Total Synthesis and Structural Elucidation of the Antifungal Agent Papulacandin D

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Condensation of the aryllithium reagents, prepared from the bromides **10** and **11** and *tert*-butyllithium, with lactone **19** and acid-catalyzed spirocyclization gave the papulacandin spiroketals **14** and **15**. Subsequent protection using di-*tert*-butylsilyl bis(trifluoromethanesulfonate) gave the diols **31** and **30**. Isoleucine (**37**) was converted using a double Wittig reaction sequence and propargylation of the intermediate aldehyde **46** into the alkynol **47**. Separation of the C-7 epimers of **47** was achieved using kinetic resolution *via* Sharpless epoxidation. Both alkynol epimers **53** and **57** were converted into the papulacandin side chain esters **65** and **66** using a hydrozirconation and palladium(0)-catalyzed coupling sequence. Comparisons of Mosher ester derivatives of **65** and **66** with the Mosher ester derivative of the natural papulacandin side chain and further degradation were consistent with the stereochemistry of the natural product being 7*S*,14*S*. Esterification of the spiroketals with the mixed anhydride **70** and global deprotection gave papulacandin D (**1**).

The papulacandins are a group of antifungal antibiotics extracted from the fermentation broth of the fungus *Papularia spherosperma*.[1] This family of compounds shows potent activity against fungi and yeasts such as *Candida albicans*, *Candida tropicalis*, and *Microsporum canis*[1] among others.[2−4] Such opportunistic fungal infections are responsible for increased morbidity and mortality among AIDS and other immunocompromised patients.[5] Recently a related compound, L-687,781,[6] has been shown to be effective in treating *Pneumocystis carinii*-induced pneumonia, a life threatening secondary fungal infection acquired by AIDS patients. The papulacandins antifungal activity stems from their ability to inhibit 1,3-β-D-glucan synthase, an enzyme crucial for the construction of fungal cell walls. Since eukaryotic systems do not utilize 1,3-β-D-glucans, the papulacandins are important lead compounds for the development of novel antifungal drugs.[2−4] Structurally papulacandin D (**1**) is a 1,7-dioxaspiro[5.4]decane derivative containing a glucose residue. The *O*-3′ hydroxyl of the glucose moiety is esterified with a branched C_{18} tetraunsaturated fatty acyl side chain. Neither the relative nor absolute configuration of the C-7″ hydroxyl nor the C-14″ methyl groups of the acyl side chain were established by the group at Ciba Geigy.[7] We have undertaken a total synthesis of papulacandin D (**1**) in order to resolve these stereochemical ambiguities and to provide general methodology for the synthesis of analogs.

Several methods for the elaboration of the tricyclic spiroketal nucleus of papulacandin D (**1**) have been reported. Danishefsky[8] prepared the racemic-spiroketal unit *via* a hetero-Diels−Alder reaction. Friesen[9−11] and Beau[12,13] have independently reported the palladium(0)-catalyzed coupling of (tributylstannyl)glucal derivatives with aryl bromides and subsequent oxidative spirocyclization as a key strategy. Schmidt[14] has reported the elaboration of the papulacandin tricycle via the homologation of 2,3,4,5,6-penta-*O*-benzyl-D-glucose. Finally, ourselves,[15−17] Bihovsky,[18] and Czernecki[19] have each independently reported a concise approach to the papulacandin D spirocycle. This methodology utilizes the condensation of an aryl anion with a suitably protected gluconolactone to yield, on acification, the 1,7-dioxaspiro-[5.4]decane unit of papulacandin D (**1**). Herein we report full experimental details for the structural elucidation and total synthesis of papulacandin D (**1**) previously reported in communication format.[16,17]

We considered that papulacandin D (**1**) should be obtained on the selective *O*-3′-esterification of the spiroketal **2** using the fatty acid **5**. In turn, spiroketal **2** should be easy to synthesise from the condensation of the gluconolactone derivative **3** and the aryl bromide **4**. We have utilized related carbanion-lactone condensation chemistry in other approaches to spiroketal arrays.[20−23] The fatty acid **5** should be available from isoleucine (**7**) *via* sequential Wittig olefination reactions, or equivalent

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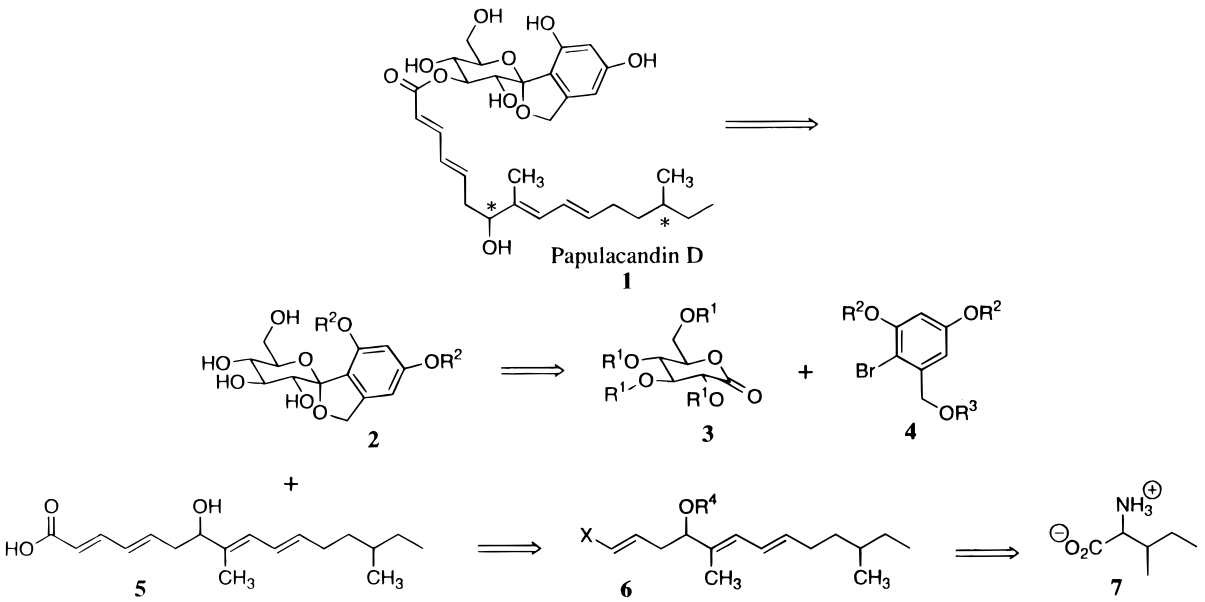
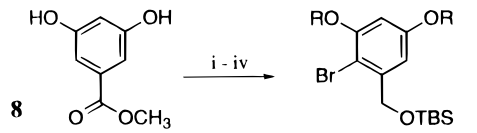
Chart 1



Scheme 1[a,b]

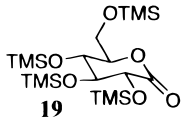


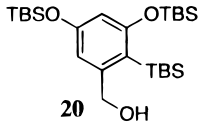
[a] Reagents and Conditions: (i) CH_3I, K_2CO_3, acetone *or* R_3SiCl, imidazole, DMAP, DMF; (ii) $LiAlH_4$, Et_2O; (iii) NBS, CCl_4; (iv) TBSCl, imidazole, DMAP. [b] In all structures TMS = Me_3Si, TES = Et_3Si, TBS = t-$BuMe_2Si$, TIPS = i-Pr_3Si.

homologation processes, the intermediacy of the triene **6** and organopalladium-catalyzed coupling with a β-stannylacrylate ester (X = Br or I, etc.) or β-bromoacrylate ester (X = $SnMe_3$ or $ZrCp_2Cl$, etc.). Such an approach has the advantage that the synthesis can be readily adapted to any of the four possible C-7″,C-14″ stereoisomers.

Synthesis of Papulacandin D Spiroketal Arrays

As a model study, methyl 3,5-dihydroxybenzoate (**8**) was protected as its dimethyl ether which, after reduction with lithium aluminum hydride and electrophilic bromination,[24] could be transformed to the desired benzylic silyl ether **9** (Scheme 1). Treatment of a solution of aryl bromide **9** in diethyl ether, with *tert*-butyllithium at −78 °C, followed by addition of the resultant solution to a precooled (−78 °C) solution of gluconolactone **19**[25] in diethyl ether, resulted in a nucleophilic addition. The intermediate, presumably **12**, was treated with an acidic ion-exchange resin which induced spirocyclization giving the tetraol **13**. Due to difficulties in isolation, the crude reaction mixture was treated with acetic anhydride and pyridine to produce the tetraacetate derivative **16** in 44% yield (Scheme 2). It is reasonable to assume that the spirocyclization reaction was reversible and therefore subject to thermodynamic control *via* the anomeric effect[26,27] thereby providing a single spirane stereoisomer, albeit in modest yield. In the light of this successful result, the synthesis was repeated with the tris(*tert*-butyldimethylsilyl)-protected aryl bromide **10**. *tert*-Butyldimethylsilylation of the diphenol **8** followed by reduction, electrophilic bromination, and further silyl protection gave the aryl bromide **10**. Again, lithium−bromine exchange of bromide **10** with *tert*-butyllithium at −78 °C followed by addition to the protected gluconolactone **19** and subsequent acidification produced the corresponding spiroketal. As before, this was conveniently isolated as its tetraacetate derivative **17** in 34% yield (Scheme 2). It was also observed that chilling (solid CO_2) the cannula used to transfer the aryllithium reagent to the lactone **19** improved the yield of the spiroketal **17** to 45%. If the aryllithium reagent was allowed to warm above −78 °C, a major byproduct was produced which has spectral properties (^1H NMR and MS) consistent with the silane **20**.





The tetraacetate **17** and all other spiroketals were shown to be the correct anomers by analysis of their ^1H NMR spectra. For example, $^1H-^1H$ coupling constants of the glucose ring in spiroketal **17** were particularly diagnostic. The key coupling constants ($J_{2,3}$ = 9.9, $J_{3,4}$ = 9.8, and, $J_{4,5}$ = 10.0 Hz) were consistent with a chair conformation ($J_{2-3} \sim J_{3-4} \sim J_{4-5} \sim$ 9.9 Hz). If spiroketal **17** was the opposite anomer, a distorted chair conformation would have resulted with different coupling constants ($J_{2-3} \sim$ 7.5 Hz, $J_{3-4} \sim$ 8.4 Hz, $J_{4-5} \sim$ 9.5 Hz).[12]

With a route to the spiroketal carbon skeleton in place, attention was turned to the problem of selective esteri-

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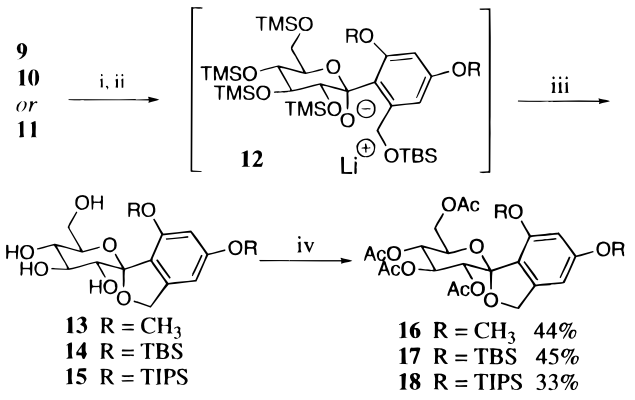
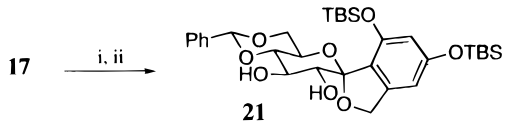
Scheme 2[a]



[a] Reagents and Conditions: (i) *tert*-BuLi, Et_2O, −78 °C; (ii) **19**, Et_2O, −78 °C; (iii) Amberlite IR-120 (Plus), MeOH; (iv) Ac_2O, pyridine.

Scheme 3[a]

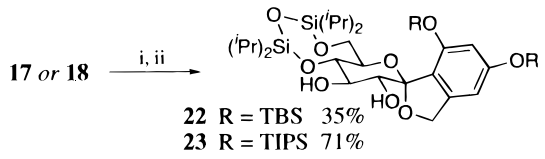


[a] Reagents and Conditions: (i) NaOMe, MeOH; Amberlite IR 120 (H^+); (ii) PhCHO, $ZnCl_2$, 0−95%.

fication of the C-3′ hydroxyl of the glucose moiety. Protection of the 4,6-diol as the benzylidene acetal and subsequent monoesterification seemed the obvious choice. Methanolysis of tetraacetate **17** gave the corresponding crude tetraol **14** which was directly condensed with benzaldehyde in the presence of zinc chloride to provide the benzylidene acetal **21** (Scheme 3)**.** Unfortunately, formation of the acetal **21** was capricious (0−95%) and proceeded with partial but variable desilylation. Attempts to convert the crude tetraol **14** into the corresponding acetals with anisaldehyde,[28] 2,4-dimethoxybenzaldehyde,[29] or 4-methoxyacetophenone[30] also proceeded in variable yet low yields. Saponification of the tetraacetate **17** gave the crude tetraol **14** which was directly condensed with 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane.[31,32] ^{1}H NMR spectroscopy of the crude reaction mixture was consistent with partial de-*tert*-butylsilylation, and chromatography gave a spiroketal tentatively assigned as the adduct **22** in only modest yield (50%). It is clear from these results that the Zemplen methanolysis step was the source of the trouble rather than acid-mediated de-*tert*-butylsilylation during acetal formation. In order to alleviate this problem, more robust phenol protection was examined.

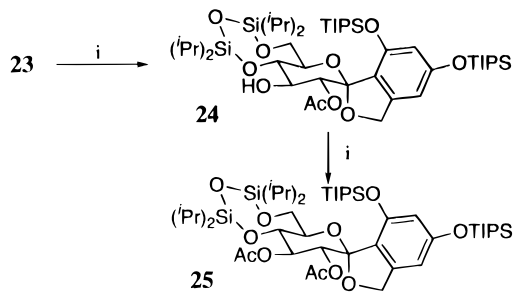
Methyl 3,5-dihydroxybenzoate (**8**) was protected as the bis(triisopropylsilyl) ether, reduced, brominated, and further protected as the *tert*-butyldimethylsilyl ether to yield **11**. Spirocyclization was carried out exactly as described previously (Scheme 2). Thus lithium−bromine exchange[33] of the aryl bromide **11** with *tert*-butyllithium at −78 °C, addition to the lactone **19**, and acidification

Scheme 4[a]



[a] Reagents and Conditions: (i) NaOMe, MeOH; (ii) $(^iPr_2)SiCl]_2O$, pyridine.

Scheme 5[a]



[a] Reagents and Conditions: (i) Ac_2O, pyridine, 94%.

gave the spiroketal tetraol **15**. Again, isolation proved easier after conversion of the crude tetraol **15** into the tetraacetate **18**. Again only the required anomer was isolated albeit in only modest yield (34%). Zemplen methanolysis and condensation of the tetraol **15** with 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane in pyridine gave the protected spiroketal **23** in 71% yield (Scheme 4). As proof of structure, acetylation of **23** with acetic anhydride in pyridine gave diacetate **25**. ^{1}H NMR analysis of **25** showed a large downfield shift of the C-2 and C-3 hydrogens indicating that the C-2,3 diol unit had indeed been esterified and therefore the 4,6-diol unit was indeed protected as the disiloxane unit depicted (Scheme 5). Upon dissolving diol **23** in pyridine and acetic anhydride, TLC showed the rapid formation of a monoacetate and this was slowly converted into the less polar diacetate **25**. Isolation of the intermediate confirmed its structure as the undesired *O*-2′ monoacetate **24**. In addition, reaction of the diol **23** with cinnamic acid, 2,4,6-trichlorobenzoyl chloride,[34] and triethylamine gave the *O*-2′ monocinnamate ester **28** and a minor monoester tentatively assigned as the *O*-3′ monocinnamate ester **27** (81%, 10:1) (Scheme 6). Clearly, monoesterification of diol **23** proceeded with the undesired regioselectivity. Silylation of diol **23** with triethylsilyl trifluoromethanesulfonate and pyridine gave only the *O*-2′ protected silyl ether **29** (84%, Scheme 7). Unfortunately, attempted cinnamoylation of **29** using cinnamoyl 2,4,6-trichlorobenzoyl mixed anhydride (**26**) was unsuccessful and only resulted in recovery of starting material. Presumably, the globally protected spiroketal alcohol **29** was just too hindered. The use of spiroketals **22** and **23** were abandoned, and alternative protection was investigated.

Zemplen methanolysis of tetraacetate **18** and condensation with di-*tert*-butylsilyl bis(trifluoromethanesulfonate)[35,36] and 2,6-lutidine gave spiroketal **30** (85%, Scheme 8). Reaction of diol **30** with acetic anhydride and

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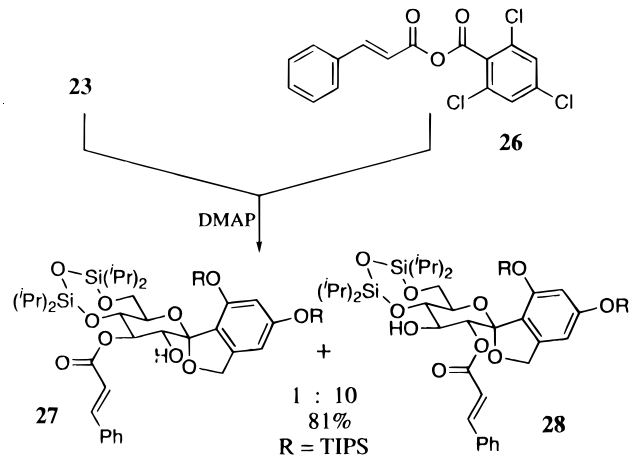
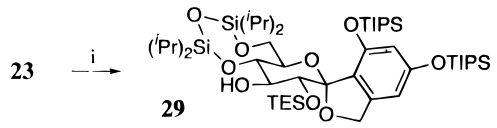
Scheme 6

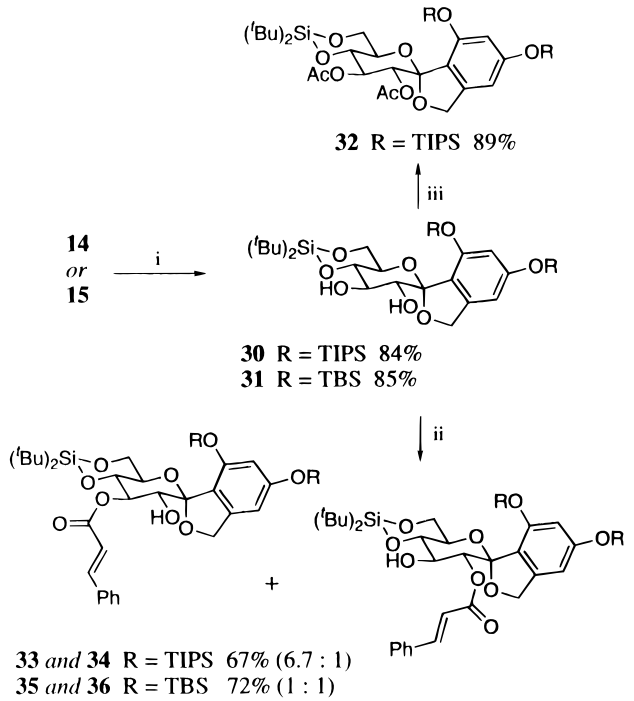


Scheme 7[a]



[a] Reagents and Conditions: (i) TESOTf, pyridine, −10 °C, 84%.

Scheme 8[a]

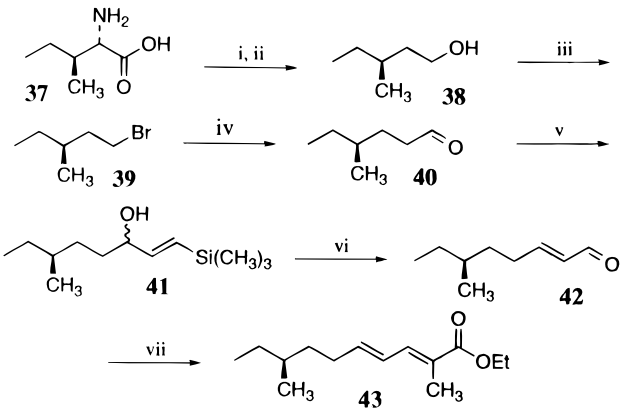


[a] Reagents and Conditions: (i) (*t*-Bu)$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) **26**, DMAP, DMF; (iii) Ac_2O, pyridine, 89%.

pyridine yielded the corresponding diacetate **32** with a spectroscopic signature that confirmed the constitution of **30**. Esterification of diol **30** with anhydride **26** proceeded smoothly in DMF at 25 °C to give both the *O*-3′ **33** and *O*-2′ **34** esters (67%, 6.7:1). Clearly, protection as the silylene-spiroketal **30**, and esterification resulted in formation of the correct papulacandin monoester.

At this point in time the *δ*-lactone to spiroketal condensation reaction was modified, and this allowed for the isolation of the spiroketal tetraols **14** and **15** directly without the need for tetraacetylation and subsequent Zemplen methanolysis. Clearly, this shortened this

Scheme 9[a]



[a] Reagents and Conditions: (i) $NaNO_2$, HCl, H_2O, 0 °C, 78 %; (ii) $LiAlH_4$, Et_2O, 80%; (iii) (a) TsCl, pyridine, (b) LiBr, acetone, 81%; (iv) (a) Mg, THF, (b) $Fe(CO)_5$, THF, AcOH; (v) *trans*-(Li)CH=CH(TMS), THF, −78 °C; (vi) (a) PhSCl, Et_3N, Et_2O, 0 °C, (b) $AgNO_3$, CH_3CN, H_2O, 62% (from bromide); (vii) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 85%, 92:8 (*E*:*Z*).

synthesis and also overcame the problems associated with partial de-*tert*-butylsilylation on Zemplen methanolysis of **17** to regenerate **14**. With this modification, the tetraol **14**, directly from the spirocyclization reaction, was allowed to react with di-*tert*-butylsilyl bis(trifluoromethanesulfonate)[35,36] and 2,6-lutidine to produce the spiroketal **31** (81%). In contrast to diol **30**, cinnamoylation of diol **31** proceeded with low regioselectivity and gave monoesters **35** and **36** (1:1). It is clear from these results that spiroketals **21**, **30**, and **31** should be suitable precusors for conversion into papulacandin D (**1**).

