4Si$: 399.2931; found: 399.3615.

(*E*)-(4*R*,5*R*,6*R*,7*S*,8*S*)-1-Tributylphosphonium-2,4,6,8-tetramethyl-7-(triisopropylsilanyloxy)dec-2-en-5-ol Bromide (4)

Unsaturated ester **29** (0.218 g, 0.5 mmol) was dissolved in freshly distilled CH_2Cl_2 (4 mL). The solution was cooled to –78 °C under an N_2 atmosphere and DIBAL-H (1.0 M in heptane;1.23 mL) was added. The solution was stirred for10 min at –78 °C before being quenched with MeOH (~1 mL). The mixture was allowed to warm to r.t. before being diluted in H_2O (30 mL). Aluminum salts were hydrolyzed with 10% aq HCl (~2 mL) before the aq phase was extracted with CH_2Cl_2 (3 × 20 mL). Combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Allylic alcohol was recovered cleanly.

Yield: (0.194 g, 99%); colorless oil; R_f 0.42 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +7.9 (*c* 3.4, $CHCl_3$).

IR (neat): 3388, 2947, 2869, 1462, 1453, 1384, 1242, 1112, 1057, 1002, 883 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.61 (dq, 1 H, *J* = 9.9, 1.1 Hz), 4.02 (d, 2 H, *J* = 2.8 Hz), 3.84 (t, 1 H, *J* = 4.4 Hz), 3.69 (s, 1 H), 3.53 (dt, 1 H, *J* = 9.9, 1.9 Hz), 2.63–2.51 (m, 1 H), 1.68 (d, 3 H, *J* = 1.4 Hz), 1.72–1.55 (m, 2 H), 1.47–1.32 (m, 2 H), 1.11–1.08 (m, 21 H), 1.07 (d, 3 H, *J* = 6.9 Hz), 0.92 (d, 3 H, *J* = 6.6 Hz), 0.90 (t, 3 H, *J* = 7.2 Hz), 0.80 (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0, 127.1, 82.1, 77.7, 69.5, 42.3, 37.9, 34.4, 26.1, 18.7, 18.43, 18.37, 17.4, 14.0, 13.9, 13.0, 12.7.

HRMS (EI^+, MH^+): *m*/*z* calcd for $C_{23}H_{49}O_3Si$: 401.3451; found: 401.3438.

The allylic alcohol (0.0561 g, 0.1 mmol) and 2,6-lutidine (0.025 mL, 0.2 mmol) were combined in freshly distilled MeCN (1.5 mL). Carbon tetrabromide (0.070 g, 0.2 mmol) was added followed by Ph_3P (0.055 g, 0.2 mmol). The reaction was stirred for 10 min at r.t. before being diluted in Et_2O (30 mL). The organic phase was washed with H_2O (20 mL) and brine (20 mL) before being dried ($MgSO_4$), filtered and concentrated. The resulting residue was filtered through a plug of silica gel (EtOAc–hexanes, 1:19) and concentrated in vacuo to cleanly afford the allylic bromide.

Yield: 0.0646 g (>99%); colorless oil; R_f 0.65 (EtOAc–hexanes, 1:19); $[\alpha]_D^{20}$ –14.6 (*c* 1.1, $CHCl_3$).

IR (neat): 3504, 2947, 2868, 1462, 1385, 1208, 1055, 1012, 883 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.83 (d, 1 H, *J* = 9.9 Hz), 4.03 (A of an AB, 1 H, *J* = 9.3 Hz), 3.98 (B of an AB, 1 H, *J* = 9.3 Hz), 3.85 (t, 1 H, *J* = 4.3 Hz), 3.76 (t, 1 H, *J* = 1.4 Hz), 3.55 (dt, 1 H, *J* = 10.0, 1.9 Hz), 2.60–2.47 (m, 1 H), 1.77 (d, 3 H, *J* = 1.4 Hz), 1.75–1.55 (m, 2 H), 1.46–1.38 (m, 1 H), 1.13–1.08 (m, 22 H), 1.07 (d, 3 H, *J* = 7.0 Hz), 0.94 (d, 3 H, *J* = 6.7 Hz), 0.91 (t, 3 H, *J* = 7.0 Hz), 0.81 (d, 3 H, *J* = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5, 131.9, 82.4, 77.8, 42.5, 77.8, 42.5, 42.2, 37.6, 35.2, 26.1, 18.44, 18.38, 18.1, 18.0, 17.7, 15.0, 13.9, 13.0, 12.7.

HRMS (EI^+, MH^+): *m*/*z* calcd for $C_{23}H_{46}O_2SiBr$: 461.2450; found: 461.2448.

Allylic bromide (0.0435 g, 0.1 mmol) was dissolved in freshly distilled CH_2Cl_2 (1 mL) under an N_2 atmosphere. Tributylphosphine (0.047 mL, 0.2 mmol, Strem) was added and the solution was stirred for 3 h at 20 °C. Solvent and excess phosphine were removed in vacuo and the material was recovered as a colorless oil which solidified on standing. Phosphonium salt **4** was utilized without further purification or characterization.

[3*S*,5*R*,5(2*R*),5(4*R*),5(5*R*)]-5-{2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl}-3-methylhexan-4-one (30)

Silyl ether **24** (0.534 g, 1.1 mmol) was dissolved in freshly distilled THF (5 mL) under an N_2 atmosphere. TBAF (1.0 M in THF; 2.24

mL) was added and the solution was stirred for 66 h at r.t. The mixture was then diluted in Et_2O (125 mL) and washed with sat. aq NH_4Cl (75 mL) and brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purified by flash chromatography (EtOAc–hexanes; 1:19, 1:9, 1:4, 1:3) afforded the alcohol.

Yield: 0.356 g (99%); as a colorless oil; R_f 0.18 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –22.3 (*c* 1.3, $CHCl_3$).

IR (neat): 3532, 2962, 2870, 2832, 1614, 1518, 1462, 1391, 1303, 1250, 1171, 1112, 1035 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.38 (d, 2 H, *J* = 8.2 Hz), 6.88 (d, 2 H, *J* = 7.9 Hz), 5.40 (s, 1 H), 4.08 (dd, 1 H, *J* = 11.4, 4.6 Hz), 3.80 (s, 3 H), 3.54–3.48 (m, 1 H), 3.43 (t, 1 H, *J* = 11.2 Hz), 2.53 (d, 1 H, *J* = 5.1 Hz), 2.39–2.28 (m, 1 H), 2.10–2.01 (m, 1 H), 1.63–1.52 (m, 2 H), 1.23–1.09 (m, 1 H), 1.04 (d, 3 H, *J* = 7.1 Hz), 0.98 (d, 3 H, *J* = 6.6 Hz), 0.91 (t, 3 H, *J* = 7.3 Hz), 0.83 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 131.3, 127.5, 113.8, 101.8, 88.7, 78.8, 73.8, 55.5, 37.6, 37.3, 33.1, 22.4, 17.5, 17.0, 12.9, 12.2.

HRMS (EI^+, M^+): *m*/*z* calcd for $C_{19}H_{30}O_4$: 322.2144; found: 322.2153.

The alcohol (0.0469 g, 0.1 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 mL). Tetrapropylammonium perruthenate (0.005 g, 0.01 mmol) and *N*-methylmorpholine oxide (0.026 g, 0.2 mmol) were added and the dark solution was stirred at r.t. for 2.5 h. The reaction mixture was concentrated then filtered through a plug of silica gel (EtOAc–hexanes, 1:1). The filtrate was concentrated in vacuo to afford ketone **30**.

Yield: 0.0453 (97%); colorless oil; R_f 0.46 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ –21.3 (*c* 1.2, $CHCl_3$).

