Convergent Synthesis of the Polyene Macrolide (–)-Roxaticin

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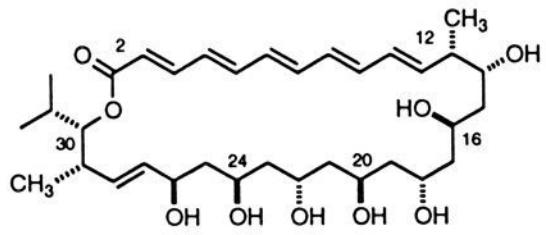
Abstract: (–)-Roxaticin has been synthesized from polyol tetraacetonide **5**, which was prepared by a threefold convergent route. Each of the optically pure building blocks (**2**, **3**, and **4**) was prepared using a Noyori asymmetric hydrogenation. Sequential alkylation of dibromide **3** with cyanohydrin acetonides **2** and **4** followed by stereoselective reductive decyanation gave tetraacetonide **5**. The initial approach to roxaticin using a 1-methylcyclopropyl ether in a key protection step was unsuccessful due to the instability of the polyene chain to oxidative deprotection. A 1,3-benzodithiolan-2-yl (BDT) ether performed well in a model study and was used in the roxaticin system. Protection of the roxaticin precursor as a BDT ether followed by elaboration of the polyene using Wollenberg's method gave a tetraenal. The macrocyclic ring was closed using an intramolecular Horner–Emmons Wittig reaction, and acid-catalyzed deprotection completed the synthesis of roxaticin. Our synthesis of roxaticin illustrates a first generation approach to the highly convergent synthesis of polyene macrolide antibiotics that should ultimately be useful for preparing stereochemical and structural analogs.

Polyene macrolide antibiotics such as amphotericin B are important in the treatment of systemic fungal infections.[2] Several of these polyene macrolide antibiotics have been synthesized in the past few years,[3] and a wide variety of new synthetic methods have been developed.[4] Our interest in the mode of action of polyene macrolide antibiotics[5] led us to search for a practical synthesis of these compounds that would be suitable for the preparation of structural analogs.[6] Roxaticin, a relatively simple polyene macrolide antibiotic, was chosen as a target with which to develop new synthetic strategies.[7,8] We report the convergent total synthesis of the unnatural enantiomer of roxaticin.[9]



(+)-Roxaticin, 1

(+)-Roxaticin (**1**) is a pentaene macrolide isolated from an unidentified streptomycete similar to *Streptomyces ruber*.[7] As with many polyene macrolides, it shows antifungal activity but not antibacterial activity.[7] The structure and stereochemistry of roxaticin was established from an X-ray crystal structure of the derived roxaticin heptaacetate (Figure 1), while the absolute stereochemistry was assigned on the basis of the optical rotation of the degradation product *syn*-2,4-dimethyl-1,3-pentanediol.[7] We initially set out to prepare the unnatural enantiomer of roxaticin to investigate the mode of action of polyene macrolide antibiotics but subsequently carried out an analogous investigation using the more readily accessible *ent*-cholesterol.[5]

Synthetic Plan. The polyene portion of roxaticin is relatively unstable, and we decided to avoid introducing the polyene until the final stages of the synthesis. The C(30) oxygen of roxaticin is very hindered, and that hindrance would disfavor a seco-acid cyclization route to the macrocyclic ring. The Horner–Emmons Wittig reaction is a well-established method for macrocyclic ring formation and should not be affected by the hindrance around the C(30) oxygen. The crystal structure of roxaticin heptaacetate (Figure 1) defines one of the accessible ring conformations of roxaticin and can guide the choice of protecting groups to favor macrocyclization. The orientation of the C(24) and C(26) oxygens would be reinforced by introducing a cyclic protecting

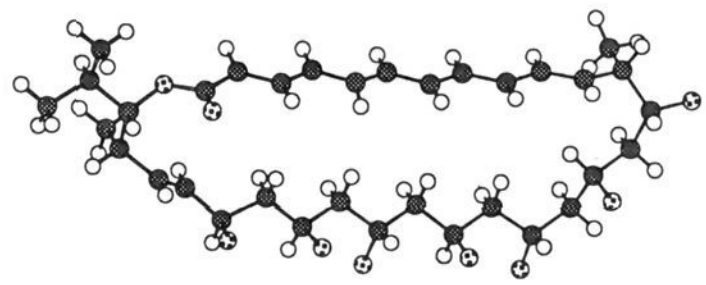


Figure 1. Crystal structure of roxaticin heptaacetate.[7] Acetates have been omitted for clarity.

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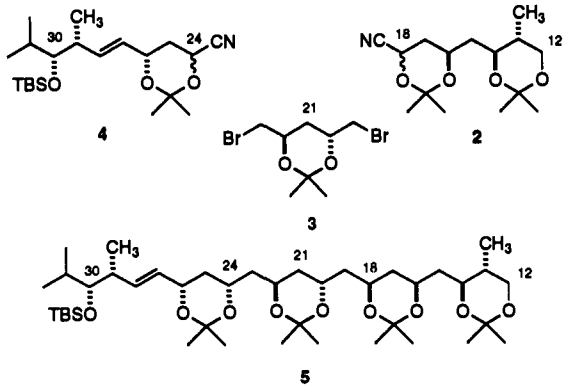


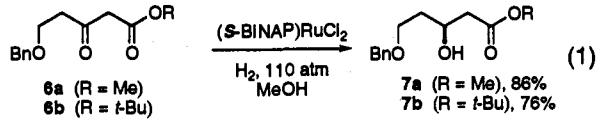
Figure 2. Key synthetic intermediates for the polyol chain of (−)-roxaticin.

group at this site, and the C(20) and C(22) oxygens require only a slight reorientation to allow cyclic protection.[10] Unfortunately, cyclic protection of the C(16) and C(18) oxygens or of the C(14) and C(16) oxygens would force a significant reorientation of the carbon chain, but synthetic considerations dictated cyclic protection of one or the other. Preparation of a suitably protected C(12) to C(30) polyol chain was the first synthetic goal.

The tetraacetonide **5** was identified as a plausible precursor to roxaticin: it incorporates the C(12) to C(30) fragment of roxaticin that includes all of the stereogenic centers.[9] Our approach to **5** was based on our previously described cyanohydrin acetonide method for convergent polyol chain synthesis.[6] Dibromide **3**[6c] was to be alkylated sequentially with cyanohydrin acetonides **4** and **2**, followed by stereoselective reductive decyanation. Synthesis of tetraacetonide **5** was thus simplified to the enantioselective preparation of compounds **2** and **4**. Compounds **2**–**5**, the key intermediates, for the polyol chain of (−)-roxaticin, are shown in Figure 2.