Synthesis and Stereochemical Assignment of the Papulacandin Side Chain

We initially sought to prepare the papulacandin D carboxylic acid with the 14*S*-stereochemistry since it is reasonable to speculate[37] that L-isoleucine is the biosynthetic precusor for this unit of the natural product. Therefore, L-isoleucine (**37**) was converted into the aldehyde **40** *via* the known (*S*)-methylpentanol (**38**),[38] toluene-4-sulfonylation, S_N2 displacement using lithium bromide, and carbonylation of the Grignard reagent derived from bromide **39** (Scheme 9). Subsequent addition of (*E*)-1-lithio-2-(trimethylsilyl)ethylene[39] gave the allylic alcohol **41** which was converted into the enal **42** on sequential reaction with phenylsulfenyl chloride and silver nitrate. This transformation, which involves an allyl sulfenate to allyl sulfoxide [2,3] sigmatropic rearrangement, silyl-Pummerer rearrangement, and silver nitrate-mediated hydrolysis, is modeled upon chemistry previously published by Parsons.[40] Aldehyde **42** was treated with (carbethoxyethylidene)triphenylphosphorane to yield the diene ester **43**. On a large scale, ester **43** was more conveniently prepared from alcohol **38** *via* reaction of the derived 4-toluenesulfonate with potassium cyanide followed by DIBAL-H reduction (Scheme 10). The resultant aldehyde **40** was homologated by reaction with (carbethoxymethylene)triphenylphosphorane yielding a readily separable mixture of isomeric esters **45** (*E*:*Z* = 98:2).

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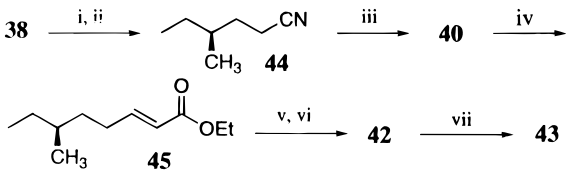
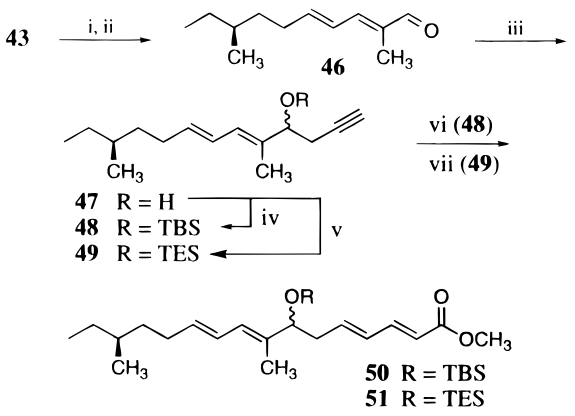
Scheme 10[a]



[a] Reagents and Conditions: (i) TsCl, pyridine; (ii) KCN, 18-crown-6, THF, 67 °C, 80% (two steps); (iii) DIBAL-H, Et_2O, −78 °C; (iv) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 85% (two steps), 98:2 (*E*:*Z*); (v) DIBAL-H, Et_2O, −78 °C, 95%; (vi) PCC, CH_2Cl_2, 80%; (vii) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 85%, 92:8 (*E*:*Z*).

Scheme 11[a]



[a] Reagents and Conditions: (i) DIBAL-H, Et_2O, −78 °C, 94%; (ii) MnO_2, CH_2Cl_2, 95%; (iii) Zn dust, propargyl bromide, THF, 0 °C, 95%; (iv) TBSCl, imidazole, DMAP, CH_2Cl_2, 85%; (v) TESCl, imidazole, DMAP, CH_2Cl_2, 95%; (vi) (a) $Cp_2Zr(H)Cl$, THF, (b) I_2, THF, (c) (*E*)-$Bu_3SnCH{=}CHCO_2Me$, $(CH_3CN)_2PdCl_2$, THF, 30%; (vii) $Cp_2Zr(H)Cl$, (*E*)-$BrCH{=}CHCO_2Me$, [$(Ph_3P)_2PdCl_2$, DIBAL-H], THF, 82%.

DIBAL-H reduction of the pure *trans*-unsaturated ester **45** to the corresponding allylic alcohol, followed by reoxidation to the aldehyde **42** and condensation with (carbethoxyethylidene)triphenylphosphorane gave the diene ester **43** which was chromatographically separated from trace amounts of the *Z*-isomer (∼8%).

Reduction of the diene ester **43** and reoxidation of the resultant allylic alcohol yielded the diene aldehyde **46** (Scheme 11). Addition of the diene aldehyde **46** to a mixture of activated zinc dust and propargyl bromide,[41] at reduced temperatures, gave the homopropargylic alcohol **47** as an inseparable mixture of C-4 diastereoisomers. In addition, this alkyne was contaminated with variable amounts (2−8%) of the isomeric allenyl alcohols. However, these allene contaminants were easily removed by chromatography following *tert*-butyldimethylsilylation[42] to produce silyl ether **48**. In the same way alkyne was converted into the triethylsilyl ether **49**. Although both **48** and **49** each consisted of two inseparable diastereoisomers, these were indistinguishable by normal spectroscopic techniques. Hydrozirconation[43,44] of alkyne **48** followed by iodine−metal exchange produced the corresponding unstable vinyl iodide. This was not purified but, after filtration through alumina, was directly coupled with methyl (3*E*)-(tributylstanyl)acrylate in the presence of bis(triphenylphosphine)palladium dichloride in DMF solution. The reaction mixture instantaneously turned black. Chromatography after 18 h at 25 °C gave the tetraene ester **50** in low and variable overall yield (<30%). In consequence of these failings, an alternative method was examined. The vinyl zirconocene, obtained from hydrozirconation of alkyne **49** was allowed to react with zinc chloride[45] to produce the corresponding vinyl zinc reagent. Without isolation this was treated with methyl (3*E*)-bromoacrylate[46] in the presence of tetrakis(triphenylphosphine)palladium to provide the diene ester **51** in superior yield (64%). In this reaction it was not clear whether the transmetalation reaction (Zr → Zn) was actually necessary, thus an attempt was made to couple the vinyl zirconocene intermediate directly. Hydrozirconation of alkyne **49** and direct coupling with methyl (3*E*)-bromoacrylate in the presence of the palladium(0) catalyst derived from bis(triphenylphosphine)palladium dichloride and DIBAL-H[47] gave the tetraene ester **51**. Much to our delight this was obtained in a superior 82% yield (Scheme 11).

It is clear from these results that alkyne hydrometalation and palladium(0)-catalyzed coupling is a secure strategy to assemble the delicate tetraene ester unit of the papulacandins. There remain, however, stereochemical ambiguities in structure that need to be resolved. In addition, the current synthesis gave rise to an inseparable mixture of C-7 epimers. We considered that the C-7 stereochemistry could be defined *via* asymmetric propynylation of aldehyde **46**. Unfortunately, condensation of the aldehyde **46** with chiral allenylborane reagents[48] were only marginally successful (<62% de). Since the actual stereochemistry of the papulacandin side chain needed to be elucidated, it was essential to obtain the tetraene esters **50**/**51** in very high diastereoisomeric purity. Therefore, with such modest selectivities, the use of chiral allenylborane reagents was abandoned.

Several derivatives of the alcohol **47** were prepared so as to allow the separation of the two diastereoisomers. Of the esters examined only the (*R*)-*O*-methylmandelates were amenable to chromatographic separation. Thus reaction of alcohol **47** with (*R*)-*O*-methylmandelic acid, pyridine, and trifluoromethanesulfonic anhydride[49] in the presence of 4-(*N*,*N*-dimethylamino)pyridine gave the diastereoisomeric esters **55** and **56** (30%). These derivatives were separated by chromatography in very modest yield. Unfortunately, the separation was not convenient for large scale use and, additionally, the esterification reaction proceeded with partial racemization of the (*R*)-*O*-methylmandelic acid.[50] In consequence, the diastereoisomeric enrichment of the C-4 epimers of alcohol **47** was incomplete (ds < 89%) and this method of epimer separation was abandoned.

As an alternative strategy, kinetic resolution under Sharpless epoxidation conditions[51−54] was examined.

(41) Friedrich, L. E.; de Vera, N.; Hamilton, M. *Synth. Commun.* **1980**, *10*, 637.
(42) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
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(48) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.
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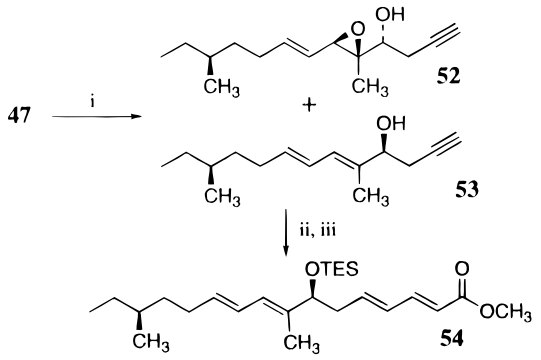
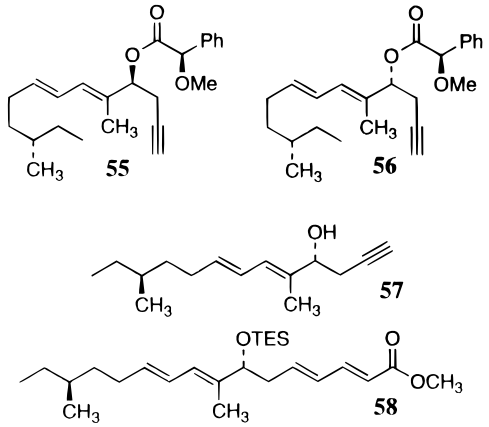
(50) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

Scheme 12[a]



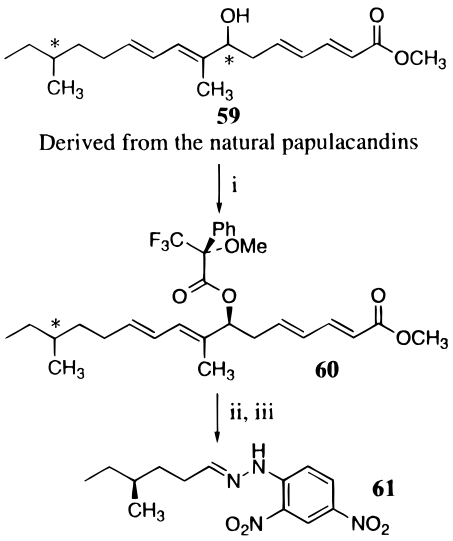
[a] Reagents and Conditions: (i) Ti(O-*i*-Pr)$_4$, D-(−)-DIPT, *t*-BuOOH, 4 Å mol sieves, CH_2Cl_2, −50 °C, 45% alcohol and 14% epoxide; (ii) TESCl, imidazole, DMAP, CH_2Cl_2, 94%; (iii) $Cp_2Zr(H)Cl$, [$(Ph_3P)_2PdCl_2$ + DIBAL-H], methyl 3-bromo-*E*-acrylate, THF, 70%.

Thus the allylic alcohol **47** was allowed to react with titanium tetraisopropoxide, D-(−)-diisopropyl tartrate, and *tert*-butyl hydroperoxide in dichloromethane at −50 °C for 3 days. This led to the recovery of alcohol **53** (45%, 90% of theory) along with of the corresponding epoxide **52** (14%, 28% of theory) (Scheme 12). The diastereoisomeric purity of the alcohol **53** was determined by conversion into the (*R*)-Mosher ester[55,56] and ^{1}H NMR and HPLC analysis. Both these analyses were consistent with alcohol **53** having a diastereoisomeric ratio of 96:4. Sharpless kinetic resolution using L-(+)-diisopropyl tartrate gave the corresponding epimeric alcohol **57**. Again Mosher ester analysis was consistent with a diastereoisomeric ratio of at least 96:4. Both alcohols **53** and **57** were separately converted into the corresponding tetraene esters **54** and **58** *via* triethylsilylation, hydrozirconation, and palladium(0)-catalyzed coupling with methyl (3*E*)-bromoacrylate.



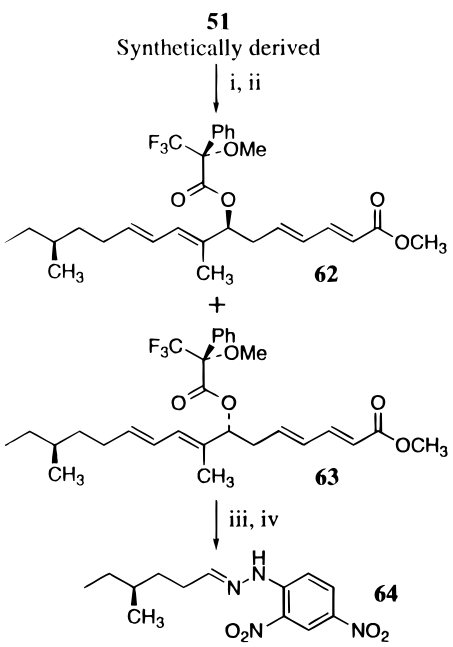
At this point we sought to establish the stereochemistry of papulacandin by correlation of the synthetic esters with the natural side chain obtained by degradation. Since we had only very limited access to authentic papulacandin D (**1**), we were obliged to obtain additional materials by reisolation. Fermentation of *P. spherosperma* and chromatography[7,57] gave a crude fraction containing several papulacandins. Without further separation, this was subject to saponification (LiOH) and methylation (CH_2N_2) to produce the authentic ester **59**.[1,7] This was converted into the (*R*)-Mosher ester **60** (Scheme 13). ^{1}H NMR and HPLC analyses showed this compound to consist of only one diastereoisomer.[55,56] In parallel, the synthetic tetraene esters **54** and **58** were converted into the corresponding (*R*)-Mosher esters **62** and **63** via tetrabutylammonium fluoride-mediated desilylation and esterification using (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride and DMAP (Scheme 14). ^{1}H NMR and HPLC analyses of each of these compounds was

Scheme 13[a]



[a] Reagents and Conditions: (i) *S*-(+)-PhC(OMe)(CF_3)COCl, DMAP, CH_2Cl_2, 93%; (ii) O_3, −78 °C, MeOH; Me_2S, −78 °C to 25 °C; (iii) (2,4-dinitrophenyl)hydrazine, H_2SO_4, 63% (both steps).

Scheme 14[a]



[a] Reagents and Conditions: (i) TBAF, THF, 0 °C, quant; (ii) *S*-(+)-PhC(OMe)(CF_3)COCl, DMAP, CH_2Cl_2, 89%; (iii) O_3, −78 °C, MeOH; Me_2S, −78 °C to 25 °C; (iv) (2,4-dinitrophenyl)hydrazine, H_2SO_4, 65% (both steps).

(51) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
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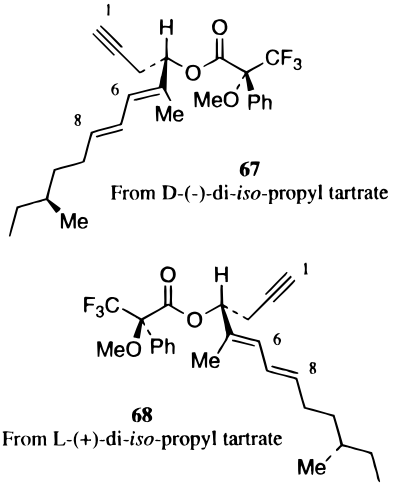


Figure 1.

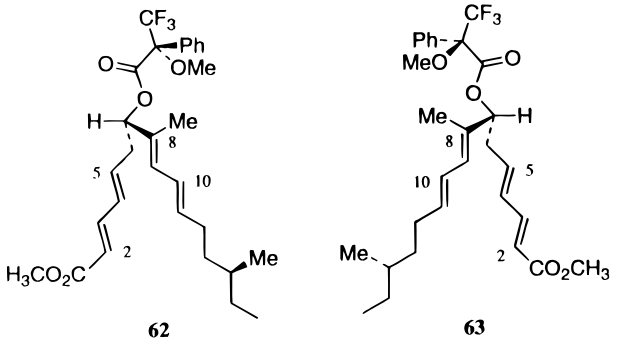
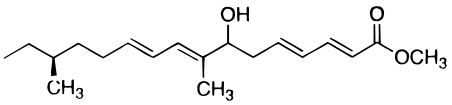


Figure 2.

consistent with high diastereoisomeric purity (>98%). In addition both compounds were very clearly distinguishable by NMR and base-line separable by HPLC. Finally, one of the diesters **62** was completely identical with the diester **60** derived from degradation of the natural papulacandins. On this basis it is reasonable to set the papulacandin side chain stereochemistry as 7*S*.

It is necessary at this point to comment on the assignment of stereochemistry of the synthetic diesters **62** and **63**; otherwise, the complete determination of configuration is a fragile house of cards. Kinetic resolution of **47** *via* Sharpless epoxidation using D-(−)-diisopropyl tartrate should proceed with selective epoxidation of the *R*-alcohol and selective recovery of the *S*-epimer **53**. Such an expectation is securely based upon the highly reliable Sharpless model and legions of examples.[51−54] In exactly the same way Sharpless kinetic resolution using L-(+)-diisopropyl tartrate should lead to recovery of the *R*-epimer **57**. Secondly, the C-7 stereochemical assignments of the two pairs of diesters **67** and **68**, and **62** and **63**, were confirmed by analysis of the ^{1}H NMR spectra according to the Mosher model.[55,56] In this analysis Mosher esters have a preferred conformation in which the trifluoromethyl group, carbonyl, and the hydrogen will be eclipsed (Figures 1 and 2). In this conformation some hydrogens of the acyl side chain are juxtaposed with the phenyl ring and others by the methoxy group of the α-methoxy-α-(trifluoromethyl)-phenylacetic ester. In the ^{1}H NMR spectrum hydrogen atoms adjacent to the phenyl substituent will be seen at higher field than the corresponding hydrogen atoms adjacent to the methoxy functionality. Since the absolute stereochemistry of the α-methoxy-α-(trifluoromethyl)-phenylacetic acid is known, detailed analysis of ^{1}H NMR spectra is useful in the assignment of the stereochemistry of secondary alcohols. The ^{1}H NMR spectra for Mosher esters **67** and **68** are summarized in Table 1. In ester **67** H-1, H-3a, and H-3b are all at lower field and 5-CH_3, H-6, H-7, H-8, H-9a, and H-9b are all at higher field than the corresponding resonances for ester **68**. The ^{1}H NMR spectra for Mosher esters **62** and **63** are given in Table 2. In ester **62** H-2, H-3, H-4, and H-5 are all at lower field and 8-CH_3, H-10, H-12a, and H-12b are all at higher field than the corresponding resonances for ester **63**. All these facts are consistent with the ester **54** derived using (D)-diisopropyl tartrate having the 7*S*-stereochemistry and the ester **58** derived using (L)-diisopropyl tartrate having the 7*R*-stereochemistry. All these facts are in full accord with the stereochemical assignments of both synthetic diesters **62** and **63** and the determination of the natural C-7 stereochemistry as *S*.

The C-14 stereochemistry of the natural ester **60** was established to be *S* by further degradation. Thus ozonolysis of **60** and condensation of the resultant aldehyde with (2,4-dinitrophenyl)hydrazine gave the hydrazone derivative **61** {$[\alpha_D] = +13.2$ ($c = 0.29$ in $CHCl_3$)}. This substance was identical in all respects with an authentic sample {$[\alpha_D] = +12.6$ ($c = 0.30$ in $CHCl_3$)} prepared from the aldehyde **40** derived from L-isoleucine (**37**). In addition, ozonolysis of the synthetic diesters **62** and **63** and condensation of the resultant aldehyde with (2,4-dinitrophenyl)hydrazine gave exactly the same hydrazone derivative **64**. Finally, circular dichroic studies showed that the natural side chain **59** and the synthetic side chain **65** were identical. Therefore, the stereochemistry of the papulacandin fatty acid side chain is 7*S*,14*S*.