IR (neat): 2968, 2870, 2840, 1710, 1613, 1589, 1514, 1462, 1391, 1303, 1248, 1173, 1116, 1082, 1034, 834 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.36 (d, 2 H, *J* = 8.6 Hz), 6.87 (d, 2 H, *J* = 8.6 Hz), 5.39 (s, 1 H), 4.05 (dd, 1 H, *J* = 11.4, 4.8 Hz), 3.80 (s, 3 H), 3.69 (dd, 1 H, *J* = 10.0, 4.5 Hz), 3.47 (t, 1 H, *J* = 11.2 Hz), 2.97 (dq, 1 H, *J* = 7.1, 4.5 Hz), 2.73 (dq, 1 H, *J* = 6.7 Hz), 2.07–1.92 (m, 1 H), 1.72–1.58 (m, 1 H), 1.38–1.27 (m, 1 H), 1.26 (d, 3 H, *J* = 7.1 Hz), 1.06 (d, 3 H, *J* = 6.9 Hz), 0.81 (t, 3 H, *J* = 6.7 Hz), 0.80 (d, 3 H, *J* = 6.7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.6, 160.1, 131.2, 127.6, 113.7, 101.6, 84.9, 73.2, 55.5, 49.8, 46.3, 32.7, 26.0, 16.4, 13.5, 13.1, 11.9.

HRMS (EI^+, M^+): *m*/*z* calcd for $C_{19}H_{28}O_4$: 320.1987; found: 320.1988.

[3*S*,4*R*,5*R*,5(2*R*), 5(4*R*),5(5*R*)]-5-{2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl}-3-methylhexan-4-ol [31-(*R*)]

Ketone **30** (0.178 g, 0.6 mmol) was dissolved in freshly distilled toluene (3 mL) under an N_2 atmosphere. The solution was chilled to 0 °C and L-Selectride (0.78 mL, 0.8 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 1 h. The solution was chilled to 0 °C once again and quenched by the dropwise addition of aq H_2O_2 (30%; ~2 mL). The biphasic mixture was allowed to warm to r.t. and stirred for an additional 15 min. The mixture was diluted in sat. aq NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:9, 1:4) afforded alcohol **31**-(*R*) as a single stereoisomer.

Yield: 0.121 g (68%); R_f 0.28 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –8.6 (*c* 1.8, $CHCl_3$).

IR (neat): 3519, 2964, 2924, 2878, 2832, 1614, 1518, 1462, 1391, 1303, 1251, 1172, 1109, 1035 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36 (d, 2 H, *J* = 8.2 Hz), 6.86 (d, 2 H, *J* = 7.9 Hz), 5.38 (s, 1 H), 4.14 (dd, 1 H, *J* = 11.2, 4.8 Hz), 3.79 (d, 3 H), 3.68 (d, 1 H, *J* = 9.3 Hz), 3.56 (d, 1 H, *J* = 9.9 Hz), 3.50 (t, 1 H, *J* = 11.0 Hz), 3.35–3.32 (m, 1 H), 2.29–2.20 (m, 1 H), 2.11–2.04 (m, 1 H), 1.57–1.49 (m, 1 H), 1.46–1.37 (m, 1 H), 1.08 (d, 3 H, *J* = 7.1 Hz), 1.01 (d, 3 H, *J* = 7.3 Hz), 0.91 (t, 3 H, *J* = 7.3 Hz), 0.78 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 130.9, 127.4, 113.9, 102.2, 89.7, 74.3, 73.2, 55.5, 37.3, 33.9, 30.9, 25.4, 15.6, 12.4, 11.2, 11.1.

HRMS (EI^+, M^+): *m*/*z* calcd for $C_{19}H_{30}O_4$: 322.2144; found: 322.2143.

(2*R*,3*R*,4*R*,5*R*,6*S*)-2,4,6-Trimethyl-5-(*tert*-butyldimethylsilanyloxy)octane-1,3-diol (33)

Alcohol **31**-(*R*) (0.211 g, 0.7 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 mL). The solution was cooled to –15 °C under an N_2 atmosphere and 2,6-lutidine (0.153 g, 1.3 mmol) was added followed by *tert*-butyldimethilsilyl trifluoromethanesulfonate (0.196 mL, 0.9 mmol). The mixture was stirred at –15 °C for 2 h before being quenched with 2-propanol (~1 mL). The solution was then diluted in Et_2O (100 mL) and washed with sat. aq NH_4Cl (75 mL) and brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexanes; EtOAc–hexanes, 1:19) afforded the silyl ether as a colorless oil. A 1:1 mixture of benzylidene isomers was observed by ^1H NMR: R_f 0.54 (EtOAc–hexanes, 1:9). This compound has been reported but not characterized previously as a single stereoisomer.[35]

The silyl ether (0.252 g, 0.6 mmol) was dissolved in 2-propanol (3 mL) under an N_2 atmosphere. Palladium hydroxide on carbon (0.030 g) was added and H_2 was bubbled through the mixture for 10 min. The mixture was stirred an additional 50 min under 1 atm of H_2 before being deemed complete by TLC. The catalyst was removed by filtration though Celite. After concentration, the crude material was subjected to flash chromatography (EtOAc–hexanes; 1:9, 1:4, 1:3) to afford diol **33**.

Yield: 0.179g (97%); colorless oil; R_f 0.29 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +2.7 (*c* 1.1, $CHCl_3$).

IR (neat): 3374, 3958, 2870, 1462, 1383, 1254, 1070, 1025, 975, 837, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.92 (d, 1 H, *J* = 10.3 Hz), 3.83 (t, 1 H, *J* = 2.6 Hz), 3.70 (dd, 1 H, *J* = 9.2, 2.8 Hz), 3.57 (dd, 1 H, *J* = 10.4, 3.5 Hz), 2.08–2.00 (m, 1 H), 1.76–1.68 (m, 1 H), 1.62–1.55 (m, 1 H), 1.47–1.37 (m, 1 H), 1.26–1.16 (m, 1 H), 1.13 (d, 3 H, *J* = 7.1 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.91 (s, 9 H), 0.89 (t, 3 H, *J* = 7.5 Hz), 0.82 (d, 3 H, *J* = 7.0 Hz), 0.14 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 80.3, 79.8, 64.7, 40.4, 36.9, 35.9, 28.6, 26.1, 18.3, 15.8, 15.5, 14.0, 12.4, –4.0, –4.3.

HRMS [EI^+, $(M - C_4H_9)^+$] *m*/*z* calcd for $C_{13}H_{29}O_3Si$: 261.1886; found: 261.1891.

(*E*)-(4*R*,5*R*,6*R*,7*R*,8*S*)-5-Hydroxy-2,4,6,8-tetramethyl-7-(*tert*-butyldimethylsilanyloxy)-dec-2-enoic Acid Ethyl Ester (34)

In an oven-dried flask under an N_2 atmosphere, DMSO (0.049 mL, 0.7 mmol) was dissolved in freshly distilled CH_2Cl_2 (1 mL). The solution was cooled to –78 °C before oxalyl chloride (0.033 mL) was added dropwise. After stirring for 5 min at –78 °C, diol **33** (0.1047 g, 0.3 mmol) was added via cannula as a solution in CH_2Cl_2 (1.5 mL plus 1.5 mL wash). The white slurry was stirred 10 min at –78 °C before Et_3N (0.190 mL, 1.4 mmol) was added slowly. After the addition was complete the solution was allowed to warm to r.t. before being diluted in Et_2O (30 mL). The organic phase was washed with sat. aq solutions of NH_4Cl (20 mL) $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The β-hydroxy aldehyde was obtained cleanly. Characterization data is in agreement with that reported in the literature for the identical compound synthesized by an independent route.[12a]

Yield: 0.097 g (94%); colorless oil.