Results and Discussion

Synthesis of the Cyanohydrin Acetonide Fragments. Synthesis of **2** began with the enantioselective hydrogenation of β-keto ester **6** to the β-hydroxy ester **7**, eq 1. The reduction was initially

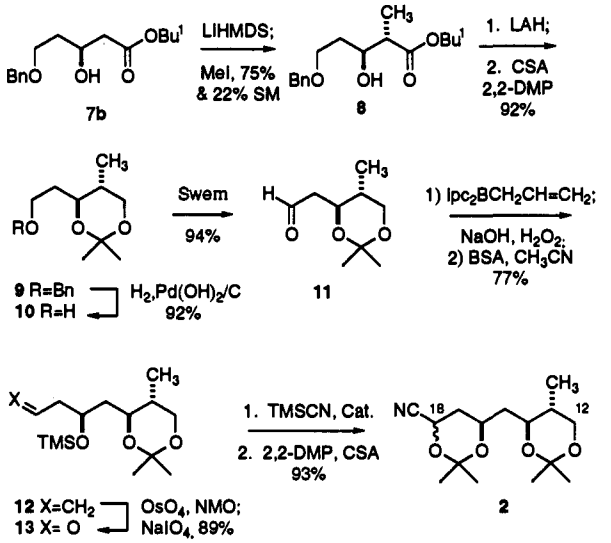


(1)

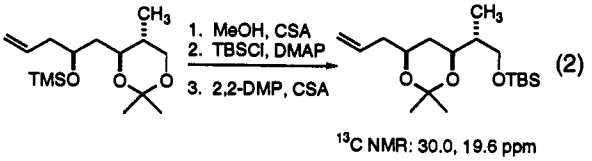
carried out on ester **6a** as described by Noyori,[11] but the preparation of **6a** by Weiler dianion alkylation of methyl acetoacetate led to product contaminated with the nearly inseparable benzyl alcohol.[12] Ester **6b** was prepared by alkylation of *tert*-butyl acetoacetate and was easily separated from the benzyl alcohol impurity. Reduction of **6b** using [((*S*)-BINAP)-$RuCl_2]_2$·Et_3N prepared in situ[13] gave **7b** in good yield. The reaction was more reliable when acidified with HCl,[14] and the highest enantioselectivity, 96% ee, was observed at 45 °C.[15]

Frater–Seebach alkylation[16] of ester **7b** gave a 10:1 mixture of *anti* and *syn* isomers, where the α-methyl ester **8** was isolated

Scheme 1



in 75% yield, Scheme 1. Reduction and protection gave the acetonide **9**, which was deprotected using Pearlman's catalyst and hydrogen to give alcohol **10**. Swern oxidation followed by enantioselective allylation using Brown's allyldiisopinocampheylborane reagent, $Ipc_2BCH_2CH{=}CH_2$, prepared from (*R*)-(+)-α-pinene[17] gave a single homoallylic alcohol, which was isolated as the TMS ether **12** in 77% overall yield. The relative stereochemistry of the two secondary alcohols was confirmed by preparing the corresponding acetonide and analyzing the ^{13}C NMR spectrum, eq 2.[18] Stepwise oxidation of the terminal alkene



(2)

^{13}C NMR: 30.0, 19.6 ppm

12 to the aldehyde **13** was more successful than ozonolysis due to difficulties in reducing the intermediate ozonide. The cyanohydrin acetonide was prepared in a one-pot reaction by treating aldehyde **13** with TMSCN and KCN/18-crown-6[19] followed by addition of acetone, 2,2-dimethoxypropane (2,2-DMP), and camphorsulfonic acid (CSA). Cyanohydrin acetonide **2** was isolated as a 1:1 mixture of isomers at the nitrile center in 11 steps from *tert*-butyl acetoacetate. The mixture of isomers is of no consequence as the C(18) stereogenic center is reset in the next step.

Unsaturated ester **18** was a key intermediate in the preparation of cyanohydrin acetonide **4**. Helquist had reported a synthesis of ester **18** via enantioselective boron aldol chemistry, Scheme 2.[20] Although we initially prepared **18** by this route,[21] there were two problems with the published procedure that limited production. First, the chiral auxiliary was reduced in the DIBAL-H step and could not be recycled, and second, the reported Wittig reaction was unacceptably slow. Changing the solvent from refluxing CH_2Cl_2 to refluxing CH_3CN reduced the Wittig reaction time from 4 weeks to 18 h and improved the yield to 96% with almost complete *E* selectivity. Even with this improvement in

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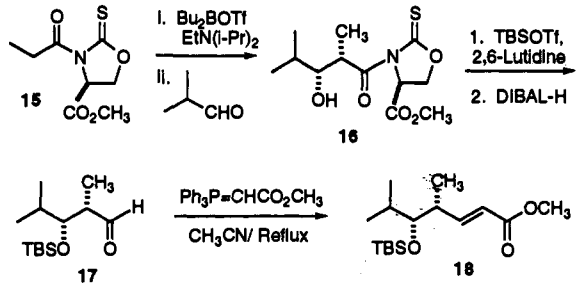
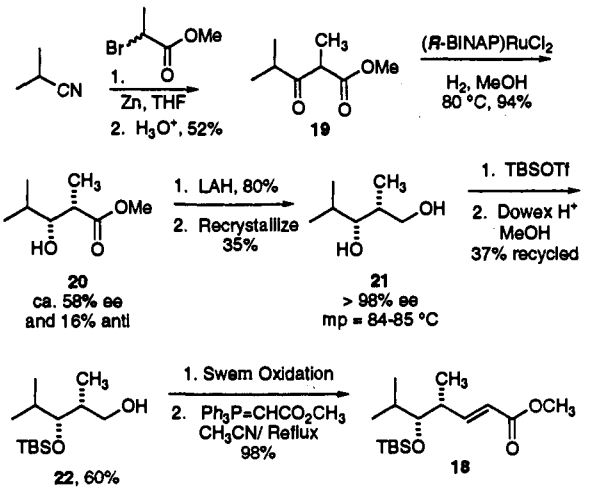
Scheme 2



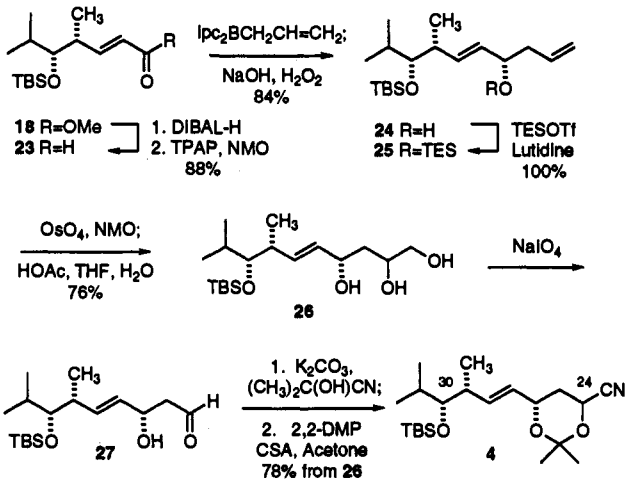
Scheme 3



the Wittig step, the boron aldol approach was still frustrating, especially when compared to the ease with which large amounts of the *anti* aldol product **8** could be prepared by the enantioselective reduction route.