65 (*S*)-OH; **66** (*R*)-OH

Completion of the Synthesis of Papulacandin D (1)

The unsaturated ester **54** was cleanly hydrolyzed to acid **69** using potassium trimethylsilanolate[58] and converted to the corresponding mixed anhydride **70** with 2,4,6-trichlorobenzoyl chloride[34] (Scheme 15). Addition of **70** to a mixture of the spiroketal diol **31** and 4-(dimethylamino)pyridine suprisingly resulted in the formation of a 1:1 mixture of *O*-3′ **71** and *O*-2′ **72** esters. In contrast, reaction of the mixed anhydride **70** with the spiroketal **30** in the presence of DMAP proceeded with good *O*-3′ selectivity to give the papulacandin D derivative **73** (57%) and the corresponding *O*-2 ester **74** (14%). Deprotection of ester **73** using tetra-*n*-butylammonium fluoride in THF gave crude papulacandin D (**1**), but chromatographic separation from the tetra-*n*-butylammonium salts was nontrivial. However tris(dimethylamino)sulfonium difluorotrimethylsilicate[59] was much more useful. Thus global deprotection of spiroketal **73** using this reagent provided pure papulacandin D (**1**) (64%). It is germane at this point to further comment on issues of protection. Firstly, while spiroketal **21** underwent selective *O*-3′ esterification using the mixed

(58) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.
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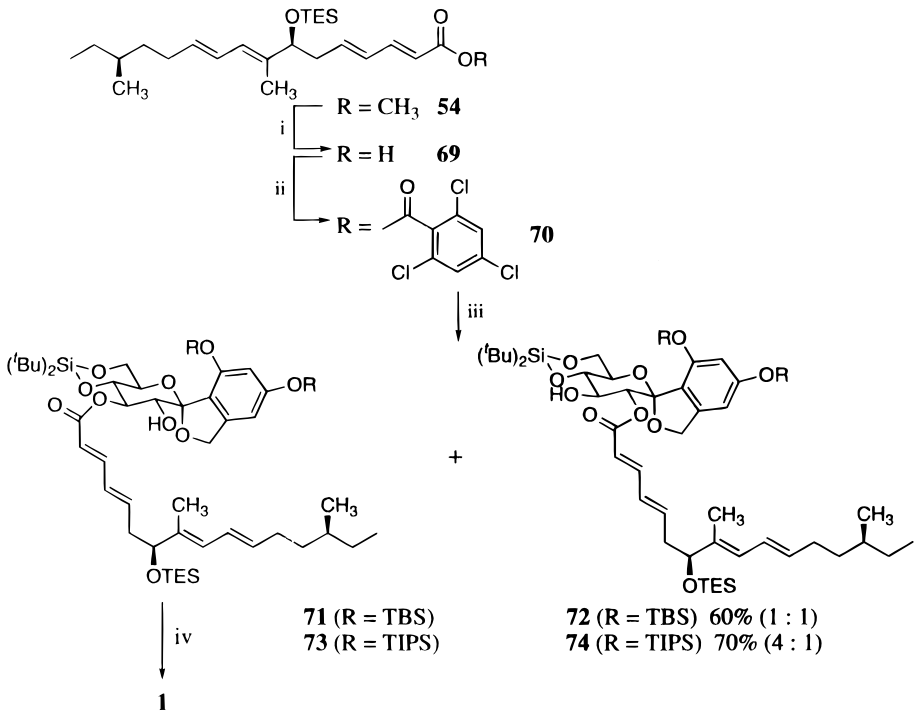
Table 1. NMR Spectra for Esters 67 and 68

	compound **67** from D-(−)-diisopropyl tartrate		compound **68** from L-(+)-diisopropyl tartrate	
proton number	chemical shift	multiplicity	chemical shift	multiplicity
1	2.02	t, $J = 2.6$ Hz	1.93	t, $J = 2.7$ Hz
3	H_{3a} 2.66	ddd, $J = 2.6, 8.5, 17.0$ Hz	H_{3a} 2.62	multiplet
	H_{3a} 2.54	ddd, $J = 2.7, 5.1, 17.1$ Hz	H_{3a} 2.50	multiplet
6	6.02	d, $J = 10.9$ Hz	6.12−6.25	multiplet
7	6.15	dd, $J = 10.9, 15.0$ Hz	6.12−6.25	multiplet
8	5.68	dt, $J = 7.0, 15.0$ Hz	5.78	dt, $J = 6.9, 14$ Hz
9	2.10−2.15	multiplet	2.05−2.20	multiplet
5-Me	1.59	singlet	1.76	singlet

Table 2. NMR Spectra for Esters 62 and 63

	compound **63** from L-(+)-diisopropyl tartrate		compound **62** from D-(−)-diisopropyl tartrate	
proton number	chemical shift	multiplicity	chemical shift	multiplicity
2	5.80	d, $J = 15.4$ Hz	5.81	d, $J = 15.4$ Hz
3	7.25	dd, $J = 11.0, 15.3$ Hz	7.30	dd, $J = 11.0, 15.3$ Hz
4	5.72	dd, $J = 11.2, 15.1$ Hz	5.78	dd, $J = 11.0, 15.2$ Hz
5	5.44−5.50	multiplet with H_9	5.51	dt, $J = 7.2, 14.7$ Hz
6	H_{6a} 2.24	dt, $J = 7.3, 14.7$ Hz	H_{6a} 2.26	dd, $J = 7.4, 14.8$ Hz
	H_{6b} 1.95−2.05	multiplet with H_{13a} and H_{13b}	H_{6b} 1.94−2.10	multiplet with H_{13a} and H_{13b}
9	6.14−6.24	multiplet with H_{10}	6.08	d, $J = 10.9$ Hz
10	6.14−6.24	multiplet with H_9	6.19	dd, $J = 10.9, 14.9$ Hz
11	5.64	dt, $J = 7.0, 14.0$ Hz	5.61	dt, $J = 7.0, 14.4$ Hz
12	1.95−2.05	multiplet with H_{6b}	1.94−2.10	multiplet with H_{6b}
8-Me	1.58	singlet	1.46	singlet

Scheme 15[a]

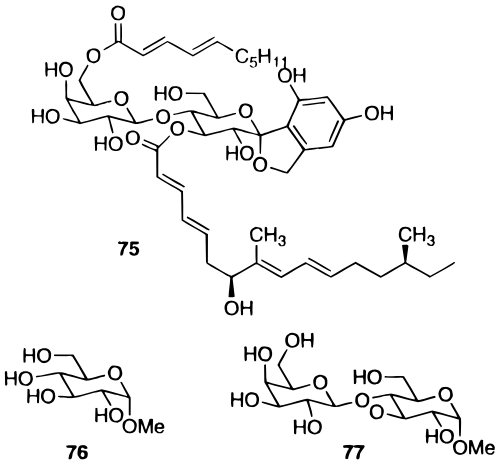


[a] Reagents and Conditions: (i) KOTMS (10 equiv), THF, quant; (ii) 2,4,6-trichlorobenzoyl chloride, Et_3N; (iii) **30** *or* **31**, DMAP; (iv) TASF, THF, 0 °C, 64%.

anhydride **70**, acidic deprotection to remove the benzylidene group resulted in extensive degradation due to the acid lability of the side chain.[15] Secondly, the mixed anhydride derived from the ester **50** could also be used in spiroketal monoesterification. However deprotection to produce papulacandin D (**1**) was inefficient due to slow and incomplete cleavage of the side chain *tert*-butyldimethylsilyl ether. For these reasons, the protecting groups of choice for papulacandin D (**1**) synthesis are *O*-7″ triethylsilyl, *O*-4″,*O*-6″-di-*tert*-butylsilylene, and phenol tris(triisopropylsilyl).

The synthetic sample of papulacandin D (**1**) was spectroscopically and chromatographically identical with an authentic sample of the natural product. However, we observed a specific rotation different from the one reported for the natural product. Traxler, Gruner, and Auden[1,57] reported an $[\alpha]_D$ value for papulacandin D (**1**) of $+7 \pm 1$(MeOH) and $+7 \pm 1$ ($c = 0.250$, $CHCl_3$). In our hands synthetic **1** was insufficiently soluble in chloroform to record an $[\alpha]_D$. In MeOH solution, the synthetic compound showed $[\alpha]_D = +27.5$ ($c = 0.245$, MeOH) which is significantly greater than the literature value. Unfortunately, we had access to only very limited quantities of natural **1** (<500 μg), and this has precluded us from obtaining an accurate rotation. This sample showed $[\alpha]_D = +17$ ($c = 0.09$, MeOH), but this is clearly of dubious

accuracy. Nonetheless, it is believed that an $[\alpha]^{20}_D$ of +27.5 is very reasonable given that the specific rotations for papulacandin A (**75**), methyl α-D-glucopyranoside (**76**), and methyl α-D-lactopyranoside (**77**) are, respectively, 30 ± 1 ($c = 0.419$, MeOH),[1,57] 159 (H_2O),[60] and 115 ($c = 1.03$, H_2O).[60] It is clear from **76** and **77** that *O*-4-(β-D-galactopyranosylation leads to a decrease in specific rotation not increase. By analogy the rotation of papulacandin D (**1**) should not be significantly lower than papulacandin A (**75**) but rather higher.



Conclusion

It is clear from these studies that the full structure of papulacandin D is represented by **1**. The side chain carboxylic acid **69** was available from L-isoleucine (**37**) using Wittig reactions, hydrozirconation, and palladium(0) coupling to establish the tetraene backbone with excellent geometric control. Kinetic resolution using Sharpless asymmetric epoxidation was used to separate the *O*-7″ epimers. The papulacandin spiroketals **14** and **15** were very conveniently prepared albeit in modest yields from the condensation reactions of lactone **19** with the aryllithium reagents derived from bromides **10** and **11**. Additionally, the derived diol **30** was monoesterified, using the mixed anhydride **70**, to provide, on deprotection, papulacandin D (**1**).

Experimental Section

All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Low reaction temperatures were recorded as bath temperatures. Chromatography was carried out on E. Merck or BDH silica gel 60, 230−400 mesh ASTM, using flash chromatography techniques.[61] Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60 F_{254} plates. Hexanes, dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), and diethyl ether (Et_2O) used as eluants were ACS reagent grade solvent or GPR grade from BDH and redistilled. The following reaction solvents were purified by distillation: methanol (MeOH) (from Mg, N_2), dimethylformamide (DMF) (from CaH_2, N_2), dichloromethane (CH_2Cl_2) (from CaH_2, N_2), diethyl ether (Et_2O) (from Ph_2CO−Na, N_2), and tetrahydrofuran (THF) (from Ph_2CO−K, N_2). Organic extracts were dried over anhydrous magnesium sulfate, filtered, and rotary evaporated at ≤50 °C bath temperature; involatile oils were further evaporated at <1 mmHg. Samples for combustion analysis were purified further by chromatography with rotary evaporation of the appropriate fraction and further evaporation (≤1 mmHg) for ≥10 h or by recrystallization. Zinc dust was activated by washing with 1 M hydrochloric acid, acetone, and ether, followed by drying at 110 °C for 6 h.[62] 2,4-Dinitrophenylhydrazone derivatives were prepared using aliquots of a solution of (2,4-dinitrophenyl)hydrazine (5 g) in concentrated sulfuric acid (25 mL), water (35 mL), and ethanol (125 mL, 95%).

***tert*-Butyl[(2-bromo-3,5-dimethoxybenzyl)oxy]dimethylsilane (9).** 2-Bromo-3,5-dimethoxybenzyl alcohol[63] (31.0 g, 125.0 mmol) was dissolved in DMF (600 mL) followed by the addition of *tert*-butyldimethylsilyl chloride (20.8 g, 0.138 mol) and imidazole (25.5 g, 0.376 mol). The reaction mixture was stirred for 18 h at room temperature, poured into water, and stirred for a further 10 min. After the addition of Et_2O (800 mL), the two layers were separated and the organic phase was washed with water (5×). After drying the organic phase and concentrating the solvents, the crude oil was chromatographed (5% EtOAc in hexanes) to yield **9** (40.5 g, 90%) as a colorless oil: R_f = (10% EtOAc in hexanes); IR (thin film) 2930, 2856, 1589, 1455, 1329, 1199, 1159, 1077, 1024, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.80 (d, 1H, $J = 2.8$ Hz), 6.38 (d, 1H, $J = 2.8$ Hz), 4.71 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8, 156.1, 142.5, 103.6, 100.6, 98.2, 64.8, 56.2, 55.4, 25.9, 18.3, −5.4; MS (EI) *m/e* 362, 360 (M^+), 305, 275, 209, 135; HRMS (EI) calcd for $C_{15}H_{25}{}^{79}BrO_3Si$: ($M^{\bullet+}$), 360.0757; found: ($M^{\bullet+}$), 360.0767. Anal. Calcd for $C_{15}H_{25}BrO_3Si$: C, 49.86; H, 6.97. Found: C, 50.02; H, 7.11%.

1,1-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-dimethoxyphenyl]-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (16). Bromide **9** (3.6 g, 10.0 mmol) was dissolved in Et_2O (50 mL) and cooled to −78 °C. *tert*-Butyllithium (1.7 M in hexanes, 12.35 mL, 2.1 equiv) was added, and the mixture was stirred for 0.5 h. The resultant solution was added, *via* cannula, to lactone **19**[25] (4.66 g, 10.0 mmol) in Et_2O (50 mL) at −78 °C. The transfer cannula was maintained at −78 °C with a dry ice pack. The mixture was stirred for 12 h at −78 °C, before being warmed up to room temperature, and quenched with water (10 mL). After the layers were separated, the organic phase was washed with brine and dried. Filtration and evaporation gave a crude yellow oil which was dissolved in MeOH (175 mL) and stirred with Amberlite IR 120 (65 g) (the Amberlite was prewashed with MeOH). After 16 h, the Amberlite was removed by filtration and the MeOH evaporated. The remaining dark green oil was further evaporated at <1 mm for 5 h and dissolved in pyridine (40 mL), acetic anhydride (25 mL) was added, and the mixture was stirred with slight warming (not exceeding 45 °C) for 3 h. The reaction mixture was added to water and extracted with Et_2O. After separating the layers, the organic phase was washed with water (2×) before being dried. After filtration and evaporation, the crude oil was chromatographed (50% EtOAc in hexanes) to yield **16** (2.18 g, 44% yield) as a colorless solid: mp 166−168 °C; $R_f = 0.36$ (50% EtOAc in hexanes); $[\alpha]^{25}_D = +7.4$ ($c = 1.47$ in $CHCl_3$); IR (KBr) 2973, 2875, 1752, 1609, 1367, 1227, 1157, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.32 (s, 1H), 6.30 (s, 1H), 5.90 (d, 1H, $J = 10.1$ Hz), 5.57 (t, 1H, $J = 9.8$ Hz), 5.32 (t, 1H, $J = 9.8$ Hz), 5.17 (d, 1H, $J = 12.7$ Hz), 5.06 (d, 1H, $J = 12.6$ Hz), 4.30 (m, 2H), 4.31 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.2, 170.6, 170.1, 169.6, 163.7, 156.6, 143.8, 115.8, 109.3, 98.6, 97.0, 73.8, 72.6, 70.9, 70.0, 69.0, 62.6, 55.99, 59.96, 21.2, 21.13, 21.10, 20.8; MS (CI) *m/e* 497 ($[M + H]^+$), 195, 60; HRMS (CI) *m/e* calcd for $C_{23}H_{29}O_{12}$: ($[M + H]^+$), 497.1659; found: ($[M + H]^+$), 497.1700.

Methyl 3,5-Bis[(*tert*-butyldimethylsilyl)oxy]benzoate. Methyl 3,5-dihydroxybenzoate (**8**) (27.0 g, 0.160 mol), *tert*-butyldimethylsilyl chloride (51.3 g, 0.340 mol), imidazole (22.1 g, 0.330 mol), and 4-(dimethylamino)pyridine (500 mg) in DMF (300 mL) were stirred at room temperature for 15 h at which time water (200 mL) and Et_2O (200 mL) were added. The layers were separated, and the organic phase was washed with

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(61) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(62) Furniss, B. S.; Hannaford, A. J. P.; Smith, W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific and Technical: London, 1989; p 467.
(63) Noire, P. D.; Frank, R. W. *Synthesis* **1980**, 882.

hydrochloric acid (1 M, 100 mL) and water (100 mL). The organic phase was dried, filtered, and chromatographed (5% EtOAc in hexanes) to yield the title compound (68 g, 98%) as a colorless oil: IR (thin film) 2955, 2931, 2859, 1729, 1590, 1446, 1341, 1254, 1168, 1030, 1013, 929, 831, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (dd, 2H, J = 2.2, 0.5 Hz), 6.50 (dt, 1H, J = 2.4, 0.6 Hz), 3.86 (d, 3H, J = 0.5 Hz), 0.96 (s, 18H), 0.18 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 156.5, 131.8, 116.8, 114.5, 52.1, 25.6, 18.2, −4.5; MS (EI) m/e 396 ($M^{\bullet+}$), 339, 307, 283, 89, 73; HRMS (EI) calcd for $C_{20}H_{36}O_4Si_2$: ($M^{\bullet+}$), 396.2152; found: ($M^{\bullet+}$), 396.2140. Anal. Calcd for $C_{20}H_{36}O_4Si_2$: C, 60.55; H, 9.14. Found: C, 60.63; H, 9.19%.

3,5-Bis[(*tert*-butyldimethylsilyl)oxy]benzyl Alcohol. Methyl 3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzoate (69 g, 175 mmol) in Et_2O (30 mL) and slowly added to a slurry of lithium aluminum hydride (7.9 g, 210 mmol) in Et_2O (1.0 L). After the addition was complete, the mixture was stirred for 1 h prior to being heated to reflux for 3 h. Upon being cooled in an ice bath, water (100 mL) was slowly added followed by aqueous KOH (1.0 M, 50 mL). The resulting slurry was filtered through Celite, the layers were separated, and the organic phase was dried. Concentration and chromatography (10% EtOAc in hexanes) yielded 3,5-bis[(*tert*-butyldimethylsilyl)oxy]-benzyl alcohol (52.2 g, 83%) as a viscous oil: R_f = 0.56 (30% EtOAc in hexanes); IR (thin film) 3328, 2930, 2886, 2858, 1590, 1452, 1361, 1335, 1254, 1164, 1029, 1004, 982, 832, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, 2H, J = 2.4 Hz), 6.25 (t, 1H, J = 2.4 Hz), 4.56 (d, 2H, J = 6.0 Hz), 1.56 (t, 1H, J = 6 Hz), 0.98 (s, 18H), 0.19 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 143.1, 111.7, 111.1, 65.0, 25.7, 25.5, 18.1, −4.0, −4.4. MS (EI) m/e 368 ($M^{\bullet+}$), 311, 255, 133, 73; HRMS (EI) calcd for $C_{19}H_{36}O_3Si_2$: ($M^{\bullet+}$), 368.2203; found: ($M^{\bullet+}$), 368.2205. Anal. Calcd for $C_{19}H_{36}O_3Si_2$: C, 61.90; H, 9.84. Found: C, 61.91; H, 9.86%.

2-Bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzyl Alcohol. NBS (1.38 g, 7.8 mmol) was added slowly in small portions to 3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzyl alcohol (2.73 g, 7.4 mmol) in CCl_4 (25 mL). After the addition was complete, the reaction mixture was stirred for 3 h and quenched with water (5 mL). The organic phase was washed with water (2×) and dried. Filtration and evaporation gave 2-bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzyl alcohol as a yellow oil which was used directly in the next step without purification: R_f = 0.25 (12% EtOAc in hexanes); IR (thin film) 3344, 3074, 2956, 2930, 2886, 1463, 1391, 1362, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.50 (d, 1H, J = 2.7 Hz), 6.31 (d, 1H, J = 2.6 Hz), 4.63 (d, 2H, J = 6.6 Hz), 1.02 (s, 9H), 0.95 (s, 9H), 0.23 (s, 6H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6, 153.1, 141.7, 113.4, 111.0, 106.8, 65.4, 25.67, 25.65, 18.3, 18.2, −4.3, −4.4; MS (EI) m/e 448, 446 ($M^{\bullet+}$), 431, 391, 309, 195, 139, 73, 57; HRMS (EI) m/e calcd for $C_{19}H_{35}{}^{79}BrO_3Si_2$: ($M^{\bullet+}$), 446.1308; found: ($M^{\bullet+}$), 446.1297. Anal. Calcd for $C_{19}H_{35}BrO_3Si_2$: C, 50.98; H, 7.88. Found: C, 50.94 H, 7.90%.

***tert*-Butyl{[2-bromo-3,5-bis[(*tert*-butyldimethylsilyl)-oxy]benzyl]oxy}dimethylsilane (10).** *tert*-Butyldimethylsilyl chloride (1.28 g, 8.5 mmol) and 4-(dimethylamino)pyridine (25 mg) were added to crude 2-bromo-3,5-bis[(*tert*-butyldimethylsilyl)oxy]benzyl alcohol (from above) and imidazole (1.57 g, 23.0 mmol) in DMF (25 mL). The mixture was stirred at 25 °C for 18 h and added to Et_2O (50 mL) and water (50 mL). After vigorous shaking the layers were separated, and the organic phase was washed with water (2×) and dried. Filtration, concentration of solvents, and chromatography (5% EtOAc in hexanes) gave **10** (3.9 g, 93%) as a colorless solid: mp 46−47 °C; R_f = 0.73 (10% EtOAc in hexanes); IR (thin film) 2956, 2930, 2858, 1583, 1442, 1344, 1254, 1166, 1025, 1002, 835, 814, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.74 (d, 1H, J = 2.8 Hz), 6.30 (d, 1H, J = 2.8 Hz), 4.65 (s, 2H), 1.03 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.23 (s, 6H), 0.19 (s, 6H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5, 152.6, 142.3, 112.1, 110.4, 105.3, 64.8, 25.9, 25.8, 25.7, 18.4, 18.3, −4.2, −4.4, −5.3; HRMS (EI) calcd for $C_{25}H_{49}{}^{79}BrO_3Si_3$: ($M^{\bullet+}$), 560.2172; found: ($M^{\bullet+}$), 560.2170. Anal. Calcd for $C_{25}H_{49}BrO_3Si_3$: C, 53.44; H, 8.79. Found: C, 53.29; H, 8.76%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranose (17). *tert*-Butyllithium (1.7 M in hexanes, 18.53 mL, 2.1 equiv) was added to bromide **10** (8.4 g, 15.0 mmol) in Et_2O (75 mL) at −78 °C, and the mixture was stirred for 0.5 h. This solution was added, *via* cannula, to lactone **19** (7.0 g, 15.0 mmol) in Et_2O (75 mL) at −78 °C. The cannula was maintained at −78 °C with a dry ice pack. The mixture was stirred for 12 h at −78 °C before being warmed up to room temperature and quenched with water (10 mL). The organic phase was dried, filtered, and evaporated. The resultant yellow oil was dissolved in MeOH (200 mL) followed by the addition of Amberlite IR 120 (75 g). After being stirred for 16 h, the Amberlite was removed by filtration and the MeOH evaporated. The remaining residue was dissolved in pyridine (50 mL) and Ac_2O (50 mL) and maintained at ambient temperature for 13 h. The reaction mixture was added to Et_2O and water and, after the layers were separated, the organic phase was washed an additional two times with water before being dried. Filtration, evaporation, and chromatography (25% EtOAc in hexanes) gave **17** (4.4 g, 45% yield) as a colorless solid: mp 42−44 °C; $[\alpha]^{25}_D$ = −27.8 (c = 2.4 in Et_2O); IR (thin film) 1756, 1600, 1474, 1227, 1035, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.24 (d, 1H, J = 1.7Hz), 6.17 (d, 1H, J = 1.8Hz), 5.82 (d, 1H, J = 9.9 Hz), 5.52 (app t, 1H, J = 9.7 Hz), 5.2 (app t, 1H, J = 9.7 Hz), 5.10, 5.0 (ABq, 1H, J = 12.7), 4.3 (m, 2H), 4.0 (m, 1H), 2.02 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.70 (s, 3H), 1.06 (s, 9H), 0.94 (s, 9H), 0.29 (s, 3H), 0.27 (s, 3H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 170.4, 169.5, 168.9, 158.7, 152.3, 143.5, 118.2, 109.9, 109.0, 104.8, 73.2, 72.4, 71.0, 69.6, 68.5, 62.3, 25.8, 25.6, 20.8, 20.7, 20.2, 18.2, −4.3, −4.4, −4.5; MS (FAB) m/e 697 ([M + H]$^+$), 639, 395, 379, 337, 73; HRMS (FAB) m/e calcd for $C_{33}H_{53}O_{12}Si_2$: ([M + H]$^+$), 697.3075; found: ([M + H]$^+$), 697.3076. Anal. Calcd for $C_{33}H_{52}O_{12}Si_2$: C, 56.87; H, 7.52. Found: C, 56.64; H, 7.59%.