In a clean dry flask, (1-ethoxycarbonylethylidene)triphenylphosphorane (0.279 g, 0.8 mmol, Lancaster) was combined with the β-hydroxy aldehyde (0.0974 g, 0.3 mmol) in freshly distilled CH_2Cl_2 (4 mL). The solution was heated to reflux and stirred for 13.5 h before being concentrated under reduced pressure. The resulting residue was purified by flash chromatography (hexanes; EtOAc–hexanes, 1:19) to afford unsaturated ester **34**. This compound has been synthesized previously under different conditions but the characterization was incomplete.[12a]

Yield: 0.096 g (78%); white solid; R_f 0.53 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +30.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3485, 2959, 2855, 1711, 1462, 1413, 1387, 1299, 1252, 1139, 1097, 1004, 837 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.98 (dq, 1 H, *J* = 10.3, 1.5 Hz), 4.47 (s, 1 H), 4.20–4.11 (m, 2 H), 3.71–3.68 (m, 2 H), 2.64–2.54 (m, 1 H), 1.86 (d, 3 H, *J* = 1.3 Hz), 1.75–1.65 (m, 1 H), 1.64–1.44 (m, 1 H), 1.39–1.17 (m, 2 H), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.11 (d, 3 H, *J* = 7.1 Hz), 1.01 (d, 3 H, *J* = 6.6 Hz), 0.92 (s, 9 H), 0.88 (t, 3 H, *J* = 7.5 Hz), 0.71 (d, 3 H, *J* = 7.0 Hz), 0.11 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 142.8, 127.7, 81.0, 77.4, 60.5, 41.9, 36.6, 35.7, 29.4, 26.1, 18.3, 17.0, 15.5, 14.5, 14.2, 12.7, 12.3, –3.9, –4.7.

HRMS [EI^+, $(M - C_4H_9)^+$]: *m*/*z* calcd for $C_{18}H_{35}O_4Si$: 343.2305; found: 343.2324.

(*E*)-(4*R*,5*R*,6*R*,7*R*,8*S*)-1-Tributylphosphonium-2,4,6,8-tetramethyl-7-(*tert*-butyldimethylsilanyloxy)dec-2-en-5-ol Bromide (5)

Unsaturated ester **34** (0.096 g, 0.2 mmol) was dissolved in freshly distilled CH_2Cl_2 (1 mL) under an N_2 atmosphere. The solution was cooled to –78 °C and DIBAL-H (1.0 M in toluene; 0.840 mL) was added. The solution was stirred 10 min at –78 °C before being quenched with MeOH (~0.5 mL). The mixture was allowed to warm to r.t. before being diluted in H_2O (30 mL). The aluminum salts were hydrolyzed with 10% aq HCl (~2 mL) before the aq phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The allylic alcohol (0.083 g, 96%) was recovered cleanly as a colorless oil. Characterization data are in agreement with that reported in the literature for the identical compound.[12a]

The allylic alcohol (0.094 g, 0.3 mmol) and 2,6-lutidine (0.046 mL, 0.4 mmol) were combined in freshly distilled CH_2Cl_2 (3 mL). Carbon tetrabromide (0.131 g, 0.4 mmol) was added and the solution was chilled to 0 °C. Ph_3P (0.104 g, 0.4 mmol) was added and the mixture was allowed to warm to r.t. After stirring for 5 min, the reaction was quenched by pouring into H_2O (30 mL). The aq phase was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The residue was filtered through a plug of silica gel (EtOAc–hexanes, 1:19) and concentrated to afford the allylic bromide.

Yield: 0.087 g (79%); colorless oil; R_f 0.76 (EtOAc–hexanes, 1:4); $[\alpha]_D^{20}$ –9.4 (*c* 0.9, $CHCl_3$).

IR (neat): 3485, 2959, 2855, 1462, 1379, 1255, 1211, 1123, 1004, 837, 771 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.80 (d, 1 H, *J* = 9.9 Hz), 4.26 (s, 1 H), 4.01 (A of an AB, 1 H, *J* = 9.3 Hz), 3.97 (B of an AB, 1 H, *J* = 9.3 Hz), 3.69 (t, 1 H, *J* = 3.1 Hz), 3.64 (d, 1 H, *J* = 10.3 Hz), 2.49–2.41 (m, 1 H), 1.78 (d, 3 H, *J* = 1.1 Hz), 1.77–1.67 (m, 1 H), 1.65–1.55 (m, 1 H), 1.38–1.30 (m, 1 H), 1.27–1.17 (m, 1 H), 1.06 (d, 3 H, *J* = 7.0 Hz), 1.00 (d, 3 H, *J* = 6.8 Hz), 0.93 (s, 9 H), 0.88 (t, 3 H, *J* = 7.3 Hz), 0.73 (d, 3 H, *J* = 7.1 Hz), 0.12 (s, 3 H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 132.0, 80.9, 77.7, 42.1, 41.6, 35.91, 35.88, 29.3, 26.1, 18.3, 17.7, 15.6, 15.0, 14.1, 12.3, –4.0, –4.6.

HRMS [EI^+, $(M - C_4H_9)^+$]: *m*/*z* calcd for $C_{16}H_{32}O_2SiBr$: 363.1355; found: 363.1365.

The allylic bromide (0.070 g, 0.2 mmol) was dissolved in freshly distilled MeCN (1.5 mL) under an N_2 atmosphere. Tributylphosphine (0.082 mL, 0.3 mmol, Strem) was added and the reaction was stirred at r.t. until the starting material was consumed (~1 h). The solution was concentrated in vacuo and the resulting phosphonium salt **5** was used in the subsequent coupling reaction without further purification or characterization.

(2*R*)-1-(*tert*-Butyldiphenylsilanyloxy)-6-(tetrahydropyran-2-yloxy)hex-4-yn-2-ol (36)

Tetrahydropyranyl propargylic ether (0.673 g, 4.8 mmol) was dissolved in freshly distilled THF (10 mL) in an oven-dried flask under an N_2 atmosphere. The solution was cooled to –78 °C and BuLi (1.92 mL, 4.8 mmol) was added. The mixture was allowed to warm to 0 °C for 15 min before being cooled to –78 °C once again. $BF_3{\cdot}Et_2O$ (0.607 mL, 4.8 mmol) was added slowly and the mixture was allowed to stir for 5 min before epoxide **35** (1.00 g, 3.2 mmol) was added via cannula as a solution in THF (5 mL plus 5 mL wash). The mixture was allowed to warm to r.t. before being diluted in EtOAc (150 mL) and washed with sat. aq NH_4Cl (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:9, 1:4, 1:3) afforded alkynyl alcohol **36**. Although THP diasteriomers were expected only a single set of ^{13}C NMR signals was observed.

Yield: 1.137 (79%); colorless oil; R_f 0.45 (EtOAc–hexanes, 1:3).

IR (neat): 3455, 3071, 2931, 2246, 1740, 1428, 1113, 871, 740, 703 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.72–7.66 (m, 4 H), 7.50–7.37 (m, 6 H), 4.79 (t, 1 H, *J* = 3.3 Hz), 4.34–4.14 (m, 2 H), 3.77–3.66 (m, 6 H), 3.59–3.48 (m, 1 H), 2.57–2.51 (m, 2 H), 1.90–1.49 (m, 6 H), 1.10 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.7, 133.2, 130.0, 128.0, 97.1, 82.4, 78.4, 70.5, 66.6, 62.2, 54.8, 30.5, 27.0, 25.5, 23.9, 19.5, 19.3.