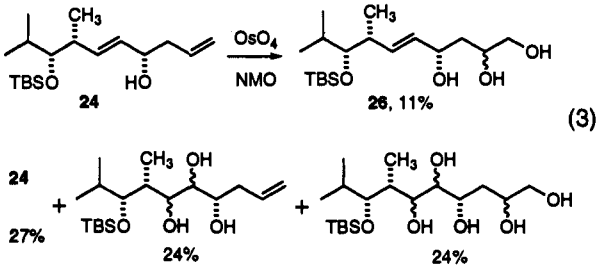
We developed an alternate procedure for the preparation of unsaturated ester **18** based on a Noyori hydrogenation, Scheme 3. Kishi's modification of the Blaise reaction[22] was very effective for preparing large amounts of methyl 2,4-dimethyl-3-oxopentanoate, **19**. Enantioselective reduction of **19** using catalytic $[((R)\text{-BINAP})RuCl_2]_2{\cdot}Et_3N$ was very slow at room temperature, so the reaction was conducted at 80 °C. Surprisingly, the methyl 2,4-dimethyl-3-hydroxypentanoate was isolated as a 7:1 mixture of *syn* and *anti* isomers rather than the 1:1 mixture expected from the previously reported reduction of methyl 2-methyl-3-oxobutanoate.[11] Epimerization of **19** is faster than reduction,[23] and the reduction itself is apparently more diastereoselective than that of the less hindered methyl 2-methyl-3-oxobutanoate. Mosher's ester analysis showed that the *syn* isomer was produced in 58% ee.[24] Reduction of the crude mixture with LAH gave a syrupy mixture of diols in 80% yield that partially crystallized on standing. Recrystallization of the solid gave the *syn* diol **21** in 35% yield, which exhibited >98% ee by GC analysis of the derived bis Mosher's ester.[25] Treatment with TBSOTf and lutidine followed by selective hydrolysis of the bis TBS ether gave the monoprotected TBS ether **22** in 60% yield. The diol **21** and bis-TBS ether were recovered in 37% combined yield and recycled. Swern oxidation followed by a Wittig coupling gave the optically pure unsaturated ester **18** in 98% yield. Although

Scheme 4



the catalytic hydrogenation showed only modest enantioselectivity, the facile recrystallization of diol **21** makes this route practical for the multigram preparation of **18**.

Cyanohydrin acetonide **4** was prepared from unsaturated ester **18**, Scheme 4. DIBAL-H reduction and Ley's catalytic perruthenate oxidation[26] gave the corresponding aldehyde **23** in 88% overall yield. The remaining stereogenic center was introduced by allyl addition using Brown's $Ipc_2BCH_2CH{=}CH_2$ reagent prepared from (*R*)-(+)-α-pinene.[17] The resulting alcohol **24** was protected as a triethylsilyl (TES) ether, oxidized with catalytic OsO_4 and 1.05 equiv of *N*-methylmorpholine *N*-oxide (NMO),[27] and hydrolyzed with 2:2:1 THF/HOAc/H_2O at 23 °C for 3 h. Triol **26** was obtained in 72% yield by this procedure, whereas the direct oxidation of **24** gave triol **26** in only 11% yield accompanied by a mixture of products arising from competitive oxidation of the internal alkene, eq 3. The bulky TES group is



(3)

necessary to block the internal alkene rather than to suppress reactions of the alcohol. Oxidation of triol **26** with $NaIO_4$ produced the β-hydroxy aldehyde **27**, which was used without further purification. Cyanide exchange from acetone cyanohydrin catalyzed by K_2CO_3 followed by treatment with acetone, 2,2-DMP, and CSA gave cyanohydrin acetonide **4** as a 1:1 mixture of isomers at the cyanohydrin center in 42% overall yield from ester **18**.[28]

Preparation of Tetraacetonide 5. The three fragments were coupled using our alkylation and reductive decyanation method, Scheme 5, which allows for the stereoselective construction of linear alternating polyols using a 1,3-dioxane ring as the control element.[6b] Dibromide **3** has C_2 symmetry, so only one monoalkylation product is possible. Overalkylation could have been a serious problem, but it was avoided by using the dibromide in excess.

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(25) The rotation of diol **21**, $[\alpha]^{24}_D = -10.42°$ ($c = 0.96$, $CHCl_3$), compares favorably with that reported for its enantiomer, $[\alpha]^{25}_D = +10.29°$ ($c = 0.91$, $CHCl_3$). (a) Garcia, J.; Kim, B.-M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831–4832. (b) Masamune, S.; Choy, W.; Kerdesky, F. A.; Imperiala, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568.
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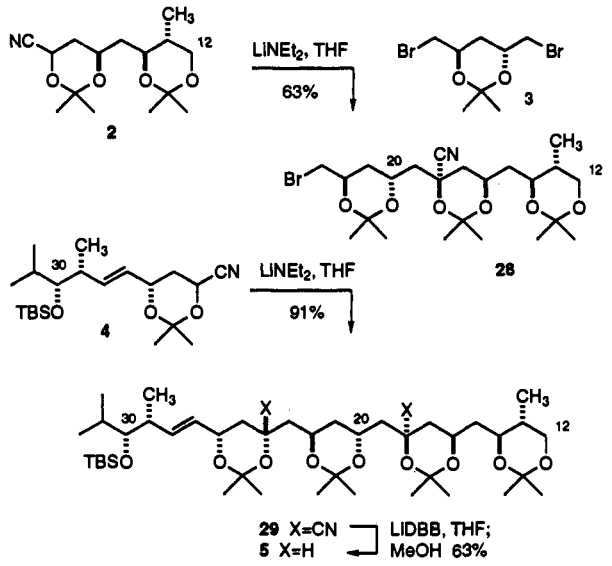
(28) The two nitrile epimers of compounds **2** and **4** can be separated by chromatography but were normally used as a mixture. In the case of compound **2**, the *syn* isomer had an R_f of 0.24 in 10% ethyl acetate/hexanes, whereas the *anti* isomer had an R_f of 0.34 in the same solvent system.