4,6-*O*-Benzylidene-1,1-anhydro-1-*C*-[6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl]-*β*-D-glucopyranose (21). Tetraacetate **17** (0.690 g, 1.00 mmol), MeOH (20 mL), and NaOMe (catalyst) were allowed to react overnight. The solution was filtered through Amberlite IR 120 with MeOH and evaporated and the yellow residue stirred at room temperature with benzaldehyde (5 mL) and $ZnCl_2$ (0.1 g) for 2 h and quenched by pouring into H_2O and Et_2O. The organic phase was dried ($MgSO_4$), filtered, and evaporated to leave a yellow oil. Chromatography (50% EtOAc in hexanes) gave **21** (0.604 g, 98%) as a white solid: mp 105−107 °C; R_f = 0.60 (50% EtOAc in hexanes), $[\alpha]_D$ = +23.2 (c = 0.25, MeOH); IR (thin film) 3418, 2930, 2859, 1600, 1473, 1367, 1253, 1163, 1086, 998, 867, 834, 781, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.3 (m, 5H), 6.3 (d, 1H, J = 2 Hz), 6.21 (d, 1H, J = 2 Hz), 5.5 (s, 1H), 5.13, 5.0 (ABq, 2H, J = 12.8 Hz), 4.4 (t, 1H, J = 9.1 Hz), 4.3 (dd, 1H, J = 4.9, 10.3 Hz), 4.1 (m, 2H), 3.65 (m, 2H), 1.03 (s, 9H), 0.95 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H), 0.17 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.4, 151.9, 143.5, 137.2, 129.0, 128.2, 126.3, 119.5, 110.9, 110.1, 105.3, 101.9, 81.0, 73.2, 72.9, 72.6, 69.0, 64.6, 25.8, 25.6, 18.3, 18.1, −4.0, −4.1, −4.5; MS (FAB) m/e 639 ([M + Na]$^+$), 617 ([M + H]$^+$), 559, 512, 395, 379, 337; HRMS (FAB) m/e calcd for $C_{32}H_{48}O_8Si_2$: ([M + H]$^+$), 617.2966; found: ([M + H]$^+$), 617.2915. Anal. Calcd for $C_{32}H_{48}O_8Si_2$: C, 62.30; H, 7.84. Found: C, 62.34; H, 7.88%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*β*-D-glucopyranose (22). NaOMe in MeOH (30%, 2 drops) was added to tetraacetate **17** (89 mg, 0.143 mmol) in MeOH (2 mL). After 3 h, citric acid (2 crystals) was added and the mixture stirred for 5 min. After filtration, the solution was evaporated under high vacuum for 2 h and the residue dissolved in pyridine (2 mL) and cooled to 0 °C. 1,1,3,3-Tetraisopropyl-1,3-dichlorodisiloxane[31] (50.5 μL, 0.158 mmol) was added at 0 °C, and the mixture was stirred for 3 h at room temperature. The mixture was poured into water and extracted with EtOAc. The organic phase was washed with water (2×) and aqueous copper sulfate (1 M, 2×), dried, filtered, and evaporated to yield an oil. Chromatography (15% EtOAc in hexanes) gave a colorless foam (55 mg, 50%) tentatively assigned as the diol **22**: ^1H NMR ($CDCl_3$, 500 MHz)

δ 6.28 (d, 1H, J = 1.8 Hz), 6.25 (d, 1H, J = 2.0 Hz), 5.05 (d, 1H, J = 12.6 Hz), 4.91 (d, 1H, J = 12.6 Hz), 4.39 (d, 1H, J = 9 Hz), 4.0−3.7 (m, 5H), 1.5−0.7 (m), 0.29 (2s, 6H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.1, 151.9, 143.7, 120.2, 110.4, 110.3, 105.3, 76.3, 74.4, 72.2, 71.9, 69.9, 61.0, 26.0, 25.6, 18.3, 18.1, 17.6, 17.5, 17.4, 17.35, 17.30, 17.18, 17.13, 17.05, 13.5, 13.3, 13.1, 13.0, 12.1, −3.8, −4.2, −4.4.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-β-D-glucopyranose (14). *tert*-Butyllithium (1.7 M in hexanes, 18.53 mL, 2.1 equiv) was added to bromide **10** (8.4 g, 15.0 mmol) in Et_2O (75 mL) at −78 °C. The mixture was stirred for 0.5 h and added, *via* cannula, to lactone **19** (7.0 g, 15.0 mmol) in Et_2O (75 mL) at −78 °C. The cannula was maintained at −78 °C with a dry ice pack. The mixture was stirred for 12 h at −78 °C before being warmed up to room temperature and quenched with water (10 mL). The separated organic phase was dried, filtered, evaporated, dissolved in MeOH (200 mL), and stirred with Amberlite IR 120 (75 g). After 16 h, the Amberlite was removed by filtration and the MeOH evaporated. The crude oil was dissolved in EtOAc and extracted with water (2×) and brine before being dried and purified by gradient chromatography (5−10% MeOH in $CHCl_3$) to yield the title compound **14** (3.32 g, 45%): mp = 199−202 °C (fine needles from MeOH/water); R_f = 0.62 (13% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +39.9 (c = 1.1 in $CHCl_3$); IR (KBr) 3361, 2956, 2940, 2890, 2861, 1604, 1473, 1434, 1365, 1251, 1162, 1076, 1060, 1035, 1000, 863, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.27 (d, 1H, J = 1.6 Hz), 6.21 (d, 1H, J = 1.8 Hz), 5.06 (d, 1H, J = 12.8 Hz), 4.90 (d, 1H, J = 12.8 Hz), 4.23 (t, 1H, J = 9.1 Hz), 4.16 (br s, 1H), 3.81−3.91 (m, 3H), 3.71−3.76 (m, 1H), 3.60 (td, 1H, J = 9.48, 3.63 Hz), 2.79 (d, 1H J = 8.5 Hz), 2.32 (t, 1H, J = 6.4 Hz), 2.09 (br s, 1H), 1.00, 0.97 (2s, 18H), 0.27 (s, 3H), 0.25 (s, 3H), 0.91 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.3, 151.9, 143.6, 119.9, 110.4, 110.0, 105.3, 75.5, 73.4, 72.6, 72.4, 71.4, 62.9, 25.8, 25.6, 18.3, 18.1, −4.0, −4.1, −4.4; MS (CI) m/e 529 ([M + H]$^+$), 471, 409, 395, 337; HRMS (CI) m/e calcd for $C_{25}H_{45}O_8Si_2$: ([M + H]$^+$), 529.2653; found: ([M + H]$^+$), 529.2698. Anal. Calcd for $C_{25}H_{44}O_8Si_2$: C, 56.79; H, 8.39. Found: C, 56.53; H, 8.10%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-β-D-glucopyranose (31). Di-*tert*-butylsilyl bis(trifluoromethanesulfonate) was added to a stirred solution of tetraol **14** (1.0 g, 1.89 mmol) and 2,6-lutidine (607 mg, 5.67 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 30 min the mixture was warmed up to room temperature and water (15 mL) was added. The aqueous solution was extracted with EtOAc, and the organic layer was washed with water and brine before being dried. Filtration, evaporation, and chromatography (20% EtOAc in hexanes) gave **31** (1.0 g, 81%): mp = 205−207 °C (fine needles); R_f = 0.39 (25% EtOAc in hexanes); $[\alpha]^{25}_D$ = +23.7 (c = 0.86, $CHCl_3$); IR (KBr) 3544, 3507, 2938, 2861, 1600, 1473, 1432, 1353, 1253, 1155, 1089, 1070, 1039, 998, 962, 863, 835, 782 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.30 (d, 1H, J = 1.4 Hz), 6.20 (d, 1H, J = 1.7 Hz), 5.12 (d, 1H, J = 12.7 Hz), 5.00 (d, 1H J = 12.7 Hz), 4.33 (t, 1H, J = 8.5 Hz), 4.11 (dd, 1H, J = 9.9, 5.0 Hz), 4.00−3.92 (m, 1H), 3.88−3.80 (m, 3H), 1.09−0.92 (4s, 36H), 0.28 (s, 3H), 0.23 (s, 3H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.4, 151.9, 143.4, 119.7, 110.6, 110.0, 105.2, 76.8, 75.6, 73.0, 72.5, 68.5, 66.6, 27.5, 27.2, 27.1, 25.8, 25.6, 22.7, 19.9, 19.8, 18.3, 18.1, −3.9, −4.3, −4.4; MS (CI) m/e 669 ([M + H]$^+$), 611, 395; HRMS (CI) m/e calcd for $C_{33}H_{61}O_8Si_3$: ([M + H]$^+$), 669.3674; found: ([M + H]$^+$), 669.3732. Anal. Calcd for $C_{33}H_{60}O_8Si_3$: C, 59.24; H, 9.04. Found: C, 59.13; H, 8.90%.

3,5-Bis[(triisopropylsilyl)oxy]benzyl Alcohol. Methyl 3,5-dihydroxybenzoate (**8**) (20.0 g, 119.0 mmol), triisopropylsilyl chloride (48.0 g, 53.5 mL, 250.0 mmol), imidazole (22.1 g, 476 mmol), and 4-(dimethylamino)pyridine (∼500 mg) in DMF (100 mL) were stirred at room temperature for 24 h. Water (200 mL) and EtOAc (200 mL) were added, the layers were separated, and the organic phase was washed with water (3×) and dried. After filtration and concentration, purification was accomplished by gradient chromatography (2.5−10% EtOAc in hexanes) to yield the title ester (53 g, 93%) as a colorless oil: R_f = 0.5 (5% EtOAc in hexanes); IR (thin film) 2946, 2868, 1729, 1589, 1451, 1345, 1240, 1175, 1032, 1014, 882, 771, 681 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (d, 2H, J = 2.6 Hz), 6.61 (t, 1H, J = 2.4 Hz), 3.88 (s, 3H), 1.32−1.15 (m, 6H), 1.10 (d, 36H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.9, 156.9 131.7, 116.3, 114.1, 52.1, 17.9, 12.6; MS (CI) m/e 481 ([M + H]$^+$), 454, 437; HRMS (CI) m/e calcd for $C_{29}H_{49}O_4Si_2$: ([M + H]$^+$), 481.3169; found: ([M + H]$^+$), 481.3185. The crude ester (58.0 g, 121.0 mmol) in Et_2O (400 mL) was slowly added to a slurry of $LiAlH_4$ (5.5 g, 145.0 mmol) in Et_2O (500 mL). After the addition was complete, the mixture was stirred for 1 h prior to being heated at reflux for 3 h. Upon being cooled in an ice bath, water (100 mL) was slowly added followed by aqueous KOH (1.0 M, 50 mL). The resulting slurry was filtered through Celite, the layers were separated, and the organic phase was dried. Filtration and concentration of solvents gave the title compound as a viscous oil, which was used directly in the next step: R_f = 0.31 (10% EtOAc in hexanes); IR (thin film) 3335, 2948, 2890, 1590, 1460, 1337, 1170, 1031, 1004, 985, 882, 855, 823, 765, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (d, 2H, J = 1.9 Hz), 6.34 (t, 1H, J = 2.1 Hz), 4.56 (s, 2H), 1.3−1.0 (m, 42H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.1, 143.0, 111.4, 110.8, 65.2, 17.9, 17.7, 12.7, 12.3; MS (CI) m/e 453 ([M + H]$^+$), 426, 255, 148, 94; HRMS (CI) m/e calcd for $C_{25}H_{49}O_3Si_2$: ([M + H]$^+$), 453.3220; found: ([M + H]$^+$), 453.3258. Anal. Calcd for $C_{25}H_{48}O_3Si_2$: C, 66.33; H, 10.70. Found: C, 66.63; H, 10.56%.

2-Bromo-3,5-bis[(triisopropylsilyl)oxy]benzyl Alcohol. NBS (1.38 g, 7.8 mmol) was slowly added in small portions to 3,5-bis[(triisopropylsilyl)oxy]benzyl alcohol (2.73 g, 7.4 mmol) in CCl_4 (25 mL), the mixture was stirred for 3 h and quenched with water (5 mL), and the separated organic phase was dried. Filtration and evaporation gave 2-bromo-3,5-bis[(triisopropylsilyl)oxy]benzyl alcohol as a yellow oil, which was used directly in the next step: R_f = 0.40 (10% EtOAc in hexanes); IR (thin film) 3331, 2945, 2867, 1578, 1463, 1442, 1421, 1348, 1174, 1016, 997, 882, 821, 768, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.65 (d, 1H, J = 2.6 Hz), 6.41 (d, 1H, J = 2.8 Hz), 4.66 (s, 2H), 1.3 (sept, 3H, J = 7.5 Hz), 1.2 (sept, 3H, J = 7.5 Hz), 1.14 (d, 18H, J = 7.4 Hz), 1.05 (d, 18H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0, 153.4, 141.6, 113.0, 110.4, 106.3, 65.5, 18.0, 17.9, 17.7, 13.0, 12.7, 12.3; MS (CI) m/e 533, 531 ([M + H]$^+$), 506, 589, 459, 91, 76, 58; HRMS (CI) m/e calcd for $C_{25}H_{48}{}^{81}BrO_3Si_2$: ([M + H]$^+$), 533.2305; found: ([M + H]$^+$), 533.2330. Anal. Calcd for $C_{25}H_{47}BrO_3Si_2$: C, 56.58; H, 8.93. Found: C, 56.67; H, 8.96%.

***tert*-Butyl{[2-bromo-3,5-bis[(triisopropylsilyl)oxy]-benzyl]oxy}dimethylsilane (11).** The crude 3,5-bis[(triisopropylsilyl)oxy]benzyl alcohol (29.0 g, 55.3 mmol), imidazole (11.3 g, 166.0 mmol), *tert*-butyldimethylsilyl chloride (10.0 g, 66.4 mmol), and 4-(dimethylamino)pyridine (100 mg) in CH_2Cl_2 (300 mL) were stirred at 25 °C for 18 h. EtOAc (300 mL) and water (300 mL) were added and, after vigorous shaking, the separated organic phase was washed with brine and dried. Filtration, evaporation, and chromatography (2.5% EtOAc in hexanes) yielded **11** (29.0 g, 80%, three steps) as a colorless oil: bp = 210 °C at 0.10 mmHg (Kugelrohr); R_f = 0.26 (hexanes); IR (thin film) 2946, 2867, 1582, 1463, 1442, 1366, 1347, 1257, 1172, 1055, 1026, 1004, 882, 858, 837, 774, 684 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 (d, 1H, J = 2.7 Hz), 6.38 (d, 1H, J = 2.8 Hz), 4.67 (s, 2H), 1.33 (sept, 3H, J = 7.7 Hz), 1.25 (sept, 3H, J = 7.8 Hz), 1.12 (d, 18H, J = 7.4 Hz), 1.09 (d, 18H, J = 7.3 Hz), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 152.9, 142.2, 111.7, 109.8, 104.7, 64.9, 25.9, 18.3, 18.0, 17.9, 13.0, 12.7, −5.4; MS (CI) m/e 647, 645 ([M + H]$^+$), 606, 589, 532, 90; HRMS (CI) m/e calcd for $C_{31}H_{62}{}^{81}BrO_3Si_3$: ([M + H]$^+$), 647.3169; found: ([M + H]$^+$), 647.3206.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (18). *tert*-Butyllithium (1.7 M in pentane, 15.65 mL, 2.2 equiv) was added to bromide **11** (8.0 g, 12.1 mmol) in Et_2O (85 mL) at −78 °C. After 0.5 h, the solution was added, *via* cannula, to lactone **19** (5.66 g, 12.1 mmol) in Et_2O (85 mL) at −78 °C. The cannula was maintained at −78 °C with a dry ice pack. The reaction mixture was stirred for 12 h at −78 °C before being warmed up to room temperature, quenched with

water (100 mL), and extracted with EtOAc. The organic phase was washed with brine, and the separated organic phase was dried, filtered, and concentrated. The resultant crude yellow oil was dissolved in MeOH (150 mL) and Amberlite IR 120 (75 g) added. After being stirred for 16 h, the Amberlite was removed by filtration and the MeOH evaporated. The remaining dark green oil was further evaporated at <1 mmHg for 5 h before being dissolved in pyridine (50 mL) and Ac_2O (50 mL) and stirred overnight. The mixture was added to EtOAc and water, and the layers were separated. The organic phase was washed with water (2×), dried, filtered, and evaporated to leave an oil. Chromatography (25% EtOAc in hexanes) gave **18** (3.00 g, 33% yield) as a colorless foam: R_f = 0.14 (25% EtOAc in hexanes); $[\alpha]^{25}_D$ = −21.0 (c = 0.50 in $CHCl_3$); IR (KBr) 2943, 2868, 1748, 1599, 1476, 1381, 1363, 1235, 1167, 1066, 1031, 1003, 880, 837, 686, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.29 (d, 1H, J = 1.5 Hz), 6.23 (d, 1H, J = 1.7 Hz), 5.84 (d, 1H, J = 9.9 Hz), 5.54 (t, 1H, J = 9.7 Hz), 5.23 (t, 1H, J = 9.8 Hz), 5.11 (d, 1H, J = 12.6 Hz), 5.02 (d, 1H, J = 12.6 Hz), 4.40−4.30 (m, 2H), 3.90 (dd, 1H, J = 1.8, 10.0 Hz), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.72 (s, 3H), 1.40−1.25 (m, 42H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 170.4, 169.5, 168.8, 159.1, 152.6, 143.4, 117.9, 109.7, 109.1, 104.5, 73.3, 72.5, 71.2, 69.6, 68.7, 62.6, 20.7, 20.6, 20.2, 18.05, 17.97, 17.8, 13.1, 12.6; MS (FAB) m/e 781([M + H]$^+$), 737, 479, 435, 173, 87, 73, 59; HRMS (FAB) m/e calcd for $C_{39}H_{65}O_{12}Si_2$: ([M + H]$^+$), 781.4015; found: ([M + H]$^+$), 781.4017. Anal. Calcd for $C_{39}H_{64}O_{12}Si_2$: C, 59.97; H, 8.26. Found: C, 60.32; H, 7.81%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-*β*-D-glucopyranose (15). *tert*-Butyllithium (1.7 M in pentane, 15.65 mL, 2.2 equiv) was added to bromide **11** (8.0 g, 12.1 mmol) in Et_2O (85 mL) at −78 °C and the mixture was stirred for 0.5 h before being added, *via* cannula, to lactone **19** (5.66 g, 12.1 mmol) in Et_2O (85 mL) at −78 °C. The cannula was maintained at −78 °C with a dry ice pack. The mixture was stirred for 12 h at −78 °C and then warmed up to room temperature, quenched with water (100 mL), and extracted with EtOAc. The organic phase was washed with brine, dried, filtered, and concentrated. The resultant yellow oil was dissolved in MeOH (150 mL), and Amberlite IR 120 (75 g) was added. After stirring for 16 h, the Amberlite was removed by filtration and the MeOH evaporated. The oil was dissolved in EtOAc and extracted with water (2×) and brine. The organic layer was dried and purified by gradient chromatography (5−10% MeOH in $CHCl_3$) to give the title tetraol **15** (3.04 g, 34%) as an oil: R_f = 0.45 (13% MeOH in $CHCl_3$); $[\alpha]^{25}_D$ = +14.2 (c = 1.03 in $CHCl_3$); IR (KBr) 3369, 2942, 2867, 1598, 1465, 1363, 1168, 1060, 1000, 881, 846, 686 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 6.36 (d, 1H, J = 1.5 Hz), 6.26 (d, 1H, J = 1.7 Hz), 5.07 (d, 1H, J = 12.6 Hz), 5.00 (d, 1H, J = 12.6 Hz), 4.24 (d, 1H J = 9.6 Hz), 3.89−3.83 (m, 2H), 3.73 (t, 1H, J = 9.3 Hz), 3.56 (dd, 1H, J = 12.2, 7.9 Hz), 3.30 (m, 1H), 1.35 (sept, 3H, J = 7.5 Hz), 1.25 (sept, 3H, J = 7.5 Hz), 1.20−1.10 (m, 36H); ^{13}C NMR (CD_3OD, 125 MHz) δ 159.7, 153.6, 145.8, 121.9, 112.0, 110.3, 105.8, 76.6, 76.3, 73.8, 73.6, 72.8, 64.0, 18.68, 18.66, 18.4, 14.5, 14.0; MS (CI) m/e 613 ([M + H]$^+$), 493, 479, 435, 148; HRMS (CI) m/e calcd for $C_{31}H_{57}O_8Si_2$: ([M + H]$^+$), 613.3592; found: ([M + H]$^+$), 613.3611. Anal. Calcd for $C_{31}H_{56}O_8Si_2$: C, 60.75; H, 9.21. Found: C, 60.54; H, 9.09%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*β*-D-glucopyranose (23). NaOMe in MeOH (30%, 1 drop) was added to a stirred solution of tetraacetate **18** (100 mg, 0.128 mmol) in MeOH (1 mL). After 5 h, excess Amberlite 120 IR ion exchange resin (H^+ form) was added and the mixture stirred for 5 min. After filtration, the solution was evaporated under high vacuum for 2 h and the residue dissolved in pyridine (2 mL) and cooled to 0 °C. 1,1,3,3-Tetraisopropyl-1,3-dichlorodisiloxane[31] (45.1 μL, 0.141 mmol) was added, and the mixture was stirred for 1 h at 0 °C and 6 h at room temperature. The mixture was poured into water and extracted with EtOAc. The organic phase was washed with water (2×) and aqueous copper sulfate (1 M, 2×), dried, filtered, and evaporated to yield an oil. Chromatography (15% EtOAc in hexanes) gave diol **23** as a colorless foam (78 mg, 71%): R_f = 0.26 (15% EtOAc in hexanes); $[\alpha]^{25}_D$ = +20.2 (c = 1.44 in $CHCl_3$); IR (KBr) 3400, 2940, 2868, 1597, 1461, 1357, 1167, 1070, 1029, 1000, 891, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.22 (d, 1H, J = 1.7 Hz), 6.15 (d, 1H, J = 1.8 Hz), 5.00 (d, 1H J = 12.5 Hz), 4.85 (d, 1H, J = 12.5 Hz), 4.34 (d, 1H, J = 9.0 Hz), 4.1−3.65 (m, 5H), 1.30−0.8 (m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.5, 152.4, 143.7, 119.5, 110.5, 109.4, 104.8, 76.5, 74.4, 72.3, 72.1, 70.2, 61.2, 21.1, 18.2, 17.9, 17.6, 17.5, 17.43, 17.36, 17.32, 17.23, 17.19, 17.17, 14.2, 13.5, 13.23, 13.17, 12.7, 12.6; MS (CI) m/e 855 ([M + H]$^+$), 811, 479, 435, 380; HRMS (FAB) m/e calcd for $C_{43}H_{83}O_9Si_4$: ([M + H]$^+$), 855.5114; found: ([M + H]$^+$), 855.5181.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2-*O*-acetyl-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*β*-D-glucopyranose (24) and 1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2,3-di-*O*-acetyl-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-*β*-D-glucopyranose (25). Ac_2O (0.75 mL) was added to diol **23** (50 mg) in pyridine (1 mL) and the mixture stirred at room temperature for 8 h and poured into water. The mixture was extracted with EtOAc and the organic phase was extracted with water (3×), aqueous copper sulfate (1 M), and brine. Drying, filtration, and evaporation gave a yellow oil which was chromatographed (10% EtOAc in hexanes) to give **24** and **25** both as colorless foams. The 2-ester **24** showed: R_f = 0.42 (10% EtOAc in hexanes); IR (KBr) 3516, 2944, 2867, 1752, 1599, 1465, 1369, 1249, 1166, 1031, 1000, 884, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.30 (d, 1H, J = 1.6 Hz), 6.24 (d, 1H, J = 1.7 Hz), 5.72 (d, 1H, J = 9.7 Hz), 5.08, 5.00 (ABq, 2H, J = 12.5 Hz), 4.11−3.86 (m, 5H), 1.83 (s, 3H), 0.87−0.61 (m, 70H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 158.6, 152.6, 143.5, 118.9, 109.6, 109.4, 104.5, 74.8, 74.2, 73.9, 72.6, 71.5, 61.6, 29.7, 20.6, 18.1, 17.8, 17.7, 17.4, 17.3, 17.2, 13.5, 13.2, 13.1, 12.6; MS (FAB) m/e 897 ([M + H]$^+$), 853, 837, 535, 479, 435, 261, 173, 115, 87, 73, 59; HRMS (FAB) m/e calcd for $C_{45}H_{85}O_{10}Si_4$: ([M + H]$^+$), 897.5258; found: ([M + H]$^+$), 897.5258. The diester **25** showed: R_f = 0.50 (10% EtOAc in hexanes); IR (KBr) 2949, 2867, 1753, 1599, 1465, 1367, 1241, 1030, 1002, 883, 837, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.29 (d, 1H, J = 1.5 Hz), 6.23 (d, 1H, J = 1.6 Hz), 5.80 (d, 1H, J = 9.9 Hz), 5.51 (t, 1H, H = 9.4 Hz), 5.10, 5.00 (ABq, 2H, J =12.5 Hz), 4.20 (t, 1H, J = 9.4 Hz), 4.08 (dd, 1H, J = 2.5, 12.5 Hz), 4.00 (d, 1H, J = 9.6 Hz), 3.90 (d, 1H, J = 12.5 Hz), 2.03 (s, 3H), 1.74 (s, 3H), 1.61−0.88 (m, 70H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 169.3, 158.7, 152.6, 143.6, 118.5, 109.6, 109.3, 104.5, 75.2, 74.2, 72.8, 72.1, 68.9, 61.7, 21.1, 20.4, 18.1, 18.0, 17.8, 17.6, 17.4, 17.3, 17.2, 17.1, 17.0, 13.6, 13.5, 13.2, 13.1, 12.6; MS (FAB) m/e 939 ([M + H]$^+$), 895, 479, 435, 303, 277, 261, 173, 115, 87, 73, 59; HRMS (FAB) m/e calcd for $C_{47}H_{87}O_{11}Si_4$: ([M + H]$^+$), 939.5326; found: ([M + H]$^+$), 939.5329.