(*Z*)-(5*R*)-6-(*tert*-Butyldiphenylsilanyloxy)hex-2-ene-1,5-diol (37)

Tetrahydropyranyl ether **36** (0.813 g, 1.8 mmol) was dissolved in absolute EtOH (10 mL). PPTS (0.045 g, 0.2 mmol) was added and the reaction was heated to 50 °C. After 3 h the mixture was diluted in EtOAc (150 mL) and washed with H_2O (100 mL) and brine (100 mL). The aq washes were back extracted with EtOAc (50 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:2, 1:1, 2:1) afforded the alkynyl diol.

Yield: 0.672 g (>99%); colorless oil which solidified upon standing. The solid could be recrystallized from hexanes–Et_2O to provide a crystalline white solid; mp 79–82 °C (hexanes–Et_2O); R_f 0.14 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ –1.2 ($CHCl_3$, *c* 6.0).

IR (neat): 3382, 3071, 2931, 2858, 2246, 1472, 1428, 1391, 1113, 909, 824 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.69–7.64 (m, 4 H), 7.48–7.35 (m, 6 H), 4.19 (s, 2 H), 3.90–3.83 (m, 1 H), 3.71 (dq, 2 H, *J* = 12.7, 4.2), 2.56 (br, 1 H), 2.49 (dt, 2 H, *J* = 6.2, 2.2 Hz), 1.60 (br, 1 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 133.2, 130.1, 128.0, 82.4, 80.7, 70.5, 66.6, 51.5, 27.1, 23.7, 19.5.

HRMS [EI$^+$, (M – C_4H_9)$^+$]: *m*/*z* calcd for $C_{18}H_{19}O_3Si$: 311.1103; found: 311.1104.

Alkynyl diol (10.716 g, 29.4 mmol) was dissolved in freshly distilled toluene (100 mL) under an N_2 atmosphere. Lindlar's catayst (0.956 g) was added and flask was flushed with H_2 and kept under 1 atm of H_2. After stirring for 3 h at r.t. the reaction mixture was filtered through a pad of Celite then concentrated in vacuo to cleanly afford alkenyl diol **37** with no apparent over-reduction.

Yield: 10.710 g (99%); colorless oil; R_f 0.47 (EtOAc–hexanes, 1:1); $[\alpha]_D^{20}$ +8.6 ($CHCl_3$, *c* 3.7).

IR (neat): 3356, 3071, 2931, 1739, 1472, 1428, 1243, 1113, 824, 740, 702 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69–7.63 (m, 4 H), 7.49–7.36 (m, 6 H), 5.91–6.80 (m, 1 H), 5.65–5.54 (m, 1 H), 4.17 (A of an ABX, 1 H, *J* = 12.4, 7.6 Hz), 4.04 (B of an ABX, 1 H, *J* = 12.4, 6.6 Hz), 3.81–3.71 (m, 1 H), 3.65 (A of an ABX, 1 H, *J* = 10.1, 3.9 Hz), 3.56 (B of an ABX, 1 H, *J* = 10.1, 7.6 Hz), 2.88 (br, 1 H), 2.51 (b, 1 H), 2.37–2.14 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5, 133.0, 131.4, 129.9, 128.6, 127.8, 70.8, 67.5, 57.6, 30.6, 26.8, 19.2.

HRMS [EI$^+$, (M – C_4H_9)$^+$]: *m*/*z* calcd for $C_{18}H_{21}O_3Si$: 313.1260; found: 313.1254.

(6*R*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-2-isopropoxy-5,6-dihydro-2*H*-pyran (38)

The (*Z*)-alkenyl diol **37** (4.97 g, 13.5 mmol) was dissolved in freshly distilled CH_2Cl_2 (150 mL). Manganese(IV) oxide (11.73 g, 134.9 mmol) was added and the heterogeneous mixture was stirred at r.t. for 13 h. The mixture was then filtered through Celite and concentrated. The residue was subjected to flash chromatography (EtOAc–hexanes; 1:4, 1:3, 1:2, 1:1) to afford the lactol as well as starting diol **37** (1.630 g, 33%) and isomerized (*E*)-enal (0.168 g, 3%), each as a viscous oils.

Yield: 2.474 g (50%); R_f 0.43 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +36.5 ($CHCl_3$, *c* 1.9).

IR (neat): 3408, 3061, 2930, 1428, 1184, 1113, 1005, 708 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71–7.63 (m, 4 H), 7.45–7.32 (m, 6 H), 6.06–6.00 (m, 1 H), 5.77 (dq, 1 H, *J* = 4.2, 1.7 Hz), 5.39–5.36 (m, 1 H), 4.16–4.09 (m, 1 H), 3.79 (A of an ABX, 1 H, *J* = 10.4, 5.3 Hz), 3.66 (B of an ABX, 1 H, *J* = 10.4, 5.3 Hz), 3.01 (d, 1 H, *J* = 4.9 Hz), 2.11–1.97 (m, 3 H), 1.06 (d, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 133.7, 129.8, 128.8, 127.8, 126.3, 89.2, 67.3, 66.8, 27.2, 27.0, 19.4.

HRMS [EI$^+$, (M – C_4H_9)$^+$]: *m*/*z* calcd for $C_{18}H_{19}O_3Si$: 311.1103; found: 311.1099.

The lactol (0.235, 0.6 mmol) was dissolved in 2-propanol and PPTS (0.008 g, 0.03 mmol) was added. The mixture was stirred at r.t. for 0.75 h before being diluted in Et_2O (100 mL) and washed with H_2O (75 mL) and brine (75 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:9, 1:4, 1:3) afforded *i*-Pr-lactol **38**. Spectra and properties matched those described in the literature.[9]

Yield: 0.243 g (95%); colorless oil.

(*R*)-2-Methyl-1,4-butandiol (39)

In an oven dried flask under an N_2 atmosphere, (*R*)-(+)-α-methylsuccinic acid (2.45 g, 18.5 mmol) was dissolved in freshly distilled THF (60 mL). The solution was chilled to 0 °C and $LiAlH_4$ (2.11 g, 55.6 mmol) was added portionwise over 1.5 h. After the addition was complete the heterogeneous mixture was allowed to warm to r.t. and stirred for 10 h. Sodium potassium tartrate (31.4 g, 111.3 mmol) was added followed by the cautious addition of H_2O (5 mL). The mixture stirred at r.t. for 17.5 h before being filtered through a pad of Celite washing with copious amounts of THF. The filtrate was concentrated under reduced pressure and the crude material was purified by flash chromatography (EtOAc) to afford diol **39**.

Yield: 1.68 g (87%); colorless oil; R_f 0.37 (EtOAc); $[\alpha]_D^{20}$ +24.5 (*c* 2.2, $CHCl_3$).

IR (neat): 3300, 2953, 2876, 1462, 1451, 1431, 1384, 1062, 1037, 1006 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.81–3.60 (m, 2 H), 3.56 (A of an ABX, 1 H, *J* = 10.6, 4.6 Hz), 3.41 (B of an ABX, 1 H, *J* = 10.6, 7.2 Hz), 3.19 (br, 2 H), 1.91–1.70 (m, 1 H), 1.63–1.53 (m, 2 H), 0.92 (d, 3 H, *J* = 6.8 Hz)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.1, 60.9, 37.6, 34.2, 17.4.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_5H_{13}O_2$: 105.0916; found: 105.0910.