Scheme 5



Cyanohydrin acetonide **2** was deprotonated with $LiNEt_2$ in THF at −78 °C, 2.0 equiv of dibromide **3** was added, the reaction vessel was transferred to a −18 °C MeOH/ice bath, and the bath was allowed to warm to 10 °C overnight. The monoalkylated product **28** was isolated in 63% yield, and 84% of the unreacted dibromide was recovered. Bromide **28** was used as the limiting reagent in the second alkylation, and the cyanohydrin acetonide **4** was used in 2-fold excess. Deprotonation of **4** and alkylation with **28** was carried out as described for the first coupling to give the adduct **29** in 91% yield along with a small amount of recovered **4**. Reductive removal of the cyano groups is normally carried out with lithium in ammonia, but model studies suggest that the allylic ether present in **29** would also be susceptible to reduction. To avoid this difficulty, dinitrile **29** was added to 10 equiv of lithium di-*tert*-butylbiphenylide (LiDBB)[29] in THF at −78 °C, and the reaction was stirred for 1 h before being quenched with MeOH. The reduced product **5** was isolated in 63% yield as a single isomer. The ^{13}C chemical shifts of acetonide methyl groups confirmed the presence of three *syn* (chair) acetonide rings (30.3, 30.3, 29.8, 20.0, 19.8, 19.0 ppm) and one *anti* (twist-boat) acetonide ring (24.4, 24.4 ppm), demonstrating that the two new protons were axial.[18]

Methylcyclopropyl (MCP) Ether Approach to Roxaticin. Transformation of tetraacetonide **5** into roxaticin required introducting the polyene chain at C(12) and the ester at C(30). The C(30) oxygen was uniquely protected as a TBS ether and could be selectively deprotected, but the C(12) oxygen was one of eight acetonide-protected oxygens and needed to be differentiated from the others. The methylcyclopropyl (MCP) ether protecting group was designed with this problem in mind.[30] Treatment of tetraacetonide **5** with TESOTf and Hunig's base in 1,2-dichloroethane for 20 h at 110 °C led to selective opening of the terminal acetonide to give the TES enol ether **30**, Scheme 6. The reaction is initiated by selective complexation of the bulky TESOTf with the least hindered, terminal oxygen followed by elimination of a proton. The enol ether was immediately cyclopropanated, and the resulting MCP-protected ether was isolated in 80% overall yield from **5**, along with 8% of recovered tetraacetonide **5**. Deprotection of both silyl ethers gave diol **31** in quantitative yield. This remarkably selective reprotection sequence freed the two desired alcohols for further elaboration and left the remaining seven oxygens protected.

Completion of the roxaticin macrocyclic ring was routine. Diol **31** was esterified with diethyl phosphonoacetic acid, BOP, and DMAP to give the bis ester, followed by the addition of ammonia saturated methanol to give ester alcohol **32** in 91% yield. Selective cleavage of the unhindered C(12) ester in the presence of the hindered C(30) ester provided a nice solution to the problem of functionalizing the more hindered alcohol. Ley's TPAP oxidation gave the aldehyde **33**. The Grignard reagent **34** was prepared from the corresponding tributyltin by transmetalation with BuLi and then $MgBr_2$. Addition to the aldehyde **33** followed by elimination using MsCl and Et_3N gave the corresponding dienal, and repeating this sequence gave the tetraenal **35** in 58% overall yield. This sequence is more tolerant of the phosphonate ester than the original by Wollenberg, which uses the corresponding lithium reagent.[31] Macrocyclization was carried out using either K_2CO_3 and 18-crown-6 under high dilution conditions[32] or LiCl and DBU[33] with comparable results. The macrocycle **36** was isolated in 25–45% yield along with variable amounts of higher R_f alkene isomers. Protection of the C(16) and C(18) alcohols as an acetonide may lead to a conformation unfavorable to cyclization, accounting for the modest yield. The structure of **36** was confirmed by ^1H and ^{13}C NMR, HRMS, and a COSY. On standing in air or exposure to light, **36** isomerized to a higher R_f mixture of inseparable alkene isomers. The acetonide protecting group could be removed by treatment with Dowex in methanol. Unfortunately, the MCP ether could not be removed under any conditions compatible with the polyene. Treatment with DDQ, I_2 in buffered aqueous THF, CAN, or NBS, which were all capable of removing the MCP ether in model compounds, led to complex mixtures with loss of the alkene protons in the ^1H NMR spectra. Recent attempts to remove a PMB ether in the presence of a polyene were similarly unsuccessful.[34] The MCP route led to a very effective synthesis of the roxaticin ring system but did not lead to a synthesis of roxaticin.

A New Protection Strategy from Model Studies. The polyene of roxaticin had proved to be more sensitive than anticipated, and without an authentic sample, roxaticin's stability to different deprotection conditions could not be directly evaluated. We needed a model system to evaluate possible protection strategies and chose *anti*-2,5-dimethyl-1,3-hexanediol (**41**).[35] This model mimics the C(12) to C(16) fragment of tetraacetonide **5** and was used to evaluate reprotection, polyene synthesis, and deprotection strategies for the synthesis of roxaticin.

A PMB ether approach to roxaticin was evaluated using acetal **37**, Scheme 7.[36] Regioselective reduction with DIBAL-H gave the secondary PMB ether **38** in 90% yield and 96:4 selectivity.[37] Ley's catalytic perruthenate oxidation[26] gave the aldehyde, and two iterations of the modified Wollenberg procedure gave the tetraenal **39** in 46% yield. Intermolecular Horner–Emmons Wittig condensation with LiCl and DBU gave the all-*E* polyene ester **40** in 54% yield. Attempted deprotection with DDQ or CAN was not successful, and on closer examination we found that the polyene protons of the starting material were absent from the ^1H spectrum within 15 min of DDQ addition. There was little change by TLC in this time; the polyene probably polymerized and/or isomerized. Attempted deprotection of the MCP-protected roxaticin **36** with DDQ required a day or two,

(29) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

(30) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7219–7222.

(31) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717–720.

(32) (a) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010–4011. (b) Nicolaou, K. C.; Seitz, S. P., Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011–4013. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030–2031.