1,1-Anhydro-1-*C*-{6-hydroxymethyl-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2-*O*-cinnamoyl-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-D-glucopyranose (28). Et_3N (25 μL, 0.175 mmol) and 2,4,6-trichlorobenzoyl chloride (18 μL, 0.117 mmol) were added to *trans*-cinnamic acid (17.3 mg, 0.117 mmol) in THF (0.3 mL). After 30 min, the solvent was evaporated under high vacuum and the residue dissolved in CH_2Cl_2 (0.3 mL) and added, *via* a cannula, to diol **23** (100 mg, 0.12 mmol) and 4-(dimethylamino)pyridine (29 mg, 0.23 mmol) in CH_2Cl_2 (1 mL). After 3 h, the mixture was added to water and extracted with EtOAc. The organic phase was washed with brine and dried, filtered, concentrated, and purified by gradient chromatography (5−15% EtOAc in hexanes) to yield ester **28** (83.6 mg, 73%): R_f = 0.21 (5% EtOAc in hexanes); $[\alpha]^{25}_D$ = −51.6 (c = 1.18 in $CHCl_3$); IR (KBr) 2952, 2948, 2937, 2866, 1724, 1698, 1465, 1364, 1167, 1032, 998, 883, 839, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50−7.30 (m, 6H), 6.25 (d, 1H, J = 1.7 Hz), 6.23 (s, 1H), 6.20 (d, 1H, J = 2.1 Hz), 5.80 (d, 1H, J = 9.8 Hz), 5.16 (d, 1H, J = 12.6 Hz), 5.10 (d, 1H, J = 12.6 Hz), 4.20−4.05 (m, 3H), 3.98 (t, 1H, J = 9.2 Hz), 3.88 (t, 1H, J = 10.0 Hz), 1.38−1.30 (m, 2H), 0.98−1.20 (m, 70 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 158.9, 152.5, 144.7, 143.1, 134.5, 130.1, 128.7, 128.0, 118.4, 117.7, 109.7, 109.6, 104.5, 77.5, 73.6, 68.5, 66.6, 27.4, 27.1, 22.8, 20.0, 18.13, 18.06, 17.8, 13.2, 12.6; MS (FAB) m/e 985 ([M + H]$^+$), 941, 837, 623, 505,

461, 131, 103, 59; HRMS (FAB) *m/e* calcd for $C_{52}H_{89}O_{10}Si_4$: ([M + H]$^+$), 985.5533; found: ([M + H]$^+$), 985.5560.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-4,6-*O*-(tetraisopropyldisiloxane-1,3-diyl)-2-*O*-[(triethylsilyl)oxy]-*β*-D-glucopyranose (29). Triethylsilyl trifluoromethanesulfonate (22.5 μL, 26.2 mL, 0.10 mmol) was added to diol **22** (77 mg, 0.09 mmol) in pyridine (2 mL) at −10 °C. After 2 h, the mixture was added to water and extracted with EtOAc (2×). The organic phase was washed with aqueous copper sulfate (1 M, 2×), water (1×), and brine and dried. Filtration, evaporation, and chromatography (5% EtOAc in hexanes) gave **29** (55 mg, 84%): R_f = 0.46 (5% EtOAc in hexanes); $[\alpha]^{25}_D$ = −5.2 (c = 1.25 in $CHCl_3$); IR 3621, 3467, 2942, 2869, 1600, 1465, 1365, 1249, 1164, 1091, 1029, 1002, 883, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.31 (d, 1H, J = 1.5 Hz), 6.26 (d, 1H, J = 1.6 Hz), 5.12, 4.98 (ABq, 2H, J = 12.5 Hz), 4.29 (d, 1H, J = 8.6 Hz), 4.00 (dd, 1H, J = 10.0, 2.2 Hz), 3.90−3.80 (m, 4H), 2.17 (br s, 1H), 1.4−0.9 (m, 70 H), 0.77 (t, 9H, J = 7.9 Hz), 0.09−0.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.3, 152.3, 144.0, 120.7, 111.3, 109.8, 104.7, 76.8, 76.6, 74.5, 73.8, 73.1, 70.9, 62.3, 18.3, 18.2, 17.9, 17.7, 17.5, 17.3, 17.2, 16.7, 13.7, 13.5, 13.2, 13.1, 12.8, 6.8, 4.9; MS (FAB) *m/e* 969 ([M + H]$^+$), 925, 837, 479, 435, 261, 87, 59; HRMS (FAB) *m/e* calcd for $C_{49}H_{97}O_9Si_5$: ([M + H]$^+$), 569.5979; found: ([M + H]$^+$), 569.6009.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-*β*-D-glucopyranose (30). 2,6-Lutidine (335 μL, 308 mg, 2.88 mmol) and di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (419 μL, 507 mg, 1.15 mmol) were added sequentially to tetraol **15** (590 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min, the solution was allowed to warm up to room temperature and added to water. The mixture was extracted with EtOAc, and the organic phase was washed with water and brine and dried. Filtration, concentration, and chromatography (20% EtOAc in hexanes) gave **30** (605 mg, 85%): R_f = 0.38 (25% EtOAc in hexanes), 0.18 (15% EtOAc in hexanes); $[\alpha]^{25}_D$ = +20.9 (c = 1.15 in $CHCl_3$); IR (KBr) 2949, 2867, 1613, 1599, 1471, 1362, 1166, 1084, 1068, 1001, 881, 827, 768, 687, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.31 (d, 1H, J = 1.6 Hz), 6.24 (d, 1H, J = 1.8 Hz), 5.12 (d, 1H, J = 12.6 Hz), 5.00 (d, 1H, J = 12.6 Hz), 4.35 (br s, 1H), 4.14−4.09 (m, 1H), 4.00−3.9 (m, 1H), 3.89−3.79 (m, 3H), 1.00−1.38 (m, 60H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.8, 152.3, 143.4, 119.1, 110.7, 109.5, 104.8, 75.6, 73.1, 72.5, 68.5, 66.7, 27.5, 27.1, 22.8, 20.0, 18.0, 17.9, 13.2, 12.7; MS (CI) *m/e* 753 ([M + H]$^+$), 479, 336, 278, 215, 148; HRMS (CI) *m/e* calcd for $C_{39}H_{73}O_8Si_3$: ([M + H]$^+$), 753.4613; found: ([M + H]$^+$), 753.4648. Anal. Calcd for $C_{39}H_{72}O_8Si_3$: C, 62.19; H, 9.63. Found: C, 61.96; H, 9.64%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2,3-di-*O*-acetyl-4,6-*O*-(di-*tert*-butylsilylene)-*β*-D-glucopyranose (32). Ac_2O (1.5 mL) was added to diol **30** (88 mg, 0.12 mmol) in pyridine (2 mL). After being stirred overnight, the mixture was added to water and extracted with EtOAc. The organic phase was washed with aqueous copper sulfate (1 M, 2×), water (2×), and brine and dried. Filtration, evaporation, and chromatography (10% EtOAc in hexanes) gave **32** (86 mg, 88%): R_f = 0.16 (5% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.27 (d, 1H, J = 1.3 Hz), 6.20 (d, 1H, J = 1.6 Hz), 5.73 (d, 1H, J = 9.9 Hz), 5.46 (t, 1H, J = 9.6 Hz), 5.12, 5.03 (ABq, 2H, J = 12.6 Hz), 4.15 (m, 2H), 4.05 (t, 1H, J = 9.4 Hz), 3.85 (m, 1H), 2.05 (s, 3H), 1.72 (s, 3H), 1.00−1.32 (m, 60H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.0, 159.0, 152.5, 143.4, 118.1, 109.7, 109.5, 104.5, 75.1, 73.9, 73.4, 71.6, 68.7, 66.6, 27.3, 27.0, 22.7, 20.8, 20.2, 20.0, 18.1, 18.0, 17.8, 13.4, 13.2, 13.0, 12.9, 12.6, 12.4; MS (FAB) *m/e* 837 ([M + H]$^+$), 793, 479, 435; HRMS (FAB) *m/e* calcd for $C_{43}H_{77}O_{10}Si_3$: ([M + H]$^+$), 837.4824; found: ([M + H]$^+$), 837.4817. Anal. Calcd for $C_{43}H_{76}O_{10}Si_3$: C, 61.69; H, 9.16. Found: C, 61.81; H, 8.98%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-3-*O*-cinnamoyl-4,6-*O*-(di-*tert*-butylsilylene)-*β*-D-glucopyranose (33) and 1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-2-*O*-cinnamoyl-4,6-*O*-(di-*tert*-butylsilylene)-*β*-D-glucopyranose (34). Et_3N (32 μL, 33 mg, 0.23 mmol) and, after 10 min, 2,4,6-trichlorobenzoyl chloride (23 μL, 36 mg, 0.15 mmol) were added to *trans*-cinnamic acid (22 mg, 0.145 mmol) in THF (0.5 mL). After 45 min at room temperature, the mixture was evaporated and the residue dissolved in CH_2Cl_2 (1 mL). This solution was added to diol **30** (100 mg, 0.13 mmol) and 4-(dimethylamino)pyridine (36 mg, 0.29 mmol) in DMF (5 mL). After 15 h at room temperature, the mixture was added to water and extracted with EtOAc, and the organic phase was washed with water (2×) and brine. The solution was dried, evaporated, and purified by gradient chromatography (5−10% EtOAc in hexanes) giving **33** (49 mg, 42%) and **34** (28 mg, 24%) [67%, 6.7:1 ratio, (3-ester:2-ester)]. The 3-ester **33** showed: R_f = 0.24 (10% EtOAc in hexanes); $[\alpha]^{25}_D$ = +1.4 (c = 1.46 in $CHCl_3$); IR (KBr) 3463, 2946, 2865, 1720, 1637, 1600, 1477, 1434, 1365, 1309, 1251, 1172, 1074, 1000, 883, 833, 767, 686, 655 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, 1H, J = 16.0 Hz), 7.78−7.57 (m, 2H), 7.43−7.38 (m, 3H), 6.55 (d, 1H J = 16.0 Hz), 6.35 (d, 1H, J = 1.5 Hz), 6.28 (d, 1H, J = 1.7 Hz), 5.42 (t, 1H, J = 9.4 Hz), 5.20 (d, 1H, J = 12.8 Hz), 5.05 (d, 1H, J = 12.8 Hz), 4.50 (t, 1H, J = 10Hz), 4.25−4.10 (m, 3H), 3.90−3.84 (m, 1H), 2.02 (d, 1H, J = 10.4 Hz), 1.5−1.0 (m, 60H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 158.8, 152.2, 144.8, 143.3, 134.7, 130.1, 128.8, 128.1, 119.2, 118.5, 111.1, 109.6, 104.9, 76.8, 76.6, 74.9, 73.4, 71.6, 86.9, 66.8, 30.4, 29.7, 27.4, 27.0, 22.8, 20.0, 18.1, 17.9, 13.2, 12.7; MS (FAB) *m/e* 883 ([M + H]$^+$), 479, 435, 199, 131; HRMS (FAB) *m/e* calcd for $C_{48}H_{79}O_9Si_3$: ([M + H]$^+$), 883.5031; found: ([M + H]$^+$), 883.5043. Anal. Calcd for $C_{48}H_{78}O_9Si_3$: C, 65.27; H, 8.91. Found: C, 64.98; H, 8.16%. The 2-ester **34** showed: R_f = 0.29 (10% EtOAc in hexanes); $[\alpha]^{25}_D$ = −65.0 (c = 0.95 in $CHCl_3$); IR (thin film) 3473, 2944, 2866, 1726, 1639, 1601, 1474, 1367, 1167, 1070, 1001, 828, 767, 684, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.30 (m, 5H), 7.45 (d, 1H, J = 15.9 Hz), 6.28 (d, 1H, J = 1.7 Hz), 6.22 (d, 1H, J = 1.7 Hz), 6.24 (d, 1H, J = 15.9 Hz), 5.83 (d, 1H, J = 9.7 Hz), 5.20, 5.10 (ABq, 2H, J = 12.6 Hz), 4.21−3.87 (m, 5H), 2.73 (br s, 1H), 1.45−1.26 (m, 6H), 1.2−1.0 (m, 54H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 158.9, 152.5, 144.7, 143.1, 134.5, 130.1, 128.8, 128.0, 118.4, 117.7, 109.71, 109.65, 104.5, 73.6, 73.5, 73.4, 68.5, 66.6, 27.5, 27.1, 22.8, 20.0, 18.2, 18.1, 17.8, 13.2, 12.6; MS (FAB) *m/e* 883 ([M + H]$^+$), 839, 735, 623, 435, 131, 103, 73, 59; HRMS (FAB) *m/e* calcd for $C_{48}H_{79}O_9Si_3$: ([M + H]$^+$), 883.5032; found: ([M + H]$^+$), 883.5054. Anal. Calcd for $C_{48}H_{78}O_9Si_3$: C, 65.27; H, 8.91. Found: C, 65.50; H, 8.61%.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-3-*O*-cinnamoyl-4,6-*O*-bis-(*tert*-butylsilylene)-*β*-D-glucopyranose (35) and 1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-2-*O*-cinnamoyl-4,6-*O*-bis(*tert*-butylsilylene)-*β*-D-glucopyranose (36). Et_3N (81 μL, 59 mg, 0.57 mmol) and 2,4,6-trichlorobenzoyl chloride (61 μL, 95 mg, 0.39 mmol) were added sequentially to *trans*-cinnamic acid (50 mg, 0.34 mmol) in DMF (2 mL). After 45 min, the solution was added to diol **31** (271 mg, 0.41 mmol) in DMF (5 mL). After 15 h, water (10 mL) was added and the mixture extracted with EtOAc. The organic phase was washed with water (3×) and brine and dried. Filtration, evaporation, and chromatography (10% EtOAc in hexanes) gave **35** and **36** (195 mg, 1:1, 72%). Fractions containing the 3-ester **35** showed: R_f = 0.22 (10% EtOAc in hexanes); $[\alpha]^{25}_D$ = +8.4 (c = 1.53 in $CHCl_3$); IR (KBr) 3473, 2958, 2886, 2863, 1722, 1640, 1600, 1473, 1363, 1255, 1166, 1076, 1033, 1000, 865, 838, 781, 653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, 1H, J = 16.0 Hz), 7.60−7.50 (m, 2H), 7.5−7.2 (m, 3H), 6.55 (d, 1H, J = 16.0 Hz), 6.31 (d, 1H, J = 1.4 Hz), 6.21 (d, 1H, J = 1.6 Hz), 5.38 (t, 1H, J = 9.3 Hz), 5.20 (d, 1H, J = 12.7 Hz), 4.89 (d, 1H, J = 12.7 Hz), 4.44 (t, 1H, J = 10.1 Hz), 4.05−3.60 (m, 3H), 3.95−3.80 (m, 1H), 2.02 (d, 1H, J = 9.6 Hz), 1.06 (s, 9H), 1.04 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.31 (s, 3H), 0.27 (s, 3H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 158.4, 151.8, 144.8, 143.3, 134.6, 130.1, 128.8, 128.1, 119.7, 118.3, 110.9, 109.9, 105.2, 76.7, 74.8, 73.3, 71.6, 68.8, 66.7, 27.4, 27.0, 25.8, 25.6, 22.7, 19.9, 18.3, 18.1, −3.9, −4.3, −4.4; MS (FAB) *m/e* 799 ([M + H]$^+$), 651, 593, 395, 379, 337, 199, 131, 103, 73; HRMS (FAB) *m/e* calcd for $C_{42}H_{67}O_9Si_3$: ([M + H]$^+$), 799.4093; found: ([M + H]$^+$), 799.4078. Anal. Calcd for $C_{42}H_{66}O_9Si_3$:

C, 63.12; H, 8.32. Found: C, 62.81; H, 8.15%. Fractions containing the 2-ester **36** showed: $R_f = 0.28$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = -62.2$ ($c = 1.49$ in $CHCl_3$); IR (thin film) 3484, 2929, 2859, 1725, 1604, 1473, 1367, 1255, 1164, 1070, 1000, 962, 867, 836, 781, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, 1H, $J = 16.0$ Hz), 7.43−7.37 (m, 2H), 7.37−7.28 (m, 3H), 6.26 (d, 1H, $J = 16.0$ Hz), 6.25 (d, 1H, $J = 1.7$ Hz), 6.19 (d, 1H, $J = 1.8$ Hz), 5.84 (d, 1H, $J = 9.8$ Hz), 5.18, 5.10 (ABq, 2H, $J = 12.6$ Hz), 4.22 (dd, 1H, $J = 4.9, 9.5$ Hz), 4.18−4.08 (m, 2H), 4.02 (d, 1H, $J = 9.1$ Hz), 4.0−3.9 (m, 1H), 2.71 (b rs, 1H), 1.12 (s, 9H), 1.11 (s, 9H), 1.06 (s, 9H), 0.94 (s, 9H), 0.39 (s, 3H), 0.29 (s, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 158.5, 152.3, 144.7, 143.2, 134.4, 130.1, 128.8, 128.0, 118.7, 117.7, 109.7, 109.6, 104.7, 77.4, 73.5, 73.4, 73.2, 68.5, 66.6, 27.5, 27.1, 25.8, 25.6, 22.8, 20.0, 18.2, 18.1, −4.6, −5.1, −5.3, −5.5; MS (FAB) *m/e* 799 ($[M + H]^+$), 741, 651, 395, 379, 337, 131, 103, 73; HRMS (FAB) *m/e* calcd for $C_{42}H_{67}O_9Si_3$: ($[M + H]^+$), 799.4093; found: ($[M + H]^+$), 799.4070. Anal. Calcd for $C_{42}H_{66}O_9Si_3$: C, 63.12; H, 8.32. Found: C, 63.14; H, 8.60%.

(3*S*)-1-Bromo-3-methylpentane (39). Alcohol **38**[38] (32.6 g, 320 mmol), TsCl (66.6 g, 350 mmol), and pyridine (77 mL) in CH_2Cl_2 (50 mL) were stirred for 2 days under N_2. The mixture was added to water and Et_2O, and the aqueous layer was extracted with several portions of Et_2O. The combined organic layers were washed with water, dried, filtered, and evaporated *in vacuo* to leave the crude tosylate as a light brown oil. This was dissolved in Me_2CO (250 mL), and LiBr (70 g, 800 mmol) was added. The mixture was stirred overnight at room temperature, diluted with pentane, and washed with several portions of water. The pentane layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave a dark pink liquid. Double fractional distillation gave bromide **39** (30.8 g, 69%) as a clear liquid: bp 134 °C at 760 mmHg; $[\alpha]^{22}_D = +21.8$ (neat); IR (neat) 2980, 2940, 1470, 1390, 1260 cm^{-1}; ^1H ($CDCl_3$) δ 3.39−3.49 (m, 2H), 1.89−1.86 (m, 1H), 1.69−1.64 (m, 1H), 1.6−1.5 (m, 1H), 1.40−1.33 (m, 1H), 1.22−1.16 (m, 1H), 0.90−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.6, 33.1, 31.9, 28.9, 18.3, 11.1; HRMS (EI) calcd for $C_6H_{13}{}^{79}Br$: ($M^{\bullet+}$), 164.0201, $C_6H_{13}{}^{81}Br$: ($M^{\bullet+}$), 166.0180; found: ($M^{\bullet+}$), 166.0178, 164.0195.