(*R*)-4-(*tert*-Butyldiphenylsilanyloxy)-2-methylbutan-1-ol (40)

In an oven dried flask under an N_2 atmosphere, diol **39** (0.518 g, 5.0 mmol) and *tert*-butylchlorodiphenylsilane (1.36 mL, 5.2 mmol) were combined in anhyd DMF (20 mL). The solution was cooled to –50 °C before DBU (1.12 mL, 7.5 mmol) was added dropwise. Stirring was continued at –50 °C for 25 min before the solution was diluted in EtOAc (150 mL) and washed with sat. aq solutions of NH_4Cl (100 mL), $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:19, 1:9, 1:4) afforded alcohol **40** along with bis-silated material (0.413 g, 14%; R_f 0.81, EtOAc–hexanes, 1:4) and mixed mono-silated material (0.101 g, 6%; unwanted; R_f 0.27, EtOAc–hexanes, 1:4) as a 2:1 mixture favoring unwanted isomer material by NMR.

Yield: 1.038 g (61%); $[\alpha]_D^{20}$ +6.6 (*c* 1.9, $CHCl_3$), identical to material synthesized by the literature route.[9]

(*E*)-(4*R*,5*R*,6*R*,7*S*,8*S*)-1-Tributylphosphonium-2,4,6,8-tetramethyl-7-(triisopropylsilanyloxy)-5-(trimethylsilanyloxy)dec-2-ene Bromide (48)

Alcohol **52** (0.0204 g, 0.04 mmol) was combined with 2,6-lutidine (0.008 mL, 0.07 mmol) in freshly distilled CH_2Cl_2 (0.5 mL) under an inert atmosphere. The solution was cooled to –78 °C and trimethylsilyl trifluoromethanesulfonate (0.009 mL, 0.05 mmol) was added. After 10 min, the reaction was quenched with 2-propanol before being allowed to warm to r.t. and concentrated under a stream of N_2. The residue was filtered through a pipette column of SiO_2 (hexanes).

Yield of the silyl ether: 0.0223 g (95%); colorless oil; R_f 0.95 (EtOAc–hexanes, 1:19); $[\alpha]_D^{20}$ –16.3 (*c* 1.2, $CHCl_3$).

IR (neat): 2960, 2870, 1461, 1453, 1383, 1251, 1212, 1093, 1037, 883, 842, 731 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.70 (d, 1 H, *J* = 9.5 Hz), 3.96 (s, 2 H), 3.93 (t, 1 H, *J* = 4.0 Hz), 3.62 (dd, 1 H, *J* = 9.0, 1.8 Hz), 2.61–2.53 (m, 1 H), 1.83–1.76 (m, 1 H), 1.75 (d, 3 H, *J* = 1.3 Hz), 1.71–1.61 (m, 1 H), 1.52–1.43 (m, 1 H), 1.16–1.09 (m, 1 H), 1.08–1.00 (m, 21 H), 0.97 (d, 3 H, *J* = 7.0 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 0.87 (t, 3 H, *J* = 7.5 Hz), 0.82 (d, 3 H, *J* = 7.3 Hz), 0.14 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.0, 131.1, 79.1, 76.6, 45.3, 42.2, 38.5, 36.0, 25.6, 18.8, 18.6, 17.5, 15.0, 13.3, 12.6, 11.4, 1.3.

HRMS [EI$^+$, (M – Me)$^+$]: *m*/*z* calcd for $C_{25}H_{52}O_2Si_2Br$: 519.2689; found: 519.2704.

The allylic bromide (0.0416 g, 0.1 mmol) was dissolved in freshly distilled CH_2Cl_2 (1.5 mL) under an N_2 atmosphere. Tributylphosphine (0.047 mL, 0.2 mmol, Strem) was added and the solution was stirred for 2.5 h at 20 °C. Solvent and excess phosphine were re-

moved in vacuo and the phosphonium salt **48** was utilized without further purification or characterization.

(*E*)-(4*R*,5*R*,6*R*,7*R*,8*S*)-1-Tributylphosphonium-2,4,6,8-tetramethyl-7-(*tert*-butyldimethylsilanyloxy)-5-(trimethylsilanyloxy)-dec-2-ene Bromide (49)

Alcohol **53** (0.0237 g, 0.1 mmol) was combined with Et_3N (0.020 mL, 0.1 mmol) in freshly distilled CH_2Cl_2 (1 mL) under an inert atmosphere. The solution was cooled to –78 °C and trimethylsilyl trifluoromethanesulfonate (0.013 mL, 0.1 mmol) was added. After 10 min, the mixture was diluted in Et_2O (20 mL) and washed with sat. aq solutions of NH_4Cl (10 mL), $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered then concentrated. Purification by flash chromatography (hexanes; EtOAc–hexanes, 1:19) afforded the trimethylsilyl ether as well as alcohol **53** (0.0053 g, 22%).

Yield: 0.0195g (70%); colorless oil; R_f 0.82 (EtOAc–hexanes, 1:19); $[\alpha]_D^{20}$ –6.1 (*c* 1.8, $CHCl_3$).

IR (neat): 2958, 2865, 1462, 1380, 1251, 1209, 1091, 1060, 1036, 963, 882, 841, 774 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.73 (d, 1 H, *J* = 9.7 Hz), 4.01 (A of an AB, 1 H, *J* = 9.3 Hz), 3.98 (B of an AB, 1 H, *J* = 9.3 Hz), 3.61 (t, 1 H, *J* = 3.8 Hz), 3.50 (dd, 1 H, *J* = 7.7, 2.2 Hz), 2.52–2.44 (m, 1 H), 1.76 (d, 3 H, *J* = 1.3 Hz), 1.66–1.58 (m, 1 H) 1.53 (m, 1 H), 1.39–1.32 (m, 1 H), 1.15–1.04 (m, 1 H), 0.95 (d, 3 H, *J* = 7.0 Hz), 0.90 (s, 9 H), 0.88 (t, 3 H, *J* = 7.3 Hz), 0.83 (d, 3 H, *J* = 6.8 Hz), 0.75 (d, 3 H, *J* = 7.1 Hz), 0.15 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.4, 130.6, 79.4, 76.4, 42.5, 41.8, 41.5, 35.6, 29.9, 26.4, 19.0, 18.8, 15.0, 13.8, 12.7, 12.5, 1.3, –3.1, –3.4.

HRMS [EI^+, $(M - C_4H_9)^+$]: *m*/*z* calcd for $C_{29}H_{40}O_2Si_2Br$: 435.1750; found: 435.1741.

The allylic bromide (0.0207 g, 0.04 mmol) was dissolved in freshly distilled MeCN (1.5 mL) under an N_2 atmosphere. Tributylphosphine (0.016 mL, 0.1 mmol, Strem) was added and the reaction was stirred at r.t. until the starting material was consumed (~1 h). The solution was concentrated in vacuo and the resulting phosphonium salt **49** was used in the subsequent coupling reaction without further purification or characterization.

(8*E*,10*E*,14*Z*,16*E*)-[3*S*,4*S*,5*R*,6*R*,7*R*,13*R*,17(2*R*),17(6*R*)]-15-Ethyl-17-(6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-3,5,7,9,13-pentamethyl-4-(triisopropylsilanyloxy)-6-(trimethylsilanyloxy)heptadeca-8,10,14,16-tetraene (50)

Phosphonium salt **48** (0.1 mmol) and aldehyde **3** (0.0248 g, 0.1 mmol, 1.1 equiv) were combined in freshly distilled toluene (1.5 mL). The solution was chilled to 0 °C and *t*-BuOK (1.0 M in THF; 0.078 mL, 0.1 mmol, 1 equiv) was added dropwise. The mixture was stirred 5 min at 0 °C before being diluted in Et_2O (20 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexanes; Et_2O–hexanes, 1:19) afforded coupled material **50**.

Yield: 0.0560 g (99%); colorless oil; R_f 0.49 (EtOAc–hexanes, 1:19); $[\alpha]_D^{20}$ +38.4 (*c* 2.1, $CHCl_3$).