(33) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

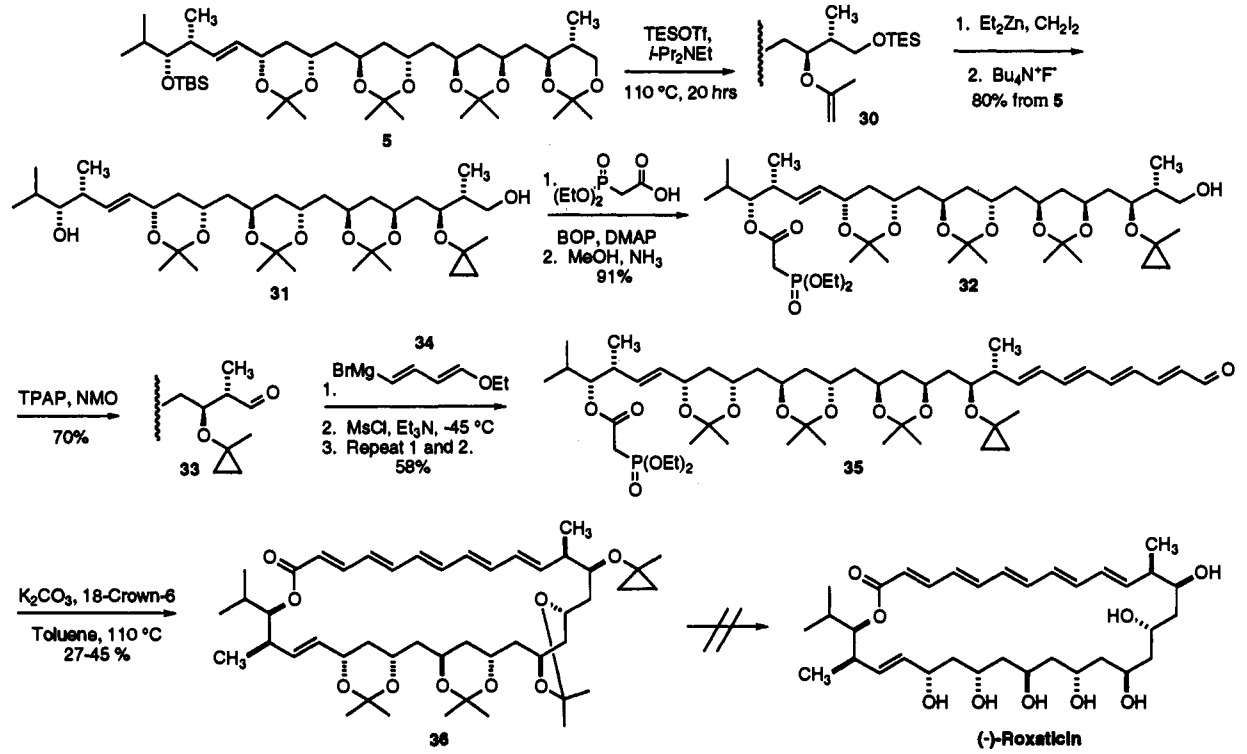
(34) (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964–1966. (b) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.

(35) Diol **41** was prepared from ethyl acetate: (1) (i) LDA, THF, −78 °C, (ii) i-PrCHO, (iii) LDA, 0 °C, (iv) MeI; (2) LAH. See ref 16.

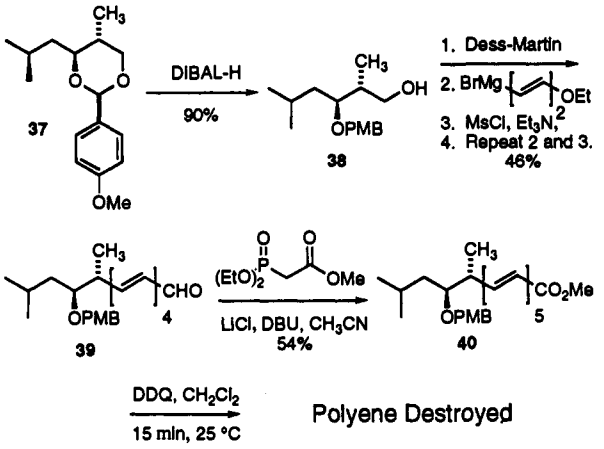
(36) Compound **37** was prepared from the diol **41** by treatment with 4-methoxybenzyl methyl ether and DDQ: Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037–4040.

(37) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593–1596.

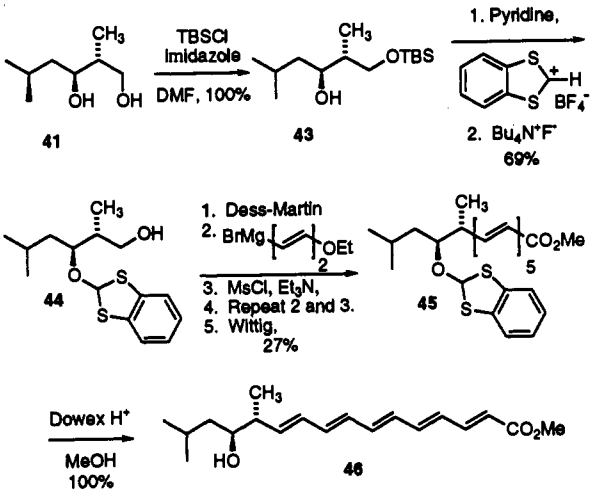
Scheme 6



Scheme 7

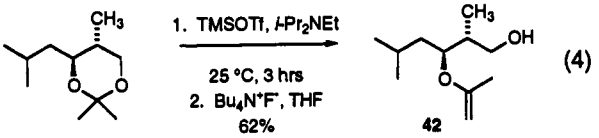


Scheme 8



and the rapid destruction of the polyene brought to light in this model study doomed the MCP route to roxaticin. The PMB ether is not removable in the presence of the complete pentaene ester, which rules out this strategy for the synthesis of roxaticin.

With oxidative deprotections no longer viable, the focus turned to acid-catalyzed deprotection schemes. In the MCP route to roxaticin, we found that the acetonide protecting groups of **36** could be cleanly deprotected on treatment with Dowex and methanol for several hours at room temperature. The polyene was stable to these conditions, and so replacing the C(14) MCP ether with an acid-labile protecting group should allow clean deprotection. A C(14) THP ether would fulfill these requirements, but the protection step was fraught with the danger of acid-catalyzed acetal migration. One appealing option was simply to carry the enol ether **30** through the final sequence. Unfortunately, oxidation of the enol ether alcohol **42**, prepared from the corresponding acetonide, eq 4,[38] to the aldehyde was



(4)

unsuccessful under all conditions attempted. Narasaka's procedure[39] using the 1,1′-(diazocarbonyl)dipiperidine oxidant is compatible with enol ethers, but it led to complex mixtures with **42**, suggesting that the target enol ether aldehyde was unstable.