(4*S*)-Methylhexanal (40). Bromide **39** (4.0 g, 24.2 mmol) in THF (5 mL) was added dropwise to Mg turnings (0.64 g, 26.6 mmol) and THF (30 mL) to maintain reflux. The mixture was subsequently heated to reflux for 1 h and cooled to 25 °C, and $Fe(CO)_5$ (3.35 mL, 25.4 mmol) was added. The resultant black mixture was stirred at 25 °C for 2 h, HOAc (3mL) was added, and the green solution was partitioned between Et_2O and H_2O. The aqueous layer was further extracted with Et_2O (3×) and the combined organic solutions were dried, filtered, and evaporated. Chromatography of the green residue (4% EtOAc in hexanes) and distillation gave aldehyde **40** (1.78 g, 64.5%) as a clear liquid: bp 84 °C at 45 mmHg; $R_f = 0.42$ (12% EtOAc in hexanes); $[\alpha]^{25}_D = +7.2$ (neat); IR (thin film) 2975, 2925, 2870, 2710, 1740, 1725, 1460, 1370, 1245, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, $J = 1.9$ Hz), 2.46−2.39 (m, 2H), 1.80−1.65 (m, 1H), 1.55−1.22 (m, 3H), 1.30−1.15 (m, 1H), 0.88 (t, 3H, $J = 7.1$ Hz), 0.88 (d, 3H, J = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 41.5, 33.8, 29.0, 28.3, 18.6, 11.0; MS (EI) *m/z* 114 ($M^{\bullet+}$), 96, 70. 2,4-Dinitrophenylhydrazone: mp = 79−82 °C (plates from EtOH); $R_f = 0.41$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +12.6$ ($c = 0.30$ in $CHCl_3$); IR (KBr) 3292, 2962, 2920, 1620, 1592, 1514, 1335, 1307, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.0 (s, 1H), 9.10 (d, 1H, $J = 2.5$ Hz), 8.29 (dd, 1H, $J = 2.5, 9.6$ Hz), 7.92 (d, 1H, $J = 9.6$ Hz), 7.54 (t, 1H, $J = 5.4$ Hz), 2.51−2.38 (m, 2H), 1.69−1.60 (m, 1H), 1.46−1.36 (m, 3H), 1.27−1.18 (m, 1H), 0.98−0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9, 145.1, 137.8, 130.0, 128.8, 123.5, 116.5, 34.0, 32.9, 30.2, 29.2, 18.9, 11.3; MS (CI) *m/e* 295 ($[M + H]^+$), 265, 259, 231, 171, 154, 114; HRMS (EI) *m/e* calcd for $C_{13}H_{19}N_4O_4$: ($[M + H]^+$), 295.1406; found: ($[M + H]^+$), 295.1408. Anal. Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.03. Found: C, 52.99; H, 6.15; N, 19.11%.

(3*RS*,6*S*)-6-Methyl-1-(trimethylsilyl)-1*E*-octen-3-ol (41). BuLi (1.8 M, 13.8 mL, 25 mmol) was added dropwise to 1*E*-(tributylstannyl)-2-(trimethylsilyl)ethene[39] (9.73 g, 25 mmol) in Et_2O (70 mL) and THF (70 mL) at −78 °C. After 1.5 h, aldehyde **40** (2.85 g, 25 mmol) in Et_2O (100 mL) was added dropwise (cannula), and the solution was subsequently allowed to warm up to room temperature over 1.5 h. The solution was added to aqueous NH_4Cl and Et_2O, and the aqueous phase was extracted with H_2O. The combined organic extracts were washed with H_2O, dried, filtered, and evaporated. Chromatography (4% EtOAc in hexanes) gave **41** (4.37 g, 82%) as a pale yellow oil: $R_f = 0.61$ (12% EtOAc in hexanes); bp 89 °C at 0.06 mmHg; IR (neat) 3360, 2980, 1630, 1470, 1260, 1000, 875, 850 cm^{-1}; ^1H ($CDCl_3$) δ 5.9 (dd, 1H, $J = 5.0, 18.5$ Hz), 5.7 (d, 1H, $J = 18.7$ Hz), 4.0 (br s, 1H), 3.4 (q, 1H $J = 7.5$ Hz), 1.5−1.0 (m, 7H), 0.8 (m, 6H), 0.0 (s, 9H); ^{13}C ($CDCl_3$) δ 148.73, 148.67, 129.1, 129.0, 75.00, 74.96, 34.4, 34.3, 32.1, 32.0, 29.4, 29.3, 19.2, 19.1, 11.3, −1.3; MS (EI) *m/e* 214 ($M^{\bullet+}$), 199, 157, 144, 129; HRMS (EI) calcd for $C_{12}H_{26}OSi$: ($M^{\bullet+}$), 214.1753; found: ($M^{\bullet+}$), 214.1739.

(6*S*)-6-Methyl-2*E*-octenal (42). PhSCl (0.431 g, 2.98 mmol) was added to alcohol **41** (0.533 g, 2.48 mmol) and Et_3N (0.52 mL, 3.72 mmol) in Et_2O (20 mL) at 0 °C. The white slurry was stirred at 0 ° for 0.5 h and at 25 °C for 2 h and washed with H_2O (3×) and the organic phase evaporated. The resultant oil was dissolved in MeCN and water (3:1; 20 mL), and $AgNO_3$ (0.422 g, 2.5 mmol) was added. After stirring overnight, the mixture was diluted with water and extracted with Et_2O (3×). The organic phase was washed with water, dried, filtered, and evaporated. Chromatography (12% EtOAc in hexanes) gave **42** (246 mg, 77%) as an oil: $R_f = 0.16$ (2.5% EtOAc in hexanes); IR (thin film) 2962, 2928, 2875, 2810, 2731, 1693, 1637, 1462, 1146, 1100, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.50 (d, 1H, $J = 7.4$ Hz), 6.80 (dt, 1H, $J = 6.8, 15.6$ Hz), 6.10 (ddt, 1H, $J = 1.3, 7.4, 15.6$ Hz), 3.00−2.29 (m, 2H), 1.62−1.45 (m, 1H), 1.31−1.23 (m, 3H), 1.25−1.05 (m, 1H), 1.00−0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.0, 159.2, 132.8, 34.5, 33.9, 30.4, 29.2, 18.9, 11.2; MS (EI) *m/e* 140 ($[M + H]^+$). 2,4-Dinitrophenylhydrazone: mp = 127−129 °C (fine needles from EtOH); $R_f = 0.24$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +12.3$ ($c = 1.47$, $CHCl_3$); IR (KBr) 3283, 2960, 2927, 2871, 1615, 1591, 1515, 1504, 1329, 1311, 1139, 1069, 990, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.07 (s, 1H), 9.10 (d, 1H, $J = 2.5$ Hz), 8.28 (dd, 1H, $J = 2.5, 9.6$ Hz), 7.90 (d, 1H, $J = 9.5$ Hz), 7.75 (d, 1H, $J = 8.6$ Hz), 6.49−6.22 (m, 2H), 2.38−2.22 (m, 2H), 1.52−1.47 (m, 1H), 1.42−1.23 (m, 3H), 1.23−1.12 (m, 1H), 0.95−0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 150.3, 146.5, 144.8, 138.0, 129.9, 129.2, 126.3, 123.4, 116.6, 35.3, 33.9, 30.7, 29.3, 19.0, 11.3; MS (EI) *m/e* 321 ($[M + H]^+$), 302, 291, 212, 140, 69; HRMS (EI) *m/e* calcd for $C_{15}H_{21}N_4O_4$: ($[M + H]^+$), 321.1563; found: ($[M + H]^+$), 321.1575; calcd for $C_{15}H_{24}N_5O_4$: ($[M + NH_4]^+$), 338.1828; found: ($[M + NH_4]^+$), 338.1825. Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.48. Found: C, 56.17; H, 6.28; N, 17.44%.

(*S*)-4-Methylhexanenitrile (44). TsCl (72.3 g, 0.38 mol) and pyridine (75.3 mL, 73.7 g, 0.93 mol) were added to (*S*)-3-methylpentanol[38] (**38**) (34.9 g, 0.35 mol) in dry CH_2Cl_2 (500 mL), and the mixture was stirred for 15 h at room temperature. The brown suspension was added to hydrochloric acid (1 M, 200 mL) and, after being shaken, the layers were separated. The organic layer was washed with water (2×) and dried. Filtration and evaporation gave a light brown oil, which was used without further purification. The crude tosylate and 18-crown-6 (1 g) were dissolved in THF (800 mL), and KCN (37.0 g, 0.56 mmol) was added. The mixture was heated to reflux for 2 days, at which point GC-MS analysis showed that all tosylate had been consumed. The mixture was added to Et_2O and water (1:1). The organic layer was extracted with water (4×), dried, filtered, and concentrated by distillation at ambient pressure. Fractional distillation gave nitrile **44** (30.8 g, 80%) as a colorless liquid: bp 167 °C; $[\alpha]^{25}_D = +12.4$ ($c = 1.86$ $CHCl_3$); IR (thin film) 2964, 2933, 2878, 2246, 1464, 1428, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38−2.31 (m, 2H), 1.71−1.62 (m, 1H), 1.51−1.27 (m, 3H), 1.21−1.09 (m, 1H), 0.92−0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 120.0, 33.5, 31.8, 28.7, 18.3, 14.9, 11.1; MS (EI) (*m*/z) 112 ($[M + H]^+$), 96, 82, 69, 55, 41; HRMS calcd for $C_7H_{14}N$: ($[M + H]^+$), 112.1126 and ($[M - H]^+$), 110.0970; found: ($[M + H]^+$) 112.1114 and ($[M - H]^+$), 110.0969.

Ethyl (*S*)-6-Methyl-2*E*-octenoate (45). DIBAL-H (1 M in hexanes, 79.0 mL, 79.0 mmol) was slowly added to nitrile **44** (8.0 g, 72.0 mmol) in Et_2O (250 mL) at −78 °C. The mixture was stirred for 2 h, at which time GC-MS analysis showed no **44** remaining. After warming up to 0 °C, sulfuric acid (5 N, 200 mL) was cautiously added, and the mixture was stirred vigorously for 1.5 h. The layers were separated, and the organic layer was washed with water (2×) and saturated aqueous $NaHCO_3$. The organic phase was dried to leave the crude aldehyde **40**, which was used without further purification. [(Ethoxycarbonyl)methylene]triphenylphosphorane (35.1 g, 100.0 mmol) was added to the crude aldehyde **40** in CH_2Cl_2 (100 mL), and the mixture was stirred overnight at room temperature. After concentration, the residue was dissolved in hexanes, and solids were removed by filtration. The filtrate was concentrated and the resultant yellow oil chromatographed (5% Et_2O in hexanes) to give ester **45** (11.3 g, 85%) as a colorless oil: $R_f = 0.65$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +10.7$ ($c = 2.22$, $CHCl_3$); IR (thin film) 2962, 2931, 1724, 1655, 1266, 1175, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (dt, 1H, $J = 7.0$, 15.6 Hz), 5.78 (dt, 1H, $J = 1.6$, 15.6 Hz), 4.14 (q, 2H, $J = 7.1$ Hz), 2.28−2.08 (m, 2H), 1.50−1.05 (m, 8H), 1.25 (t, 3H, $J = 7.1$ Hz), 0.83 (t, 3H, $J = 7.2$ Hz), 0.83 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 149.7, 121.0, 60.1, 34.7, 33.8, 29.8, 29.2, 18.9, 14.2, 11.2; MS (CI) *m*/*e* 185 ($[M + H]^+$), 173, 156, 139, 110, 96, 81; HRMS (CI) *m*/*e* calcd for $C_{11}H_{21}O_2$: ($[M + H]^+$), 185.1542; found: ($[M + H]^+$), 185.1558. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.51; H, 10.89%.

(*S*)-6-Methyl-2*E*-octen-1-ol. DIBAL-H (1 M in hexanes, 120 mL, 120.0 mmol) was added dropwise to ester **45** (9.57 g, 52.0 mmol) in Et_2O (200 mL) at −78 °C. After 30 min, the mixture was allowed to warm up to 0 °C and stirred for an additional 30 min. Water (40 mL) was slowly added at 0 °C, and the mixture was vigorously stirred for 20 min. The resulting gelatinous precipitate was removed by filtration through Celite, and the two layers were separated. The organic phase was washed a second time with water followed by brine. Drying, filtration, evaporation, and chromatography (10% EtOAc in hexanes) gave the title alcohol (7.30 g, 97%) as a colorless oil: $R_f = 0.15$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +11.1$ ($c = 1.55$, $CHCl_3$); IR (thin film) 3325, 2961, 2924, 2874, 2856, 1462, 1377, 1089, 1004, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.73−5.52 (m, 2H), 4.04 (d, 2H, $J = 4.6$ Hz), 2.10−1.90 (m, 2H), 1.59 (s, 1H), 1.41−1.22 (m, 5H), 0.83 (t, 3H, $J = 7.2$ Hz), 0.83 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 128.6, 63.8, 35.9, 33.9, 29.7, 29.3, 19.0, 11.3; MS (EI) *m*/*e* 142 ($M^{\bullet+}$), 124, 109, 95, 83, 70, 57, 43; HRMS (EI) *m*/*e* calcd for $C_9H_{18}O$: ($M^{\bullet+}$), 142.1358; found: ($M^{\bullet+}$), 142.1339. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.70; H, 12.46%.

Ethyl (*S*)-2,8-Dimethyldeca-2*E*,4*E*-dienoate (43). Pyridinium chlorochromate (16.40 g, 76.0 mmol) was added in small portions to (*S*)-6-methyl-2*E*-octenol (7.18 g 50.6 mmol), silica gel (50 g), and CH_2Cl_2 (200 mL). The slurry was stirred at 25 °C for 3 h, filtered through silica, and evaporated to leave crude aldehyde **42** identical with the previous sample and which was used without further purification. [(Ethoxycarbonyl)ethylidene]triphenylphosphorane (22.0 g, 60.7 mmol) was added to **42** in CH_2Cl_2 (200 mL). After being stirred overnight at room temperature, the mixture was evaporated and the residue was dissolved in hexanes. Filtration through Celite, concentration, and chromatography (2% EtOAc in hexanes) gave ester **43** (7.60 g, 67%) as a colorless oil: $R_f = 0.32$ (4% EtOAc in hexanes); $[\alpha]^{25}_D = +9.8$ (neat); IR (thin film) 2985, 1720, 1650, 1250, 1115, 985, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, 1H, $J = 11.1$ Hz), 6.30 (dd, 1H, $J = 11.2$, 15.0 Hz), 6.09 (m, 1H), 4.20 (q, 2H, $J = 7.1$ Hz), 2.30−2.10 (m, 2H), 1.92 (s, 3H), 1.58−1.05 (m, 5H), 1.29 (t, 3H, $J = 7.2$ Hz), 0.85 (d, 3H, $J = 6.1$ Hz), 0.80 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.4, 143.2, 138.4, 125.7, 60.2, 35.6, 33.8, 30.8, 29.2, 18.8, 14.2, 12.4, 11.2; MS (EI) *m*/*e* 224 ($M^{\bullet+}$), 179, 139; HRMS (EI) *m*/*e* calcd for $C_{14}H_{24}O_2$: ($M^{\bullet+}$), 224.1776; found: ($M^{\bullet+}$), 224.1764. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.86; H, 10.80%.

(*S*)-2,8-Dimethyldeca-2*E*,4*E*-dien-1-ol. DIBAL-H (1 M in hexanes, 2.20 mL) was slowly added to ester **43** (200 mg, 0.89 mmol) in Et_2O (5 mL) at −78 °C. After 30 min at −78 °C and 30 min at 0 °C, water (5 mL) was added, the gelatinous mixture was filtered through Celite, and the layers were separated. The organic solution was washed with water and brine, dried, and evaporated. Chromatography (10 to 25% EtOAc in hexanes) gave the title dienol (156 mg, 98%) as a colorless, unstable oil: $R_f = 0.14$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +10.1$ ($c = 0.082$, ether); IR (thin film) 3317, 2960, 1462, 1377, 1008, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.25 (ddt, 1H, $J = 10.9$, 15.0, 1.3 Hz), 6.00 (d, 1H, $J = 10.7$ Hz), 5.70 (dt, 1H, $J = 15.0$, 7.0 Hz), 4.01 (s, 2H), 2.20−2.00 (m, 2H), 1.78 (s, 3H), 1.68 (s, 1H), 1.42−1.28 (m, 3H), 1.22−1.08 (m, 2H), 0.84 (t, 3H, $J = 7.2$ Hz), 0.84 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5, 134.6, 125.6, 125.3, 68.6, 36.2, 33.8, 30.5, 29.3, 19.0, 14.0, 11.3; MS (CI) *m*/*e* 181 ($[M + H]^+$), 163, 110, 95, 81, 58, 44; HRMS (CI) *m*/*e* calcd for $C_{12}H_{21}O$: ($[M + H]^+$), 181.1592; found: ($[M + H]^+$), 181.1609.

(*S*)-2,8-Dimethyl-2*E*,4*E*-dienal (46). Manganese dioxide (671 mg, 7.72 mmol) was added to (*S*)-2,8-dimethyldeca-2*E*,4*E*-dienol (174 mg, 0.96 mmol) in CH_2Cl_2 (20 mL) and the mixture stirred for 18 h. Filtration through silica gel (20% EtOAc in hexanes), evaporation, and chromatography (5% EtOAc in hexanes) gave **46** (166 mg, 96%) as a colorless oil: $R_f = 0.48$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +10.1$ ($c = 0.135$, Et_2O); IR (thin film) 2960, 2925, 2874, 2708, 1681, 1634, 1461, 1211, 1008, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.37 (s, 1H), 6.82 (d, 1H, $J = 10.9$ Hz), 6.52 (ddt, 1H, $J = 11.1$, 15.0, 1.4 Hz), 6.20 (dt, 1H, $J = 7.0$, 15.0 Hz), 2.30−2.10 (m, 2H), 1.79 (s, 3H), 1.50−1.05 (m, 5H), 0.90−0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.0, 149.3, 146.2, 135.8, 125.6, 35.5, 33.9, 31.0, 29.2, 18.9, 11.2, 9.3; MS (EI) *m*/*e* 180 ($M^{\bullet+}$), 151, 95, 82, 55, 41; HRMS (EI) *m*/*e* calcd for $C_{12}H_{20}O$: ($M^{\bullet+}$), 180.1513; found: ($M^{\bullet+}$), 180.1514. 2,4-Dinitrophenylhydrazone: mp = 128−130 °C (fine needles from EtOH); $R_f = 0.29$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = +16.1$ ($c = 0.16$, $CHCl_3$); IR (KBr disk) 3293, 2964, 2853, 1615, 1599, 1512, 1332, 1135, 1081, 977, 829, 741, 723, 608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 11.15 (br s, 1H), 9.10 (d, 1H, $J = 2.3$ Hz), 8.30 (dd, 1H, $J = 2.5$, 9.6 Hz), 7.95 (d, 1H, $J = 9.6$ Hz), 7.71 (s, 1H), 6.49 (m, 1H), 6.38 (d, 1H, $J = 11.1$ Hz), 6.00 (dt, 1H, $J = 7.2$, 14.3 Hz), 2.35−2.15 (m, 2H), 2.05 (s, 3H), 1.55−1.15 (m, 5H), 0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 144.7, 141.9, 139.5, 137.9, 130.8, 129.9, 129.1, 125.9, 123.5, 116.7, 35.9, 34.0, 31.0, 29.3, 19.0, 11.6, 11.3; MS (CI) 361 ($[M + H]^+$), 331, 212, 180, 171, 94; HRMS (CI) *m*/*e* calcd for $C_{18}H_{25}N_4O_4$: ($[M + H]^+$), 361.1876; found: ($[M + H]^+$), 361.1902. Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.54. Found: C, 59.97; H, 6.72; N, 15.46%.

Standard preparation of (*R*)-Mosher Esters from Alcohols. (*N*,*N*-Dimethylamino)pyridine (0.33 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.33 mmol) were added to the alcohol (0.11 mmol) in CH_2Cl_2 (1 mL). After 2 h at room temperature, water (5 mL) and EtOAc (5 mL) were added. The organic phase was washed with saturated aqueous $NaHCO_3$ (2×), dried, and filtered. The crude ester fraction was filtered through silica to provide the Mosher ester for ^1H NMR analysis.

(4*RS*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-ol (47). Propargyl bromide (9.40 mL, 1.05 mmol) was added to activated zinc dust (66.7 mg, 1.05 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred for 1 h. Aldehyde **46** (95.0 mg, 0.52 mmol) in THF (2 mL) was added, and the mixture stirred for 1 h at 0 °C. After warming up to room temperature, saturated aqueous NH_4Cl (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with water (2×) and brine, dried, filtered, and evaporated. Chromatography (10% EtOAc in hexanes) gave **47** (120 mg, 96%) as a colorless, unstable oil: $R_f = 0.21$ (10% EtOAc in hexanes); IR (thin film) 3312, 3026, 2961, 2918, 2874, 2221, 1462, 1378, 1015, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.22 (ddt, 1H, $J = 11.1$, 14.5, 1.4 Hz), 6.05 (d, 1H, $J = 10.8$ Hz), 5.70 (dt, 1H, $J = 7.0$, 14.3 Hz), 4.19 (t, 1H, $J = 6.7$ Hz), 2.45 (dd, 2H, $J = 2.5$, 6.4 Hz), 2.20−2.03 (m, 2H), 2.03 (t, 1H, $J = 2.4$ Hz), 1.72 (s, 3H), 1.50−1.08 (m, 5H), 0.89 (d, 3H, $J = 5.8$ Hz), 0.83 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 136.1, 134.8, 126.3, 125.4, 80.8, 75.1, 70.5, 36.1, 33.9, 30.5, 29.3, 25.8, 19.0, 12.1, 11.2; MS (CI) *m*/*e* 220 ($[M + NH_4 - H_2O]^+$), 203, 181, 163,

133, 119, 93, 81; HRMS (CI) *m/e* calcd for $C_{15}H_{26}N$: ([M − H_2O + NH_4]$^+$), 220.2065; found: ([M − H_2O + NH_4]$^+$), 220.2054. The mixture of Mosher esters **67** and **68** was prepared according to the general procedure, key ^{1}H NMR data are listed in Table 1; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention times 14.21, 15.57 min (ratio 31:32).

***tert*-Butyldimethyl[[(4*RS*,11*S*)-5,11-dimethyltrideca-5*E*,7*E*-dien-1-yn-4-yl]oxy]silane (48).** *tert*-Butyldimethylsilyl chloride (249 mg, 1.65 mmol), imidazole (126 mg, 1.86 mmol), and 4-(dimethylamino)pyridine (10 mg) were added to alcohol **47** (340 mg, 1.50 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 4.5 h, quenched by the addition of saturated aqueous NH_4Cl (2 mL), and extracted with Et_2O (3×). The organic extracts were washed with water (3×), dried, filtered, and evaporated. The resultant pale yellow oil was chromatographed (5% EtOAc in hexanes) to yield **48** (500 mg, 95%) as a colorless, viscous oil: R_f = 0.25 (neat hexanes); IR (thin film) 3314, 2958, 2929, 2857, 1471, 1463, 1388, 1378, 1361, 1252 1078, 1006, 966, 937, 838, 777, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (ddt, 1H, J = 1.4, 10.8, 15.0 Hz), 5.95 (d, 1H, J = 10.7 Hz) 5.65 (dt, 1H, J = 6.9, 14.9 Hz), 4.17 (t, 1H, J = 6.5 Hz), 2.50−2.30 (m, 2H), 2.20−2.00 (m, 2H), 1.94 (t, 1H, J = 2.6 Hz), 1.69 (s, 3H), 1.50−1.10 (m, 5H), 0.95−0.80 (m, 15H), 0.07 (2s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.9, 135.3, 126.2, 125.7, 81.9, 77.1, 69.6, 36.2, 34.1, 30.6, 29.4, 27.1, 25.8, 19.1, 18.2, 11.5, 11.3, −4.8, −5.0. Anal. Calcd for $C_{21}H_{38}OSi$: C, 75.37; H, 11.44. Found: C, 75.28; H, 11.42%.