IR (neat): 2964, 2870, 1462, 1453, 1381, 1251, 1180, 1101, 1055, 1033, 1002, 968, 883, 831 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.59 (d, 1 H, *J* = 15.9 Hz), 6.07–5.98 (m, 2 H), 5.77–5.69 (m, 2 H), 5.49–5.41 (m, 2 H), 5.19 (d, 1 H, *J* = 9.3 Hz), 5.13 (s, 1 H), 4.54–4.48 (m, 1 H), 4.03 (sept, 1 H, *J* = 6.2 Hz), 3.95 (t, 1 H, *J* = 3.8 Hz), 3.59 (dd, 1 H, J = 9.0, 2.0 Hz), 2.71–2.60 (m, 2 H), 2.20 (q, 2 H, *J* = 7.5 Hz), 2.15–1.97 (m, 4 H), 1.86–1.78 (m, 1 H), 1.72–1.64 (m, 1 H), 1.70 (s, 3 H), 1.52–1.45 (m, 1 H), 1.26 (d, 3 H, *J* = 6.2 Hz), 1.18 (d, 3 H, *J* = 6.0 Hz), 1.14–1.08 (m, 1 H), 1.06–1.00 (m, 21 H), 0.99 (d, 3 H, *J* = 7.1 Hz), 0.96 (d, 3 H, *J* = 7.0 Hz), 0.95 (d, 3 H, *J* = 7.0 Hz), 0.86 (t, 3 H, *J* = 7.3 Hz), 0.84 (t, 3 H, *J* = 7.3 Hz), 0.13 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 135.95, 135.92, 132.8, 132.3, 128.8, 128.7, 127.6, 126.4, 125.2, 93.5, 79.7, 76.5, 69.9, 67.4, 45.3, 41.2, 38.4, 36.0, 32.3, 31.1, 26.6, 25.6, 24.1, 22.4, 20.7, 19.2, 18.6, 18.5, 17.5, 13.7, 13.3, 12.9, 12.6, 11.5, 1.4.

HRMS (EI^+, M^+): *m*/*z* calcd for $C_{44}H_{82}O_4Si_2$: 730.5752; found: 730.5764.

(8*E*,10*E*,14*Z*,16*E*)-[3*S*,4*R*,5*R*,6*R*,7*R*,13*R*,17(2*R*),17(6*R*)]-4-(*tert*-Butyldimethylsilanyloxy)-15-ethyl-17-(6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-3,5,7,9,13-pentamethyl-6-(trimethylsilanyloxy)-heptadeca-8,10,14,16-tetraene (51)

Phosphonium salt **49** (0.04 mmol) and aldehyde **3** (0.013 g, 0.04 mmol) were combined in freshly distilled toluene (1 mL). The solution was chilled to 0 °C and *t*-BuOK (1.0 M in THF; 0.042 mL, 0.04 mmol) was added dropwise. The mixture was stirred 5 min at 0 °C before being diluted in Et_2O (20 mL). The organic phase was washed with H_2O (10 mL) and brine (10 mL) before being dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexanes; Et_2O–hexanes, 1:19) afforded coupled material **51**.

Yield: 0.0271 g (94%); colorless oil; R_f 0.41 (EtOAc–hexanes, 1:19); $[\alpha]_D^{20}$ +53.9 (*c* 2.3, $CHCl_3$).

IR (neat): 2960, 2926, 2878, 1462, 1451, 1381, 1316, 1252, 1182, 1101, 1057, 1031, 1003, 966, 841, 773 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.59 (d, 1 H, *J* = 15.9 Hz), 6.08–5.99 (m, 2 H), 5.76–5.70 (m, 2 H), 5.51–5.42 (m, 2 H), 5.19 (d, 1 H, *J* = 9.5 Hz), 5.13 (s, 1 H), 4.53–4.48 (m, 1 H), 4.02 (sept, 1 H, *J* = 6.2 Hz), 3.66 (t, 1 H, *J* = 3.5 Hz), 3.48 (dd, 1 H, *J* = 7.7, 2.2 Hz), 2.81–2.73 (m, 1 H), 2.71–2.55 (m, 2 H), 2.44–2.34 (m, 1 H), 2.23–2.16 (m, 2 H), 2.15–2.00 (m, 4 H), 1.70 (s, 3 H), 1.68–1.60 (m, 1 H), 1.42–1.34 (m, 1 H), 1.25 (d, 3 H, *J* = 6.2 Hz), 1.18 (d, 3 H, *J* = 6.2 Hz), 1.08–1.00 (m,1 H), 1.05 (t, 3 H, *J* = 7.5 Hz), 1.00–0.93 (m, 6 H), 0.89 (s, 9 H), 0.87 (t, 3 H, *J* = 7.3 Hz), 0.82 (d, 3 H, *J* = 6.8 Hz), 0.74 (d, 3 H, *J* = 7.0 Hz), 0.14 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.9, 136.0, 135.9, 132.43, 132.37, 128.7, 128.6, 127.6, 126.4, 125.0, 93.5, 80.1, 76.2, 69.8, 67.3, 41.8, 41.5, 41.1, 35.4, 32.3, 31.1, 26.6, 26.4, 24.6, 24.4, 24.1, 22.4, 20.8, 19.6, 18.8, 13.8, 13.7, 12.8, 12.6, 1.4, –3.1, –3.5.

(8*E*,10*E*,14*Z*,16*E*)-[3*S*,4*S*,5*R*,6*R*,7*R*,13*R*,17(2*R*)]-15-Ethyl-17-(6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)-3,5,7,9,13-pentamethyl-4-(triisopropylsilanyloxy)heptadeca-8,10,14,16-tetraen-6-ol (54)

Silyl ether/*i*-Pr-lactol **50** (0.0088 g, 0.01 mmol) was dissolved in THF (0.5 mL). H_2O (0.2 mL) was added followed by glacial HOAc (0.2 mL) and the solution was stirred at r.t. for 24 h. The reaction was quenched by pouring into sat. aq $NaHCO_3$ (15 mL). The aq phase was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Et_2O–hexanes; 1:19, 1:9, 1:4) afforded lactol **54** as well as (*E*)-enal **56** (0.0005 g, 7%). Yield: 0.0047 g (63%); colorless oil; R_f 0.50 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +63.0 (*c* 0.86, $CHCl_3$).

IR (neat): 3418, 2960, 2872, 1462, 1453, 1384, 1256, 1182, 1094, 1056, 993, 969, 939, 885 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.63 (d, 1 H, *J* = 15.9 Hz), 6.13–5.98 (m, 2 H), 5.86–5.81 (m, 1 H), 5.74 (dd, 1 H, *J* = 15.9, 6.6 Hz), 5.58 (d, 1 H, *J* = 9.7 Hz), 5.53–5.43 (m, 2 H), 5.19 (d, 1 H, *J* = 9.7 Hz), 4.59–4.53 (m, 1 H), 3.85 (t, 1 H, *J* = 3.8 Hz), 3.68 (s, 1 H), 3.55 (d, 1 H, *J* = 9.9 Hz), 2.99 (d, 1 H, *J* = 4.8 Hz), 2.75–2.61 (m, 2 H), 2.19 (q, 2 H, *J* = 7.5 Hz), 2.14–2.01 (m, 4 H), 1.70 (s, 3 H), 1.66–

1.58 (m, 1 H), 1.45–1.35 (m, 2 H), 1.13–1.08 (m, 22 H), 1.07 (d, 3 H, *J* = 7.0 Hz), 1.05 (t, 3 H, *J* = 7.3 Hz), 0.98 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 0.92 (t, 3 H, *J* = 7.1 Hz), 0.79 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 136.3, 135.8, 133.5, 131.2, 129.0, 128.4, 128.0, 126.4, 125.3, 89.5, 82.2, 77.9, 67.9, 42.3, 41.0, 38.1, 35.0, 32.1, 31.1, 26.7, 26.1, 21.1, 18.8, 18.5, 18.4, 17.4, 14.1, 13.8, 13.1, 12.8, 12.7.