The acid-labile 1,3-benzodithiolan-2-yl (BDT) protecting group[40] was next investigated, Scheme 8. Diol **41** was protected with TBSCl and imidazole to give the TBS alcohol **43**. Protection of the secondary alcohol with the $BDT^+BF_4^-$ salt and pyridine gave the BDT ether in 88% yield, and subsequent removal of the silyl ether gave primary alcohol **44** in 79%. Dess–Martin oxidation[41] proceeded uneventfully, as did the Wollenberg

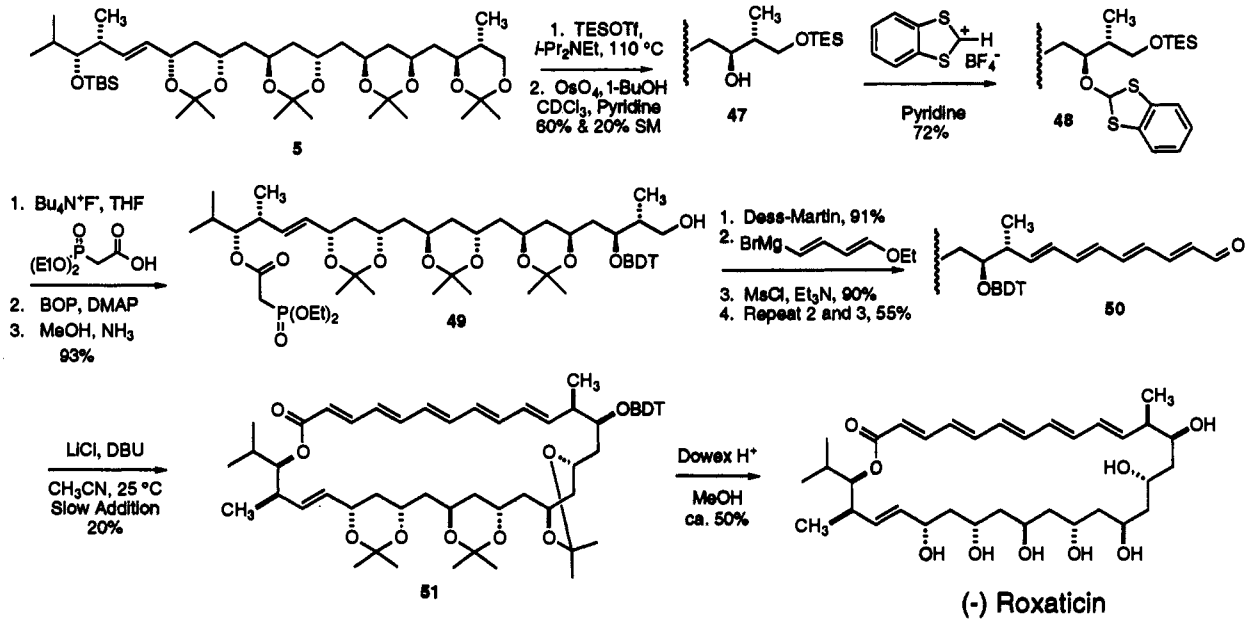
(38) Prepared from the diol **41** by treatment with acetone, 2,2-DMP, and CSA.

(39) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773.

(40) (a) Sekine, M.; Hata, T. *J. Am. Chem. Soc.* **1983**, *105*, 2044–2049. (b) Sekine, M.; Hata, T. *J. Org. Chem.* **1983**, *48*, 3112–3114.

(41) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

Scheme 9



sequence. The Horner–Emmons Wittig reaction gave protected pentaene ester **45** in 68% yield. Deprotection with Dowex in methanol was complete in 30 min and gave the final pentaene ester **46** in quantitative yield as a single alkene isomer. The BDT protecting group could be attached under neutral conditions, was stable to the polyene homologation procedure, and could be removed under mildly acidic conditions. The BDT group fulfilled all the requirements for a C(14) alcohol protecting group in the roxaticin synthesis.

Synthesis of (-)-Roxaticin. The synthesis of roxaticin was completed as shown in Scheme 9. The TES enol ether **30** was prepared as before, followed by selective hydrolysis of the enol ether to give alcohol **47** in 60% yield; side products could be reprotected to return 20% of the starting material **5**. The I_2 oxidation used in the model study was messy, but osmium tetraoxide cleavage of the enol ether in $CDCl_3$/pyridine proceeded cleanly. Further investigation revealed that this was not an oxidative deprotection: catalytic osmium tetraoxide was effective, and the side product was acetone, not 1-hydroxyacetone! It is unclear what role if any the osmium tetraoxide was playing, but these conditions selectively hydrolyzed the enol ether.[42] The BDT protection was uneventful and gave **48** in 72% yield. The remainder of the synthesis was as developed in the MCP approach. Silyl deprotection and phosphonoacetate introduction gave alcohol **49** in 93% yield. Oxidation and modified Wollenberg polyene synthesis gave the tetraenal cyclization precursor **50**. Roush–Masamune cyclization gave the macrocyclic lactone **51** in modest yield, and deprotection proceeded uneventfully to give (-)-roxaticin. The ^1H NMR spectrum, TLC mobility, and HRMS of (-)-roxaticin were identical to those reported for natural (+)-roxaticin. Because of the small optical rotation reported for natural roxaticin, (-)-roxaticin was further converted to its heptaacetate and found to have a ^1H NMR spectrum and a HRMS identical with those of natural roxaticin heptaacetate as well as an optical rotation of comparable magnitude and opposite sign.[43]

(42) Deprotection of the TES ether of **42** under the same conditions gave the expected alcohol and hydroxyacetone. Steric hindrance in enol ether **30** may account for the different outcome.

(43) Natural roxaticin heptaacetate (ref 7): $[\alpha]^{25}_D = -106.5°$ ($c = 0.14$, dioxane). Synthetic roxaticin heptaacetate: $[\alpha]^{24}_D = +169°$ ($c = 0.083$, dioxane). The accuracy of this rotation is unlikely to be better than within a factor of 2 considering the small sample size of synthetic roxaticin heptaacetate.

Conclusions

We have completed the first total synthesis of the unnatural isomer of roxaticin, and only the second nonrelay synthesis of a polyene macrolide antibiotic. The polyol tetraacetonide **5** was prepared in a threefold convergent route by sequential alkylation of dibromide **3** with cyanohydrin acetonides **2** and **4**. Selective reprotection of tetraacetonide **5** proved the key to the synthesis of roxaticin, leading first to the roxaticin ring system using MCP protection and then to a successful synthesis of (-)-roxaticin using the BDT protection scheme. Our synthesis of roxaticin illustrates a first generation approach to the highly convergent synthesis of polyene macrolide antibiotics that should ultimately be useful for preparing stereochemical and structural analogs.