[[(4*RS*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-yl]oxy]triethylsilane (49). Et_3SiCl (252 mg, 281 μL, 1.68 mmol), imidazole (274 mg, 2.23 mmol), and 4-(dimethylamino)-pyridine (114 mg, 1.67 mmol) were added to alcohol **47** (246 mg, 1.11 mmol) in CH_2Cl_2 (5 mL). After 30 min, water (2 mL) was added and the mixture extracted with EtOAc. The organic layer was washed with water and brine, dried, filtered, and evaporated. Chromatography (5% CH_2Cl_2 in hexanes) gave **49** (355 mg, 95%) as a colorless, viscous oil: R_f = 0.25 (hexanes); IR (thin film) 3314, 2956, 2876, 2100, 1460, 1239, 1074, 1006, 966, 743, 635 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.20 (ddt, 1H, J = 1.4, 12.3, 15.1 Hz), 5.95 (d, 1H, J = 10.9 Hz), 5.65 (dt, 1H, J = 6.9, 15.0 Hz), 4.15 (t, 1H, J = 6.6), 2.42−2.30 (m, 2H), 2.18−2.00 (m, 2H), 1.92 (t, 1H, J = 2.6 Hz), 1.68 (s, 3H), 1.45−1.10 (m, 5H), 0.96−0.90 (m, 6H), 0.81−0.88 (m, 9H), 0.60−0.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.9, 135.4, 126.2, 125.6, 81.8, 69.6, 36.2, 34.0, 30.6, 29.4, 27.0, 19.1, 11.5, 11.3, 6.8, 4.8; MS (CI) *m/e* 352 ([M + NH_4]$^+$), 295, 205; HRMS (CI) *m/e* calcd for $C_{21}H_{42}NOSi$: ([M + NH_4]$^+$), 252.3036; found: ([M + NH_4]$^+$), 252.3067. Anal. Calcd for $C_{21}H_{38}OSi_4$: C, 75.38; H, 11.45. Found: C, 75.45; H, 11.73.

Methyl (7*RS*,14*S*)-8,14-Dimethyl-7-[(*tert*-butyldimethylsilyl)oxy]-2*E*,4*E*,8*E*, 10*E*-hexadecanetetraenoate (50). Alkyne **48** (500 mg, 1.5 mmol) in THF (10 mL) was added, *via* a cannula, to a slurry of $Cp_2Zr(H)Cl$ (420 mg, 1.63 mmol) in THF (20 mL) at 0 °C. The mixture was stirred in the dark at room temperature for 6 h, cooled to 0 °C, and I_2 (390 mg, 1.5 mmol) in THF (10 mL) was added dropwise. The solution was partitioned between aqueous sodium thiosulfate and Et_2O and the aqueous phase reextracted with Et_2O (2×). The combined organic extracts were washed with water, dried, and evaporated to leave a yellow oil. This was dissolved in DMF (10 mL) to which was added methyl 3-(tributylstannyl)-*E*-acrylate[64] (560 mg, 1.5 mmol) and $(MeCN)_2PdCl_2$ (10 mg, 5 mol %). After 1 h, the black reaction mixture was added to aqueous ammonia and extracted with Et_2O (3×). The combined organic extracts were washed with water, dried, evaporated, and chromatographed (4% EtOAc in hexanes) to give ester **50** (120 mg, 30%) as a yellow oil: R_f = 0.41 (4% EtOAc in hexanes); IR (thin film) 2956, 2929, 2856, 1723, 1645, 1259, 1136, 1067, 1001, 966, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31−7.24 (dd, 1H, J = 10.7, 15.4 Hz), 6.26−6.17 (m, 2H), 6.13−6.07 (pentet, 1H, J = 7.4, 14.8 Hz), 5.95 (d, 1H, J = 11.3 Hz), 5.8 (d, 1H, J = 15.4 Hz), 5.7−5.6 (app pentet, 1H, J = 7.2, 14.6 Hz), 4.1 (dt, 1H, J = 5.2, 7.2 Hz), 3.77 (s, 3H), 2.5−2.3 (m, 2H), 2.2−2.0 (m, 2H), 1.71 (s, 3H), 1.5−1.1 (m, 5H), 0.90 (m with s, 15H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 145.1, 141.1, 136.6, 135.1, 132.4, 130.1, 125.6, 125.5, 119.0, 77.5, 51.3, 40.6, 36.2, 34.0, 30.6, 29.3, 25.8, 19.0, 18.1, 11.9, 11.3, −4.7, −5.1; MS (FAB) *m/e* 419, 363, 295; HRMS (FAB) *m/e* calcd for $C_{18}H_{35}OSi$: ([M − $C_7H_9O_2$]$^+$), 295.2457; found: ([M − $C_7H_9O_2$]$^+$), 295.2432.

Methyl (7*RS*,14*S*)-8,14-Dimethyl-7-[(triethylsilyl)oxy]-2*E*,4*E*,8*E*,10*E*-hexadecanetetraenoate (51). Alkyne **49** (500 mg, 1.49 mmol) in THF (5 mL) was added, *via* a cannula, to a slurry of $Cp_2Zr(H)Cl$ (462 mg, 1.79 mmol) in THF (5 mL). The mixture was stirred in the dark at room temperature until a homogenous solution was formed (45 min). Separately, DIBAL-H (1 M in hexanes, 300 μL, 0.30 mmol) was added to a slurry of $(Ph_3P)_2PdCl_2$ (104 mg, 0.15 mmol) in THF (1 mL) at room temperature. After stirring for 10 min, the black palladium mixture followed by a solution of methyl 3-bromo-*E*-acrylate[46] (296 mg, 1.79 mmol) in THF (1 mL) were added, *via* a cannula, to the zirconocene derivative. The reaction mixture was left to stir in the dark, at room temperature for 15 h and poured into water and EtOAc. The organic phase was washed with brine, dried, evaporated, and chromatographed (2.5% EtOAc in hexanes) to give **51** (514 mg, 82%) as a viscous oil: R_f = 0.45 (5% EtOAc in hexanes); IR (thin film) 2954, 2911, 2875, 1722, 1644, 1459, 1434, 1261, 1241, 1133, 1064, 1000, 964, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (dd, 1H, J = 10.8, 15.3 Hz), 6.15−6.08 (m, 2H), 6.10−6.02 (m, 1H), 5.91 (d, 1H, J = 10.8 Hz), 5.79 (d, 1H, J = 15.4), 5.64 (dt, 1H, J = 7.0, 15.0 Hz), 4.05 (t, 1H, J = 5.8 Hz), 3.76 (s, 3H), 2.43−2.30 (m, 2H), 2.18−2.02 (m, 2H), 1.69 (s, 3H), 1.48−1.30 (m, 3H), 1.28−1.10 (m, 2H), 0.98−0.85 (m, 15H), 0.60−0.50 (m 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 145.1, 141.1, 136.7, 135.2, 130.0, 125.6, 125.5, 119.1, 77.4, 51.4, 40.5, 36.2, 34.1, 30.6, 29.4, 19.1, 11.9, 11.3, 6.8, 4.8; MS (CI) *m/e* 421 ([M + H]$^+$), 391, 306, 289, 229, 132; HRMS (CI) *m/e* calcd for $C_{25}H_{45}O_3Si$: ([M + H]$^+$), 421.3138; found: ([M + H]$^+$), 421.3102. Anal. Calcd for $C_{25}H_{44}O_3Si$: C, 71.37; H, 10.54. Found: C, 71.32; H, 10.56%.

(4*S*,11*S*)-5,11-Dimethyl-4-trideca-5*E*,7*E*-dien-1-yn-4-yl (*R*)-2-Methoxy-2-phenylacetate (55) and (4*R*,11*S*)-5,-11-Dimethyl-4-trideca-5*E*,7*E*-dien-1-yn-4-yl (*R*)-2-Methoxy-2-phenylacetate (56). Trifluoromethanesulfonic anhydride (141 μL, 209 mg, 0.99 mmol) was added dropwise to (*R*)-*O*-methylmandelic acid (116 mg, 0.99 mmol) and pyridine (161 μL, 157 mg, 1.99 mmol) in CH_2Cl_2 (4 mL) at −78 °C. The mixture was stirred at −78 °C for 10 min and then added, *via* cannula, to the alcohol **47** (110 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The mixture was slowly warmed up to room temperature when saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (25 mL) were added. The separated organic phase was washed with aqueous calcium sulfate (1 M, 5 mL) and dried. Filtration, evaporation, and chromatography (5% EtOAc in hexanes) gave the more polar diastereoisomer (26 mg, 14%) and the less polar diastereoisomer (29 mg, 16%). The more polar diastereoisomer showed: R_f = 0.28 (10% EtOAc in hexanes); IR (film) 3311, 2360, 1754, 1455, 1248, 1171, 1029, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.30 (m, 5H), 6.05 (dd, 1H, J = 10.8, 14.8 Hz), 5.75 (d, 1H, J = 10.9 Hz), 5.55 (dt, 1H, J = 6.9, 15.0 Hz), 5.34 (t, 1H, J = 6.7 Hz), 4.79 (s, 1H), 3.41 (s, 3H), 2.52−2.33 (m, 2H), 2.20−1.95 (m, 2H), 1.95 (t, 1H, J = 2.1 Hz), 1.49 (s, 3H), 1.50−1.00 (m, 5H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 137.1, 136.2, 130.2, 128.6, 128.4, 128.3, 127.0, 124.9, 82.5, 79.0, 77.1, 70.3, 57.2, 35.9, 33.7, 30.4, 29.2, 22.9, 18.9, 12.3, 11.1; HRMS calcd for $C_{24}H_{32}O_3$: ($M^{\bullet+}$), 368.2351; found: ($M^{\bullet+}$), 368.2357. The less polar diastereoisomer showed: R_f = 0.33 (EtOAc in hexanes); IR (thin film) 3311, 2360, 1754, 1455, 1248, 1171, 1029, 967 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 −7.20 (m, 5H), 6.15 (dd, 1H, J = 10.9, 12.9 Hz), 6.00 (d, 1H, J = 10.9 Hz), 5.70 (dt, 1H, J = 7.0, 14.8 Hz), 5.35 (t, 1H, J = 6.8 Hz), 4.77 (s, 1H), 3.43 (s, 3H), 2.50−2.30 (m, 2H), 2.30−2.20 (m, 2H), 1.78 (t, 1H, J = 2.3 Hz), 1.64 (s, 3H), 1.50−1.00 (m, 5H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 136.7, 136.1 130.1, 128.4, 128.3, 127.9, 127.2, 124.8, 82.3, 79.3, 76.7, 70.3, 57.0, 35.9, 33.7, 29.2, 23.2, 18.8, 12.2, 11.1; HRMS calcd for $C_{24}H_{32}O_3$: ($M^{\bullet+}$), 368.2351; found: ($M^{\bullet+}$), 368.2357.

(64) Curran, D. P. *Synthesis* **1988**, 417, 489.

(4*S*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-ol (53). Titanium tetraisopropoxide (1.30 g, 4.56 mmol), D-(−)-diisopropyl tartrate (1.83 g, 5.48 mmol) and *tert*-butyl hydroperoxide in CH_2Cl_2 (4.26 M; 1.29 mL) were added to a slurry of powdered 4 Å molecular sieves (1.5 g) in CH_2Cl_2 (40 mL) at −20 °C. After 30 min, alcohol **47** (2.0 g, 9.13 mmol) in CH_2Cl_2 (10 mL) and slowly added to the mixture at −50 °C *via* a syringe pump (4 mL/h). The reaction mixture was stirred at −50 °C for 70 h and quenched with water (6 mL) at −50 °C. After being warmed up to room temperature, the mixture was filtered through Celite, and the filtrate was partitioned between EtOAc and brine. The organic phase was dried, filtered, evaporated, and chromatographed (10% EtOAc in hexanes) to give **53** (900 mg, 45%) and epoxide **52** (307 mg, 14%) both as viscous, colorless oils. Alcohol **53** showed: $[\alpha]^{25}_D = +16.5$ ($c = 1.49$, $CHCl_3$); all spectroscopic data were identical with those from **47**. The Mosher ester **67** was prepared according to the general procedure, key ^{1}H NMR data are listed in Table 1; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention times 14.21, 15.57 min (ratio 66:3). Epoxide **52** showed: $R_f = 0.12$ (10% EtOAc in hexanes); IR (thin film) 3458, 3313, 2962, 2924, 2874, 1462, 1380, 1069, 969, 849, 727, 633 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.95 (dt, 1H, $J = 7.0$, 15.5 Hz), 5.35 (ddt, 1H, $J = 1.4$, 8.0, 15.4 Hz), 3.90−3.80 (m, 1H), 3.59 (d, 1H, $J = 8.0$ Hz), 2.52−2.35 (m, 3H), 2.21−2.00 (m, 3H), 1.50−1.08 (m, 7H), 0.95−0.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.5, 139.6, 129.7, 126.7, 83.6, 78.5, 74.6, 73.9, 72.8, 66.9, 63.4, 39.1, 37.3, 33.6, 31.7, 26.2, 22.4, 17.7, 15.6, 14.6; MS (CI) *m*/*e* 237 ([M + H]$^+$), 219, 197, 179, 167, 151, 135, 123, 109, 95, 81; HRMS (EI) calcd for $C_{15}H_{25}O_2$: ([M + H]$^+$), 237.1855; found: ([M + H]$^+$), 237.1846.

(4*R*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-ol (57). Reaction of titanium tetraisopropoxide (202 μL, 0.68 mmol), L-(+)-diisopropyl tartrate (172 μL, 0.82 mmol), *tert*-butyl hydroperoxide in CH_2Cl_2 (4.27 M; 191 μL), and 4 Å molecular sieves (0.3 g) in CH_2Cl_2 (2 mL) with alcohol **47** (300 mg, 1.36 mmol) in CH_2Cl_2 (8 mL) at −20 °C and workup as for **53** gave alcohol **57** (121 mg, 40%) and an epoxide (53 mg, 33%) both as viscous, colorless oils. The alcohol **57** showed $[\alpha]^{25}_D = +4.5$ ($c = 1.07$, $CHCl_3$), with other spectroscopic data identical with that for **47** and **53**. The Mosher ester **68** was prepared according to the general procedure, key ^{1}H NMR data are listed in Table 1. The epoxide side product was not characterized further.

{**[(4*S*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-yl]oxy}triethylsilane.** Et_3SiCl (923 mg, 1.02 mL, 6.13 mmol), imidazole (1.00 g, 8.17 mmol), 4-(dimethylamino)pyridine (417 mg, 6.13 mmol), and alcohol **53** (900 mg, 4.09 mmol) in CH_2Cl_2 (12 mL) were allowed to react at room temperature for 0.5 h before being quenched by the addition of water (10 mL) and extracted with EtOAc. The organic phase was washed with water and brine, dried, filtered, and evaporated. Chromatography (5% CH_2Cl_2 in hexanes) gave the title ether (1.34 g, 98%) as a colorless, viscous oil: $[\alpha]^{25}_D = +15.2$ ($c = 1.26$ in $CHCl_3$); other spoectroscopic data were identical with those from **49**.

{**[(4*R*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-yl]oxy}triethylsilane.** Reaction of Et_3SiCl (111 μL, 0.66 mmol), imidazole (112 mg, 1.65 mmol), 4-(dimethylamino)pyridine (80 mg, 0.66 mmol), and alcohol **55** (121 mg, 0.55 mmol) in CH_2Cl_2 (1 mL) and workup as in the preceding experiment gave the title silane (165 mg, 90%): $[\alpha]^{25}_D = -4.0$ ($c = 0.885$ in $CHCl_3$) with all other data identical with that for **49** and the (4*S*)-epimer.

Methyl (7*S*,14*S*)-8,14-Dimethyl-7-[(triethylsilyl)oxy]-2*E*,4*E*,8*E*,10*E*-hexadecanetetraenoate (54). {[(4*S*,11*S*)-5,11-Dimethyltrideca-5*E*,7*E*-dien-1-yn-4-yl]oxy}triethylsilane (200 mg, 0.60 mmol) in THF (2.0 mL) was added, *via* a cannula, to a slurry of $Cp_2Zr(H)Cl$ (170 mg, 0.66 mmol) in THF (2.5 mL). The mixture was stirred at room temperature in the dark until a homogenous solution was formed (45 min). Separately, DIBAL-H (1 M in hexanes, 120 μL, 0.12 mmol) was added to a slurry of $(Ph_3P)_2PdCl_2$ (42 mg, 0.06 mmol) in THF (1 mL) at room temperature. After 10 min, the black palladium mixture was transferred, *via* a cannula, into the zirconium mixture followed by a solution of methyl 3-bromo-*E*-acrylate[46] (118 mg, 0.72 mmol) in THF (1 mL). After stirring in the dark at room temperature for 15 h, the mixture was added to water and EtOAc. The organic phase was washed with brine, dried, and evaporated. Chromatography (2.5% EtOAc in hexanes) gave **54** (176 mg, 70%) as a viscous oil: $[\alpha]^{25}_D = +16.0$ ($c = 0.85$ in $CHCl_3$); other spectroscopic data were identical with those from **51**.

Methyl (7*RS*,14*S*)-8,14-Dimethyl-4-hydroxy-2*E*,4*E*,8*E*,-10*E*-hexadecanetetraenoate (65/66). Tetrabutylammonium fluoride in THF (1 M; 200 μL) was added to ether **51** (42 mg, 0.10 mmol) in THF (1 mL) at 0 °C. After 30 min, the solution was added to water and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried, filtered, and evaporated. Chromatography (25% EtOAc in hexanes) gave the title alcohol (36 mg, 100%): $R_f = 0.31$ (25% EtOAc in hexanes); IR (thin film) 3440, 2959, 2924, 2874, 1721, 1644, 1617, 1434, 1262, 1135, 1000, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.25 (dd, 1H, $J = 10.5$, 14.5 Hz), 6.31−6.19 (m, 2H), 6.14−6.05 (m, 1H), 6.0 (d, 1H, $J = 10.8$ Hz), 5.82 (d, 1H, $J = 15.4$ Hz), 5.72 (dt, 1H, $J = 7.0$, 15.0 Hz), 4.14 (t, 1H, $J = 6.5$ Hz), 3.74 (s, 3H), 2.45 (t, 2H, $J = 6.9$ Hz), 2.25−2.05 (m, 2H), 1.75 (d, 3H, $J = 0.5$ Hz), 1.5−1.3 (m, 3H), 1.3−1.1 (m, 2H), 0.95−0.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 144.8, 140.0, 136.2, 136.0, 130.7, 126.1, 125.4, 119.6, 77.0, 51.5, 38.9, 36.3, 34.0, 30.6, 29.4, 19.1, 12.2, 11.3; MS (CI) *m*/*e* 324 ([M + NH_4]$^+$), 307 ([M + H]$^+$), 289, 229, 181, 163, 126, 93; HRMS (CI) *m*/*e* calcd for $C_{19}H_{34}NO_3$: ([M + NH_4]$^+$), 324.2539; found: 324.2543; calcd for $C_{19}H_{31}O_3$: ([M + H]$^+$), 307.2273; found: ([M + H]$^+$), 307.2291. The mixture of Mosher esters **62** and **63** was prepared according to the general procedure; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention times 22.1, 26.4 min (ratio 20.4:21.4).

Methyl (7*S*,14*S*)-8,14-Dimethyl-4-hydroxyhexadecane-2*E*,4*E*,8*E*,10*E*-tetraenoate (65). Tetrabutylammonium fluoride in THF (1 M; 238 μL) and silyl ether **54** (50 mg, 0.12 mmol) in THF (1 mL) were stirred at 0 °C for 30 min and added to water, and the resulting mixture was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried, filtered, and chromatographed (25% EtOAc in hexanes) to give alcohol **65** (43 mg, 100%): $[\alpha]^{25}_D = +4.9$ ($c = 1.31$ in $CHCl_3$, 96% de); all spectroscopic data were identical with those from **65**/**66**. The Mosher ester **62** was prepared according to the general procedure; key ^{1}H NMR data are listed in Table 2; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention times 22.1, 26.1 min (ratio 2.1:95.2); ^{1}H NMR ($CDCl_3$, 500 MHz) see Table 2; ^{13}C NMR (C_6D_6, 125 MHz) δ 166.8, 165.7, 144.2, 137.7, 137.5, 133.0, 131.7, 130.9, 129.7, 129.6, 128.5, 128.3, 128.2, 128.0, 127.8, 125.4, 123.1, 121.0, 80.6, 55.5, 51.0, 36.5, 36.4, 34.2, 30.9, 29.7, 19.1, 12.2, 11.5.

Methyl (7*R*,14*S*)-8,14-Dimethyl-4-hydroxyhexadecane-2*E*,4*E*,8*E*,10*E*-tetraenoate (66). The ester **66** was prepared from alcohol **57** via the corresponding triethylsilyl ether and **58** and desilylation using exactly the same methods as for the epimer **65**. Alcohol **66** was spectroscopically identical with the both the mixture of **65** and **66** and the sample of **65** derived via Sharpless epoxidation. The Mosher ester **63** was prepared according to the general procedure; $[\alpha]^{25}_D = +45.0$ ($c = 1.65$ in $CHCl_3$); key ^{1}H NMR data are listed in Table 2; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention time 22.1 min only; ^{1}H NMR ($CDCl_3$, 500 MHz) see Table 2; ^{13}C NMR (C_6D_6, 125 MHz) δ 166.8, 165.9, 144.3, 138.0, 137.1, 133.1, 131.6, 130.8, 130.2, 129.7, 128.6, 128.3, 128.2, 128.0, 127.8, 125.4, 120.9, 80.5, 55.3, 51.0, 36.4, 36.3, 34.2, 30.9, 30.2, 29.6, 19.1, 12.3, 11.4.