(8*E*,10*E*,14*Z*,16*E*)-[3*S*,4*R*,5*R*,6*R*,7*R*,13*R*,17(2*R*)]-4-(*tert*-Butyldimethylsilanyloxy)-15-ethyl-17-(6-hydroxy-3,6-dihydro-2*H*-pyran-2-yl)-3,5,7,9,13-pentamethylheptadeca-8,10,14,16-tetraen-6-ol (55)

Silyl ether/*i*-Pr-lactol **51** (0.0235 g, 0.03 mmol) was dissolved in THF (1 mL). H_2O (0.2 mL) and glacial HOAc (0.2 mL) were added and the solution was stirred at r.t. for 96 h. The reaction was quenched by pouring in sat. aq $NaHCO_3$ (25 mL). The aq phase was extracted with EtOAc (2 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (hexanes; EtOAc–hexanes; 1:19, 1:9, 1:4, 1:3) afforded lactol **55** as well as (*E*)-enal **57** (0.0057 g, 29%) both as colorless oils.

Yield: 0.0089 g (45%); R_f 0.49 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +66.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3480, 3405, 2959, 2919, 2872, 1465, 1377, 1255, 1185, 1094, 1060, 1030, 1003, 966 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.62 (d, 1 H, *J* = 15.9 Hz), 6.09–5.97 (m, 2 H), 5.84–5.79 (m, 1 H), 5.74 (dd, 1 H, *J* = 15.9, 6.6 Hz), 5.55–5.44 (m, 3 H), 5.20 (d, 1 H, *J* = 9.5 Hz), 4.59–4.53 (m, 1 H), 4.05 (b, 1 H), 3.70 (t, 1 H, *J* = 2.9 Hz), 3.62 (d, 1 H, *J* = 10.1 Hz), 2.83 (d, 1 H, *J* = 4.4 Hz), 2.73–2.62 (m, 1 H), 2.60–2.52 (m, 1 H), 2.20 (q, 2 H, *J* = 7.5 Hz), 2.15–2.02 (m, 4 H), 1.78–1.63 (m, 1 H), 1.72 (s, 3 H), 1.39–1.31 (m, 1 H), 1.24–1.17 (m, 1 H), 1.06 (d, 3 H, *J* = 7.1 Hz), 1.05 (t, 3 H, *J* = 6.8 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.92 (s, 9 H), 0.88 (t, 3 H, *J* = 7.5 Hz), 0.72 (d, 3 H, *J* =& nbsp;7.0 Hz), 0.10 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.7, 136.3, 135.8, 133.6, 131.3, 129.0, 128.4, 128.0, 126.4, 125.4, 89.5, 80.6, 78.0, 67.8, 41.6, 41.1, 36.3, 35.7, 32.3, 31.0, 29.9, 29.1, 26.6, 26.2, 21.0, 18.4, 15.6, 14.0, 13.8, 12.9, 12.3, –3.9, –4.5.

C19-*epi*-Callystatin A (2)

Lactol **54** (0.0017 g, 0.003 mmol) and manganese(IV) oxide (0.005 g, 0.1 mmol, 20 equiv) were combined in freshly distilled CH_2Cl_2 (0.5 mL). The mixture was stirred at r.t. for 13 h before being filtered through Celite and concentrated in vacuo to cleanly provide the lactone.

Yield: 0.0014 g (83%); colorless film; R_f 0.39 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +46.8 (*c* 0.4, $CHCl_3$).

IR (neat): 3507, 2960, 2865, 1737, 1728, 1462, 1382, 1243, 1148, 1114, 1055, 1020, 963, 882 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.89 (dt, 1 H, *J* = 9.7, 4.0 Hz), 6.64 (d, 1 H, *J* = 15.7 Hz), 6.10–6.03 (m, 2 H), 5.77 (dd, 1 H, *J* = 15.7, 6.8 Hz), 5.59 (d, 1 H, *J* = 10.1 Hz), 5.46 (dt, 1 H, *J* = 15.6, 7.9 Hz), 5.27 (d, 1 H, *J* = 9.7 Hz), 4.99 (q, 1 H, *J* = 7.3 Hz), 3.85 (t, 1 H, *J* = 4.2 Hz), 3.60 (s, 1 H), 3.55 (dd, 1 H, *J* = 9.9, 1.0 Hz), 2.70–2.60 (m, 2 H), 2.49–2.45 (m, 2 H), 2.49–2.45 (m, 2 H), 2.24–1.93 (m, 2 H), 2.08 (t, 2 H, *J* = 7.0 Hz), 1.70 (d, 3 H, *J* = 0.9 Hz), 1.65–1.58 (m, 1 H), 1.45–1.35 (m, 2 H), 1.14–1.10 (m, 1 H), 1.10 (s, 21 H), 1.09–1.03 (m, 6 H), 0.98 (d, 3 H, *J* = 6.6 Hz), 0.93 (d, 3 H, *J* = 6.8 Hz), 0.90 (t, 3 H, *J* = 7.0 Hz), 0.78 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 144.9, 137.8, 137.0, 135.3, 133.5, 131.4, 125.0, 124.9, 121.9, 82.1, 79.1, 77.8, 42.2, 41.0, 38.2, 35.0, 32.5, 30.3, 26.6, 26.1, 21.0, 18.8, 18.5, 18.4, 17.3, 14.1, 13.7, 13.1, 12.75, 12.67.

HRMS (EI$^+$, MH$^+$): *m*/*z* calcd for $C_{28}H_{67}O_3Si$: 615.4809; found: 615.4825.

The alcohol (0.0040 g, 0.006 mmol) was dissolved in freshly distilled CH_2Cl_2 (0.5 mL) and Dess–Martin periodinane (0.006 g, 0.01 mmol) was added. The heterogeneous mixture was stirred at r.t. for 45 min. The reaction mixture loaded directly onto a flash column (EtOAc–hexanes; 1:19, 1:9) to afford C19-*epi*-C19-triisopropylsilyl callystatin A.

Colorless film: R_f 0.30 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –4.3 (*c* 0.7, $CHCl_3$).

IR (neat) 2964, 2865, 1737, 1727, 1712, 1698, 1462, 1453, 1382, 1242, 1058, 1017, 996, 966, 885 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.90 (dt, 1 H, *J* = 9.9, 4.4 Hz), 6.64 (d, 1 H, *J* = 15.9 Hz), 6.07 (dt, 1 H, *J* = 9.9, 1.6 Hz), 6.02 (d, 1 H, *J* = 15.6 Hz), 5.77 (dd, 1 H, *J* = 15.7, 6.8 Hz), 5.53 (dt, 1 H, *J* = 15.6, 7.5 Hz), 5.40 (d, 1 H, *J* = 9.5 Hz), 5.26 (d, 1 H, *J* = 9.7 Hz), 4.99 (q, 1 H, *J* = 7.3 Hz), 4.10 (dd, 1 H, *J* = 6.0, 3.8 Hz), 3.65 (dq, 1 H, *J* = 9.7, 7.0 Hz), 2.91 (quintet-like, 1 H, *J* = 7.0 Hz), 2.70–2.62 (m, 1 H), 2.49–2.45 (m, 2 H), 2.22–2.14 (m, 2 H), 2.11–2.03 (m, 2 H), 1.76 (d, 3 H, *J* = 1.1 Hz), 1.61–1.49 (m, 2 H), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.11–1.02 (m, 28 H), 0.96 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 7.0 Hz), 0.86 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.8, 164.2, 144.8, 137.6, 136.1, 135.3, 134.6, 129.9, 129.8, 126.7, 125.0, 121.9, 79.0, 77.6, 49.9, 45.3, 41.1, 40.7, 32.4, 30.3, 26.6, 26.4, 20.9, 18.6, 18.5, 17.6, 15.2, 13.7, 13.4, 13.1, 12.9, 12.8.