Experimental Section

General Experimental Details. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230–400 mesh).[44] THF and ether were distilled from potassium/benzophenone ketyl. CH_2Cl_2, diisopropylamine, and toluene were distilled from CaH_2. Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using flame-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (CH_2), and primary (CH_3) carbon atoms. For overlapping signals, the number of carbon atoms is given in parentheses.

The C(12) to C(18) Fragment. 1,1-Dimethylethyl 3-Oxo-5-(phenylmethoxy)pentanoate (6b). A suspension of 60% NaH in oil (16.8 g, 0.42 mol, 1.5 equiv) was washed with hexanes (3×) and suspended in 250 mL of THF in a three-neck flask equipped with a mechanical stirrer, dropping funnel, and thermometer. A solution of 44.6 g (0.28 mol, 1 equiv) of *tert*-butyl 3-oxobutanoate in 40 mL of THF was added slowly by cannula. After H_2 evolution ceased, the flask was cooled to −10 °C and a 2.55 M solution of *n*-BuLi (121 mL, 0.31 mol, 1.1 equiv) was added dropwise. After 15 min, a solution of chloromethyl benzyl ether (43.1 mL, 0.31 mol, 1.1 equiv) in 40 mL of THF was added by cannula while the temperature was maintained below 0 °C. The mixture was allowed to warm to 25 °C overnight. The reaction was quenched with 400 mL of pH 7 phosphate buffer, and the mixture was separated and washed with ethyl acetate (3×). The combined organic layers were washed with H_2O (2×) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil (89.7 g) was purified by SiO_2 chromatography, eluting with 10% ethyl acetate/hexanes to give 38.9 g (0.14 mol, 50%) of the ester **6b** as a slightly yellow oil: IR (neat) 2979, 2932, 2869, 1714, 1454, 1393, 1368, 1315, 1252, 1205, 1148, 1103, 1047, 1028, 738, 698 cm^{-1}; ^1H

(44) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

NMR (300 MHz, $CDCl_3$) δ 7.32 (5 H, s), 4.50 (2 H, s), 3.74 (2 H, t, J = 6.3 Hz), 3.38 (2 H, s), 2.81 (2 H, t, J = 6.2 Hz), 1.45 (9 H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.8, 166.4, 138.0, 128.4 (2) , 127.7 (3), 82.0, 73.3, 65.0, 51.1, 43.0, 28.0 (3); HRMS (EI) 279.1592 (M + H).

1,1-Dimethylethyl (3*S*)-3-Hydroxy-5-(phenylmethoxy)pentanoate (7b). A sample of $[((S)\text{-BINAP})RuCl_2]_2{\cdot}Et_3N$ was prepared from 20.1 mg (0.07 mmol) of $RuCl_2{\cdot}COD$ and 52 mg (0.084 mmol) of (*S*)-BINAP as previously described.[13] A solution of 10.06 g (36 mmol) of **6b** in 20 mL of methanol was degassed with N_2 and then added to the Schlenk vessel containing the catalyst. Stirring the mixture for 30 min gave a homogenous orange solution. The mixture was acidified with 0.24 mL of 2 N HCl, transferred by cannula to a 125-mL pressure reaction vessel (Parr No. 4751), and heated to 45 °C. The vessel was pressurized to 1620 psi with H_2, and the temperature was maintained for 24 h. The mixture was concentrated and purified by SiO_2 chromatography, eluting with 20% ethyl acetate/hexanes to give 7.63 g (27.2 mmol, 76%) of the alcohol **7b** as a slightly yellow oil: IR (neat) 3495, 2977, 2931, 2866, 1727, 1454, 1392, 1367, 1292, 1253, 1214, 1153, 1101, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (5 H, s), 4.50 (2 H, s), 4.17 (1 H, m), 3.65 (2 H, m), 3.38 (1 H, d, J = 3.7 Hz), 2.39 (2 H, m), 1.76 (2 H, m), 1.44 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 172.2, 138.4, 81.3; *C*H, 128.6 (2), 127.9 (3), 67.1; CH_2, 73.5, 68.1, 42.8, 36.3; CH_3, 28.4 (3); HRMS (CI) 281.1745 (M + H). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.62; H, 8,49.

1,1-Dimethylethyl (2*S*,3*S*)-3-Hydroxy-2-methyl-5-(phenylmethoxy)-pentanoate (8). A solution of LDA was prepared from 17.0 mL (0.121 mol, 2.2 equiv) of diisopropylamine and 47.5 mL (0.121 mol, 2.2 equiv) of 2.55 M *n*-BuLi in 200 mL of THF at 0 °C. The reaction vessel was cooled to –40 °C, and a solution of 15,36 g (0.55 mol, 1.0 equiv) of **7b** in 40 mL of THF was added. The mixture was stirred at –40 °C for 1.5 h, and then 23.4 g (0.165 mol) of MeI was added in 10 mL of DMPU. After 30 min, the mixture was warmed to 25 °C and stirred for 17 h. The reaction was quenched by addition of 1 N H_2SO_4 until acidic, and the mixture was diluted with 100 mL of H_2O, separated, and washed with Et_2O (3×). The combined organic layers were washed with 1 N H_2SO_4 (2×), H_2O, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (18.9 g) was purified by MPLC on SiO2, eluting with 15% ethyl acetate/hexanes to give 3.32 g (0.012 mol, 22%) of recovered starting material and 12.14 g (0.41 mol, 75%) of **8** as a colorless oil: IR (neat) 3505, 2977, 2934, 2867, 1727, 1454, 1367, 1255, 1210, 1155, 1101, 1049, 1029, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (5 H, s), 4.50 (2 H, s), 3.85 (1 H, m), 3.68 (1 H, m), 3.63 (1 H, m), 3.19 (1 H, m), 2.41 (1 H, quintet, J = 7.3 Hz), 1.78 (1 H, m), 1.72 (1 H, m), 1.43 (9 H, s), 1.14 (3 H, d, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 175.2, 138.2, 80.8; *C*H, 128.4 (2), 127.7 (3), 72.1, 46.2; CH_2, 73.3, 68.3, 34.2; CH_3, 28.1 (3), 13.9; HRMS (CI) 295.1902 (M + H). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.17; H, 8.75.

(2*R*,3*S*)-2-Methyl-1,3-*O*-(1-methylethylidene)-5-*O*-(phenylmethyl)-1,3,5-pentanetriol (9). A solution of 5.00 g (17.0 mmol, 1 equiv) of ester **8** in 30 mL of ether was added dropwise to a stirred suspension of 1.30 g (34 mmol, 2.0 equiv) of LAH in 50 mL of ether at 0 °C. The mixture was warmed to 22 °C for 30 min. The reaction was quenched with 1.3 mL of H_2O, 2.0 mL of 15% NaOH, and 4.0 mL of H_2O, and the resulting solid was filtered. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 3.50 g (15.6 mmol, 92%) of crude diol as a viscous, colorless oil.