Fermentation of *P. spherosperma*. *P. spherosperma* was obtained stored at 4 °C as slants from the United States Department of Agriculture, Peoria, IL (NRRL 8086). An agar medium (200 mL) consisted of yeast extract (0.8 g), malt extract (2 g), glucose (0.8 g), and agar (4 g) adjusted to pH 8 before sterilization. The slants were incubated at 25 °C, and growth was observed after 48 h, with exponential growth being observed after 6 days at which point the slopes were cooled to 4 °C for storage. A nutrient broth (1300 mL) containing soybean meal (2%, 26 g) and mannitol (2%, 26 g) was prepared and adjusted to pH 8.2, with NaOH (1 M), before being divided into five flasks: Two Erlenmeyer flasks (2 L) with four baffles each containing 500 mL of broth and three Erlenmeyer flasks (500 mL) each containing nutrient broth (100 mL) were steri-

lized. Two of the 500 mL flasks, from above, were inoculated with *P. spherosperma* by washing one of the previously prepared slants with pH 7 buffer (5 mL), agitating the surface and transferring the liquid to the flask. A separate culture slant was used for each flask of nutrient broth and they were labeled A and B. Flasks A and B were then shaken at 450 rpm at 24 °C for 2 days. A small amount of the liquid used to inoculate flasks A and B was inspected for bacterial contamination by incubating at 37 °C on a nutrient agar. However, after 4 days no growth was seen. The two 2 L flasks (containing 500 mL of broth) were inoculated with the two day old broth (A and B) and these flasks were labeled A′ and B′. A′ and B′ were shaken at 750 rpm at 24 °C for 2 days. Again, both inoculants were examined for bacterial contamination and, as before, no growth was observed. A 20 L fermenter was filled with nutrient broth (15 L) made from mannitol (300 g) and soybean meal (300 g). The fermenter and nutrient broth were sterilized and inoculated with the two day old cultures A′ and B′ (500 mL of each). The mixture was stirred at 390 rpm with 0.5 L/L/min of air passing through the solution. Due to extreme foaming of the mixture, polyethylene glycol (25 mL) was added as an antifoaming agent, but due to the persistence of the foam, Dow Corning 1510 silicone antifoam (2 mL) was also added. The mixture was stirred for two days at which point the pH started to drop, and mass spectrum analysis of the efluent gases showed the presence of CO_2, while O_2 and N_2 levels remained constant. After 4 and 5 days, respectively, the pH had reached 6.5 and 7.8, and the mixture became very viscous.

The fungus was harvested and filtered through Celite to remove the mycelium which was washed with copious amounts of MeOH and the MeOH washes were concentrated, in *vacuo*, to an aqueous residue. This residue was extracted with EtOAc (3×, 1000 mL), at which time an emulsion occurred, and repeated filtrations were needed to obtain separation of the aqueous and organic phases. The organic phase was concentrated to a dark oil. The aqueous filtrate from the fermenter was also extracted with EtOAc (3 × 1000 mL), and again multiple filtrations were needed to break down emulsions. After concentration of these extracts, the oily residue was combined with the residue from the mycelium extracts and the mixture was dissolved in EtOAc (2000 mL) and dried. Filtration and concentration left a yellow oil which was dissolved in aqueous MeOH (85% MeOH) and extracted with hexanes (3 × 800 mL) to remove nonpolar impurities. Evaporation of the MeOH/water layer left an aqueous phase which was extracted with EtOAc (3 × 1000 mL), and these combined extracts were dried and filtered. Evaporation gave a yellow oil which was chromatographed (20% MeOH in $CHCl_3$) collecting all fractions with a R_f between 1.4 and 2.5 (developing solvent 20% MeOH in $CHCl_3$). These combined fractions were evaporated, and the residue was rechromatographed using gradient elution (10−20% MeOH in $CHCl_3$). Again fractions which contained compounds with R_f values between 1.4 and 2.5 were combined and evaporated. The resultant residue (1.2 g) was shown to contain a mixture of components with HPLC/UV characteristics (Spher ODS 2, H_2O:MeOH = 1:3) consistent with the papulacandins A, B, C, and D (**1**). This crude mixture was used directly in the experiments to follow.

Preparation of the Authentic Side Chain Ester (59). $LiOH·H_2O$ (372 mg) was added to the crude papulacandin fraction (621 mg) in THF (8 mL) and water (16 mL), and the mixture was stirred at ambient temperature for 4 h. The pH of the solution was adjusted to 6 with hydrochloric acid (1 M), and the aqueous mixture was extracted with EtOAc (4×). The organic phases were combined, washed with brine, and dried. After filtration and evaporation, the residue was dissolved in Et_2O (50 mL) and while being stirred, a large excess of diazomethane [from *N*-nitroso-*N*-methylurea (621 mg), Et_2O (15 mL), and aqueous KOH (40%, 15 mL)] was added. After 13 h, saturated aqueous $NaHCO_3$ was added and the organic phase washed with water and brine, dried, filtered, and evaporated. Chromatography (25% EtOAc in hexanes) gave the natural side chain methyl ester **59** (31 mg): $[\alpha]^{25}_D = +5.02$ (c = 1.05, $CHCl_3$); with all spectroscopic data identical with the samples of **65**/**66**, **65**, and **66**. The Mosher ester **60** was prepared according to the general procedure; the ^1H and ^{13}C NMR spectra were identical with those from **62** and nonidentical with those from **63**; HPLC (Apex silica 5U, EtOAc:hexanes = 2.5:97.5, 1 mL min^{-1}) retention time 26.1 min only.

(*S*)-4-Methylhexanal 2,4-Dinitrophenylhydrazone from the Authentic Papulacandin Diester (60). Ozone was bubbled through the Mosher ester **60** (79 mg) in MeOH (5 mL) at −78 °C until a faint blue color was observed. Me_2S (217 μL, 187 mg, 3.02 mmol) was added, and the mixture was allowed to slowly warm up to room temperature. After 2 h, (2,4-dinitrophenyl)hydrazine solution (30 mL) was added and the mixture stirred overnight. The solution was added to water and extracted with EtOAc (3×). The combined organic layers were washed with water and brine, dried, and chromatographed (10% EtOAc in hexanes) to give **61** (27.6 mg, 62%): mp = 79−82 °C (plates from EtOH); $[\alpha]^{25}_D = +13.2$ (c = 0.29 in $CHCl_3$), with all spectroscopic data identical with a sample prepared from **40**.

(*S*)-4-Methylhexanal 2,4-Dinitrophenylhydrazone from the Synthetic Diester Mixture 62/63. Ozonolysis of **62**/**63** (79 mg) as for **60** gave the corresponding aldehyde isolated as the 2,4-dinitrophenylhydrazone **64** (21 mg, 50%) identical with the sample prepared from isoleucine (**37**) *via* **38**, **39**, and **40**.

(7*S*,14*S*)-8,14-Dimethyl-4-[(triethylsilyl)oxy]hexadecane-2*E*,4*E*, 8*E*,10*E*-tetraenoic Acid (69). $KOSiMe_3$ (320 mg, 2.40 mmol) and ester **54** (100 mg, 0.24 mmol) in THF (4 mL) were allowed to react at room temperature for 3 h when aqueous citric acid (0.5 M, 5 mL) was added. The mixture was extracted with EtOAc and the organic layer washed with brine, dried, filtered, and evaporated. The residue was rapidly chromatographed (50% EtOAc in hexanes) to give the unstable acid **69** (98 mg, 100%) as a pale yellow oil which was used directly without further purification: R_f = 0.55 (50% EtOAc in hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (dd, 1H J = 10.2, 15.3 Hz), 6.33−6.10 (m, 2H), 5.93 (d, 1H, J = 10.8 Hz), 5.80 (d, 1H, J = 15.3 Hz), 5.67 (dt, 1H, J = 6.9, 15.0 Hz), 4.13 (t, 1H, J = 7.1 Hz), 2.55−2.30 (m, 2H), 2.25−2.05 (m, 2H), 1.71 (s, 3H), 1.50−1.10 (m, 5H), 1.00−0.83 (m, 15H), 0.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 147.2, 142.4, 136.6, 135.3, 130.0, 125.6, 118.6, 40.5, 36.2, 34.0, 30.6, 29.4, 19.1, 11.9, 11.3, 6.8, 4.8.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-3-*O*-{(7*S*,14*S*)-8,14-dimethyl-7-[(triethylsilyl)oxy]hexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl}-β-D-glucopyranose (71) and 1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(*tert*-butyldimethylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-2-*O*-{(7*S*,14*S*)-8,14-dimethyl-7-[(triethylsilyl)oxy]hexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl}-β-D-glucopyranose (72). Et_3N (50 μL, 36 mg, 0.36 mmol) and, after 10 min, 2,4,6-trichlorobenzoyl chloride (40 μL, 64 mg, 0.26 mmol) were added to acid **69** (96 mg, 0.24 mmol) in THF (3 mL). After 1 h, solvent was evaporated and the residue in DMF (2 mL) was added, *via* cannula, to diol **31** (238 mg, 0.36 mmol) and 4-(dimethylamino)pyridine (52 mg, 0.43 mmol) in DMF (1 mL). Water was added after 17 h, and the resulting mixture was extracted with EtOAc. The organic phase was washed with water and brine, dried, filtered, and evaporated. The resultant oil was purified by gradient chromatography (5−10% EtOAc in hexanes) to yield the esters **71** and **72** (130 mg, 1:1, 60%). Fractions containing the 3-ester **71** showed: R_f = 0.20 (10% EtOAc in hexanes); IR (KBr) 3471, 2962, 2938, 2861, 1720, 1644, 1602, 1471, 1434, 1363, 1259, 1164, 1076, 1000, 970, 835, 781, 744, 655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27 (dd, 1H, J = 15.3, 10.9 Hz), 6.29 (d, 1H, J = 1.6 Hz), 6.24−6.16 (m, 2H), 6.19 (d, 1H, J = 1.8 Hz), 6.20−6.02 (m, 1H), 5.92 (d, 1H, J = 10.8 Hz), 5.88 (d, 1H, J = 15.4 Hz), 5.65 (dt, 1H, J = 6.9, 15.0), 5.29 (t, 1H, J = 9.1 Hz), 5.14 (d, 1H, J = 12.7 Hz), 4.38 (t, 1H, J = 10.1 Hz), 4.13 (dd, 1H, J = 4.7, 9.9 Hz), 4.10−3.96 (m, 3H), 3.85 (t, 1H, J = 9.9 Hz), 2.45−2.30 (m, 2H), 2.20−2.04 (m, 2H), 2.00 (d, 1H, J = 10.5 Hz), 1.69 (s, 3H), 1.42−1.10 (m, 5H), 1.02 (s, 18H), 0.99 (s, 9H), 0.98 (s, 9H), 0.92 (t, 6H, J = 7.9 Hz), 0.90−0.84 (m, 6H), 0.55 (q, 9H, J = 7.9 Hz), 0.28 (s, 3H), 0.25 (s, 3H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 158.4, 151.8, 145.1, 143.4, 140.9, 136.8, 135.2, 130.2, 125.6, 125.5, 119.7, 119.6, 110.9, 109.9, 105.2, 77.5, 76.5, 74.8, 73.3,

71.6, 68.8, 66.7, 40.5, 36.2, 34.1, 30.6, 30.3, 29.3, 27.4, 27.0, 25.8, 25.6, 22.7, 19.9, 19.1, 18.3, 18.2, 11.9, 11.3, 6.8, 4.8, −3.9, −4.3, −4.4; MS (FAB) *m/e* 1057 ([M + H]$^+$), 651, 593, 395, 379, 295, 115, 87, 73; HRMS (FAB) calcd for $C_{57}H_{101}O_{10}Si_4$: ([M + H]$^+$), 1057.6455; found: ([M + H]$^+$), 1057.6361. Fractions containing the 2-ester **72** showed: $R_f = 0.38$ (10% EtOAc in hexanes); $[\alpha]^{25}_D = -30.6$ ($c = 1.70$ in $CHCl_3$); IR (KBr) 3598, 3467, 2950, 2900, 2859, 1725, 1643, 1604, 1473, 1365, 1261, 1160, 1076, 1002, 964, 836, 782, 742 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (dd, 1H, J = 10.7, 12.3 Hz), 6.20 (d, 1H, J = 1.7 Hz), 6.22−6.14 (m, 1H), 6.14 (d, 1H, J = 1.8 Hz), 6.10−5.92 (m, 2H), 5.89 (d, 1H, J = 10.9 Hz), 5.73 (d, 1H, J = 9.8 Hz), 5.64 (dt, 1H, J = 6.9, 15.0), 5.56 (d, 1H, J = 15.3 Hz), 5.11 (d, 1H, J = 12.6 Hz), 5.00 (d, 1H, J = 12.5 Hz), 4.16 (dd, 1H, J = 5.0, 9.9 Hz), 4.10−3.85 (m, 5H), 2.63 (br s, 1H), 2.40−2.24 (m, 2H), 2.20−2.00 (m, 2H), 1.67 (s, 3H), 1.45−1.10 (m, 5H), 1.07 (s, 9H), 1.05 (s, 9H), 1.02 (s, 9H), 0.94 (s, 9H), 0.90 (t, 9H, J = 8.0 Hz), 0.89−0.84 (m, 6H), 0.53 (q, 6H, J = 7.9 Hz), 0.32 (s, 3H), 0.24 (s, 3H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 158.4, 152.2, 145.0, 143.2, 140.8, 136.6, 135.2, 130.0, 125.6, 125.5, 118.9, 118.6, 109.6, 109.5, 104.7, 77.6, 77.4, 73.6, 73.3, 73.0, 68.4, 66.6, 40.4, 36.2, 34.0, 30.6, 30.3, 29.7, 29.4, 27.5, 27.1, 25.8, 25.6, 22.8, 20.0, 19.0, 18.2, 18.2, 11.9, 11.8, 11.3, 6.8, 4.8, −4.1, −4.3, −4.5; MS (FAB) *m/e* 1057 ([M + H]$^+$), 1020, 925, 651, 379, 295, 136, 115, 73.

1,1-Anhydro-1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-3-*O*-{(7*S*,14*S*)-8,14-dimethyl-7-[(triethylsilyl)oxy]hexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl}-*β*-D-glucopyranose (73) and 1,1-Anhydro1-*C*-{6-(hydroxymethyl)-2,4-bis[(triisopropylsilyl)oxy]phenyl}-4,6-*O*-(di-*tert*-butylsilylene)-2-*O*-{(7*S*,14*S*)-8,14-dimethyl-7-[(triethylsilyl)oxy]hexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl}-*β*-D-glucopyranose (74). Acid **69** (94 mg, 0.23 mmol), Et_3N (51 μL, 40 mg, 0.39 mmol), 2,4,6-trichlorobenzoyl chloride (43 μL, 68 mg, 0.28 mmol), and 4-(dimethylamino)pyridine (5 mg) in THF (3 mL) were allowed to react at room temperature for 1 h. The mixture was concentrated *via* high vacuum (0.1 mmHg), and the remaining mixed anhydride **70** in DMF (2 mL) was added, *via* a cannula, to diol **30** (260 mg, 0.34 mmol) and 4-(dimethylamino)pyridine (62 mg, 0.51 mmol) in DMF (3 mL). The resulting mixture was stirred overnight at room temperature, quenched with water, and extracted with EtOAc. The organic phase was washed with water (2×) and brine, dried, filtered, and evaporated. Chromatography (5% EtOAc in hexanes) gave the esters **73** and **74** [157 mg, 60%, 4:1 (3-ester:2-ester)] which were separated by further chromatography. The 3-ester **73** showed $R_f = 0.22$ (5% EtOAc in hexanes); $[\alpha]^{25}_D = -1.4$ (c = 1.36 in $CHCl_3$); IR (thin film) 3457, 2946, 2868, 1721, 1644, 1599, 1463, 1366, 1355, 1248, 1169, 1075, 999, 970, 835, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (dd, 1H, H = 10.9, 15.3 Hz), 6.31 (s, 1H), 6.25−6.15 (m, 2H), 6.10−6.00 (m, 1H), 5.92 (d, 1H, J = 10.8 Hz), 5.88 (d, 1H, J = 15.4 Hz), 5.65 (dt, 1H, J = 6.9, 15.0 Hz), 5.30 (t, 1H, J = 9.3 Hz), 5.15 (d, 1H, J = 12.7 Hz), 5.02 (d, 1H, J = 12.7 Hz), 4.41 (t, 1H, J = 9.8 Hz), 4.13 (dd, 1H, J = 4.7, 9.9 Hz), 4.10−3.95 (m, 2H), 3.82 (t, 1H, J = 9.8 Hz), 2.50−2.30 (m, 2H), 2.20−2.00 (m, 2H), 1.97 (d, 1H, J = 10.3 Hz), 1.70 (s, 3H), 1.45−1.18 (m, 11H), 1.13 (2d, 18H, H = 7.5Hz), 1.08 (d, 18H, J = 7.3 Hz), 1.02 (s, 9H), 0.99 (s, 9H), 0.92 (t, 9H, J = 7.9 Hz), 0.90−0.60 (m, 6H), 0.55 (q, 6H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 158.7, 152.1, 145.0, 143.3, 140.7, 136.8, 135.2, 130.2, 125.6, 125.5, 119.7, 119.2, 111.0, 109.6, 104.9, 77.5, 76.5, 74.8, 73.3, 71.5, 68.8, 66.8, 40.5, 36.2, 34.1, 30.6, 30.3, 29.3, 27.4, 27.0, 22.7, 19.9, 19.1, 18.0, 17.9, 17.7, 13.2, 12.7, 11.9, 11.3, 6.8, 4.8; MS (FAB) *m/e* 1141 (M$^{\bullet+}$), 735, 677, 505, 435, 295, 115, 103, 87, 75, 59; HRMS (FAB) *m/e* calcd for $C_{63}H_{113}O_{10}Si_4$: ([M + H]$^+$), 1141.7411; found: ([M + H]$^+$), 1141.7554. Anal. Calcd for $C_{63}H_{112}O_{10}Si_4$: C, 66.27; H, 9.90. Found: C, 65.99; H, 9.95%. The 2-ester **74** showed $R_f = 0.29$ (5% EtOAc in hexanes); $[\alpha]^{25}_D = -30.0$ (c = 1.36 in $CHCl_3$); IR (thin film) 3484, 2946, 2867, 1727, 1643, 1601, 1465, 1366, 1257, 1166, 1070, 1001, 962, 882, 828, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (dd, 1H, J = 10.7, 15.3 Hz), 6.24 (d, 1H, J = 1.5 Hz), 6.18 (d, 1H, J = 1.8 Hz), 6.26−6.16 (m, 1H), 6.10−5.92 (m, 3H), 5.88 (d, 1H, J = 10.9 Hz), 5.73 (d, 1H, J = 9.8 Hz), 5.70−5.60 (m, 1H), 5.55 (d, 1H, J = 15.4 Hz), 5.12 (d, 1H, J = 15.5 Hz), 5.00 (d, 1H, J = 12.5 Hz), 4.14 (dd, 1H, J = 9.9, 5.1 Hz), 4.10−3.92 (m, 4H), 3.86 (t, 1H, J = 10.1 Hz), 2.40−2.24 (m, 2H), 2.20−2.02 (m, 2H), 1.69 (s, 3H), 1.15−1.40 (m, 11H), 1.20−1.00 (m, 54H), 0.90 (t, 9H, J = 8.0 Hz), 0.90−0.84 (m, 6H), 0.60−0.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 158.8, 152.5, 145.0, 143.1, 140.7, 136.7, 135.2, 130.0, 125.6, 125.5, 119.0, 118.5, 109.6, 104.4, 77.6, 77.5, 73.7, 73.3, 68.4, 66.6, 40.4, 36.2, 34.1, 30.6, 29.4, 27.44, 27.39, 27.1, 27.0, 22.8, 20.0, 19.1, 18.1, 18.0, 17.9, 17.8, 17.7, 13.2, 12.7, 12.6, 11.8, 11.3, 6.8, 4.8; MS (FAB) *m/e* 1141 ([M + H]$^+$), 735, 435, 295, 115, 87, 75, 59.

1,1-Anhydro-1-*C*-[6-(hydroxymethyl)-2,4-dihydroxyphenyl]-3-*O*-[(7*S*,14*S*)-8,14-dimethyl-7-hydroxyhexadeca-2*E*,4*E*,8*E*,10*E*-tetraenoyl]-*β*-D-glucopyranose [Papulacandin D (1)]. Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) (99 mg, 0.36 mmol) and ester **73** (68 mg, 0.06 mmol) in THF (4 mL) were allowed to react at 0 °C for 4 h. Since TLC showed that the deprotection was not complete additional amount of TASF (40 mg, 0.15 mmol) was added. After 1 h, MeOH (5 mL) was added. Evaporation and chromatography (10% MeOH in $CHCl_3$) gave a colorless foam which was dissolved in EtOAc and filtered (removing traces of silica gel) to leave papulacandin D (**1**) (22 mg, 64%): $R_f = 0.24$ (10% MeOH in $CHCl_3$); $[\alpha]^{25}_D = +27.5$ ($c = 0.25$ in MeOH); IR (thin film) 3329, 2959, 2926, 2874, 1698, 1639, 1615, 1463, 1377, 1347, 1304, 1261, 1205, 1153, 1070, 1005, 977, 838 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.30 (dd, 1H, J = 10.1, 15.2 Hz), 6.25 (ddt, 1H, J = 1.3, 10.8, 15.0 Hz), 6.23 (dd, 1H, J = 10.7, 14.7 Hz), 6.20 (m, 1H), 6.19 (m, 1H), 6.12 (dt, 1H, J = 14.7, 15.2 Hz), 6.00 (dd, 1H, J = 0.7, 10.8 Hz), 5.92 (d, 1H, J = 15.3 Hz), 5.66 (dt, 1H, J = 7.0, 15.0 Hz), 5.34 (t, 1H, J = 9.7 Hz), 5.05, 4.99 (ABq, 2H, J = 12.6 Hz), 4.33 (d, 1H, J = 10.0 Hz), 4.07 (t, 1H, J = 6.6 Hz), 3.87 (ddd, 1H, J = 2.3, 4.8, 10.1 Hz), 3.70−3.66 (m, 2H), 3.68 (t, 1H, J = 9.7 Hz), 2.42 (t, 2H, J = 7.0 Hz), 2.18−2.04 (m, 2H), 1.71 (d, 3H, J = 0.5 Hz), 1.49−1.29 (m, 3H), 1.28−1.11 (m, 2H), 0.87 (t, 3H, J = 7.3 Hz), 0.87 (d, 3H, J = 6.6 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 169.0, 161.5, 154.7, 146.4, 145.5, 141.8, 137.5, 136.2, 131.5, 127.1, 127.0, 120.9, 116.7, 112.1, 103.0, 99.9, 78.4, 77.5, 75.8, 73.8, 71.9, 69.8, 62.5, 40.0, 37.5, 35.2, 31.6, 30.4, 19.4, 12.2, 11.7; MS (FAB) *m/e* 575 ([M + H]$^+$), 394, 205, 181, 167, 89, 77, 55; HRMS (FAB) *m/e* calcd for $C_{31}H_{43}O_{10}$: ([M + H]$^+$), 575.2856; found: ([M + H]$^+$) 579.2908.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **11**, **16**, **23**, **24**, **25**, **28**, **29**, **39**, **41**, **44**, (8*S*)-2,8-dimethyl-2*E*,4*E*-decadien-1-ol, **47**, **50**, **55**, **56**, **60**, **62**, **63**, **65**/**66**, **67**, **67**/**68**, **71**, **72**, **73**, **74**, and **1** (63 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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