In a plastic vial, C19-*epi*-C19-triisopropylsilyl callystatin A was dissolved in freshly distilled THF (0.2 mL) and pyridine (0.2 mL). The solution was chilled to 0 °C and HF·pyridine (70:30; 0.1 mL, Aldrich) was added dropwise. The solution was immediately allowed to warm to r.t. and was stirred for 85 h. The reaction was quenched by pouring into sat. aq $NaHCO_3$ (10 mL). The aq phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc–hexanes; 1:4, 1:3) afforded C19-*epi*-callystatin A (**2**).

Yield: 0.0024 g (81%, 2 steps); colorless oil; R_f 0.20 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ –90.8 (*c* 0.2, $CHCl_3$).

IR (neat): 3500, 2966, 2925, 2865, 1728, 1714, 1465, 1454, 1384, 1243, 1131, 1057, 1017, 963 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.90 (dt, 1 H, *J* = 9.9, 4.0 Hz), 6.63 (d, 1 H, *J* = 15.7 Hz), 6.06 (dt, 1 H, *J* = 9.9, 1.8 Hz), 6.03 (d, 1 H, *J* = 15.8 Hz), 5.76 (dd, 1 H, *J* = 15.4, 7.0 Hz), 5.58 (dt, 1 H, *J* = 15.4, 7.3 Hz), 5.25 (d, 1 H, *J* = 9.9 Hz), 5.16 (d, 1 H, *J* = 10.1 Hz), 4.98 (q, 1 H, *J* = 7.3 Hz), 3.65 (dq, 1 H, *J* = 10.1, 6.6 Hz), 3.32–3.27 (m, 1 H), 2.94–2.86 (m, 2 H), 2.66 (dq, 1 H, *J* = 9.5, 6.8Hz), 2.49–2.45 (m, 2 H), 2.22–2.15 (m, 2 H), 2.08 (t, 2 H, *J* = 7.0 Hz), 1.81 (d, 3 H, *J* = 1.3 Hz), 1.66–1.58 (m, 1 H), 1.46–1.35 (m, 1 H), 1.20 (d, 3 H, *J* = 7.3 Hz), 1.14 (d, 3 H, *J* = 6.6 Hz), 1.05 (t, 3 H, *J* = 7.3 Hz), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.87 (t, 3 H, *J* = 7.3 Hz), 0.80 (d, 3 H, *J* = 6.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.7, 164.3, 144.9, 137.4, 136.4, 135.7, 135.5, 130.2, 128.7, 127.8, 125.0, 121.9, 79.1, 79.0, 46.1, 45.9, 41.0, 38.3, 32.4, 30.3, 26.6, 24.1, 21.0, 16.5, 16.1, 15.7, 13.7, 13.3, 11.5.

HRMS (EI$^+$, M$^+$): *m*/*z* calcd for $C_{29}H_{45}O_4$: 457.3318; found: 457.3323.

Callystatin A (1)

Lactol **57** (0.0039 g, 0.007 mmol) was dissolved in freshly distilled CH_2Cl_2 (1 mL). Manganese(IV) oxide (0.012 g, 0.1 mmol) was add-

ed and the mixture was stirred at r.t. for 19 h. The mixture was filtered through Celite and concentrated in vacuo to afford lactone **126**.

Yield: 0.0028 g (72%); colorless film; R_f 0.39 (EtOAc–hexanes, 1:3); $[\alpha]_D^{20}$ +52.5 (*c* 0.3, $CHCl_3$).

IR (neat): 3493, 2960, 1725, 1465, 1381, 1252, 1057, 1021, 966 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 6.89 (dt, 1 H, *J* = 9.9, 4.0 Hz), 6.65 (d, 1 H, *J* = 15.9 Hz), 6.08–5.98 (m, 2 H), 5.76 (dd, 1 H, *J* = 15.7, 6.8 Hz), 5.55 (d, 1 H, *J* = 10.1 Hz), 5.46 (dt, 1 H, *J* = 15.6, 7.7 Hz), 5.27 (d, 1 H, *J* = 9.5 Hz), 4.99 (q, 1 H, *J* = 7.3 Hz), 4.10 (br, 1 H), 3.69 (t, 1 H, *J* = 1.0 Hz), 3.62 (d, 1 H, *J* = 9.9 Hz), 2.69–2.61 (m, 1 H), 2.60–2.52 (m, 1 H), 2.49–2.45 (m, 2 H), 2.19 (q, 1 H, J = 7.3 Hz), 2.18 (q, 1 H, *J* = 7.5 Hz), 2.08 (t, 2 H, *J* = 7.1 Hz), 1.78–1.73 (m, 1 H), 1.72 (s, 3 H), 1.63–1.54 (m, 1 H), 1.40–1.30 (m, 1 H), 1.28–1.15 (m, 1 H), 1.06 (d, 3 H, *J* = 7.0 Hz), 1.05 (t, 3 H, *J* = 7.0 Hz) 0.99 (d, 3 H, *J* = 7.1 Hz), 0.97 (d, 3 H, *J* = 7.0 Hz), 0.92 (s, 9 H), 0.88 (t, 3 H, *J* = 7.3 Hz), 0.71 (d, 3 H, *J* = 7.1 Hz), 0.10 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3, 144.9, 137.8, 137.0, 135.3, 133.5, 131.5, 130.1, 125.1, 124.9, 121.9, 80.7, 79.1, 78.0, 41.6, 41.1, 36.2, 35.7, 32.5, 30.3, 29.9, 29.2, 26.6, 26.2, 20.9, 18.4, 15.6, 14.1, 13.7, 12.9, 12.3, –3.9, –4.5.

HRMS [EI^+, $(M - C_4H_9)^+$]: *m*/*z* calcd for $C_{31}H_{51}O_4Si$: 515.3557; found: 515.3572.

The alcohol (0.0028 g, 0.005 mmol) was dissolved in freshly distilled CH_2Cl_2 (0.5 mL) and Dess–Martin periodinane (0.006 g, 0.01 mmol) was added. The mixture was stirred 30 min at r.t. before being loaded directly onto a flash column and eluted (hexanes; EtOAc–hexanes; 1:19, 1:9, 1:4) to provide C19-*tert*-butyldimethylsilyl callystatin A. Data collected is in agreement with that reported in the literature.[8–10]

Yield: 0.0023 g (82%); colorless oil.

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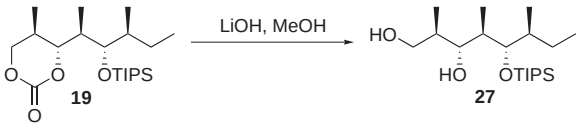
(36) We independently found the same solution to the olefination problem of intermediate **25/B** as was reported recently in the literature.[12a,35]

(37) Alternatively, diol **27** could also be prepared from intermediate **19** (Scheme 19).



Scheme 19

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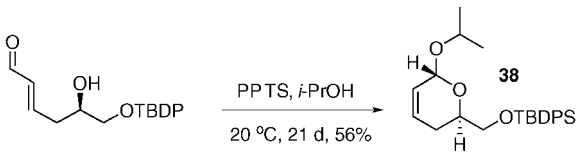
(44) (*E*)-Enal (Scheme 20) was consistently isolated from the MnO_2 allylic oxidation in approximately 4% yield. This material could be recycled by stirring in 2-propanol and PPTS, forming **38** in modest yield.



Scheme 20

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