The crude diol was dissolved in 45 mL of acetone and 15 mL of 2,2-dimethoxypropane with 30 mg of CSA. After 20 min, the reaction was quenched with 0.2 mL of Et_3N and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, eluting with 10% EtOAc/hexanes to give 4.04 g (15.3 mmol, 90% overall yield) of the product as an 94:6 mixture of *anti* (t_R = 14.40 min) to *syn* (t_R = 14.51 min) isomers by GC analysis. The acetonide **9** was isolated as a colorless oil: $[\alpha]^{24}_D$ = –49.0° (c = 0.858, $CHCl_3$); IR (neat) 3029, 2991, 2954, 2855, 1454, 1379, 1366, 1265, 1198, 1171, 1114, 1060, 737, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (5 H, s), 4.52 (1 H, d, J = 12.0 Hz), 4.48 (1 H, d, J = 12.0 Hz), 3.56 (5 H, m), 1.95 (1 H, m), 1.61 (2 H, m), 1.41 (3 H, s), 1.36 (3 H, s), 0.75 (3 H, d, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 138.8, 98.2; *C*H, 128.4, 127.6, 127.5, 72.0, 34.4; CH_2, 73.1, 66.4, 66.2, 33.5; CH_3, 29.8, 19.2, 12.7; EIMS 249 (M – 15), 107, 91, 56. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.72; H, 9.30.

(2*R*,3*S*)-2-Methyl-1,3-*O*-(1-methylethylidene)-1,3,5-pentanetriol (10). A suspension of 365 mg (1.38 mmol, 1 equiv) of benzyl ether **9** and 12 mg of 20% $Pd(OH)_2/C$ in 10 mL of MeOH was flushed with H_2 and then stirred vigorously under balloon pressure. After 2 h, the mixture was filtered through Celite, concentrated under reduced pressure, and purified by chromatography on silica gel, eluting with 50% EtOAc/hexanes to give 220 mg (1.26 mmol, 92%) of the alcohol as a colorless oil: $[\alpha]^{24}_D$ = –37.9° (c = 0.935, $CHCl_3$); IR (neat) 3425, 2992, 2954, 1461, 1383, 1262, 1201, 1167, 1137, 1111, 1061, 1004 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.74 (4 H, m), 3.52 (1 H, t, J = 11.3 Hz), 2.70 (1 H, dd, J = 4.3, 6.7 Hz), 1.90–1.70 (3 H, m), 1.45 (3 H, s), 1.38 (3 H, s), 0.75 (3 H, d, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 98.2; *C*H, 75.8, 34.6; CH_2, 65.8, 60.9, 34.6; CH_3, 29.7, 19.0, 12.4; MS (EI) 175 (M + 1), 159, 81. Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.22; H, 10.58.

(3*S*,4*R*)-3,5-Dihydroxy-4-methyl-3,5-*O*-(1-methylethylidene)pentanal (11). The Swern reagent[45] was prepared from 1.05 mL (12 mmol, 1.2 equiv) of $(COCl)_2$ and 1.78 mL (25 mmol, 2.54 equiv) of DMSO in 50 mL of CH_2Cl_2 at –60 °C. Alcohol **10** (1.73 g, 10 mmol, 1.0 equiv) was added in 10 mL of CH_2Cl_2 over 5 min. After 15 min, Et_3N (6.9 mL, 50 mmol, 5 equiv) was added, and the reaction was allowed to warm to room temperature after 5 min. After 30 min, the reaction was diluted with NH_4Cl solution, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by filtering through a silica gel plug with ether and concentration to give 1.62 g (9.4 mmol, 94%) of the product as a yellow oil: $[\alpha]^{24}_D$ = –37.6° (c = 0.95, $CHCl_3$); IR (neat) 2993, 2961, 2856, 2729, 1727, 1461, 1382, 1369, 1262, 1198, 1168, 1111, 1063, 1024, 984, 852 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.73 (1 H, dd, J = 1.8, 2.5 Hz), 4,03 (1 H, ddd, J = 4.0, 7.7, 10.4 Hz), 3.70 (1 H, dd, J = 5.3, 11.8 Hz), 3.54 (1 H, t, J = 11.0 Hz), 2.54 (2 H, m), 1.70 (1 H, m), 1.45 (3 H, s), 1.35 (3 H, s), 0.75 (3 H, d, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 98.2; *C*H, 201.3, 70.9, 33.8; CH_2, 65.6, 46.7; CH_3, 29.3, 18.7, 12.2; HRMS (EI) 157.0866 (M – CH_3).

(2*R*,3*S*,5*S*)-2-Methyl-1,3-*O*-(1-methylethylidene)-7-octene-1,3,5-triol. A solution of 91.7 mg (0.53 mmol, 1 equiv) of aldehyde **12** in 2 mL of ether was added dropwise to 0.80 mmol (1.5 equiv) of $Ipc_2BCH_2CH{=}CH_2$ (prepared by Brown's procedure from (*R*)-(+)-α-pinene)[17] in 6 mL of ether/hexanes at –78 °C. After 13 h, the solution was brought to room temperature for 1 h and then cooled to 0 °C. The reaction was quenched with 1 mL of 15% NaOH followed by dropwise addition of 0.5 mL of 30% H_2O_2. The reaction was refluxed for 1 h, cooled to room temperature, diluted with ether, washed (2× H_2O, 1× $NaHCO_3$, and brine), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting first with CH_2Cl_2 and then with 30% EtOAc/hexanes to give 99.6 mg (0.47 mmol, 88%) of the product as a colorless oil: $[\alpha]^{24}_D$ = –38.5° (c = 0.75, $CHCl_3$); IR (neat) 3508, 3074, 2992, 2945, 2858, 1641, 1460, 1383, 1368, 1265, 1204, 1167, 1111, 1061, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.84 (1 H, m), 5.05 (2 H, m), 3.83 (1 H, m), 3.66 (3 H, m), 3.49 (1 H, t, J = 11.4 Hz), 2.19 (2 H, m), 1.80 (1 H, dt, J = 14.4, 2.2 Hz), 1.67 (1 H, m), 1.44 (3 H, s), 1.42 (1 H, m), 1.35 (3 H, s), 0.71 (3 H, d, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 98.0; *C*H, 134.7, 76.9, 71.4, 34.5; CH_2, 117.1, 65.9, 41.9, 38.9; CH_3, 29.7, 19.2, 12.6. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.97; H, 10.30.

(2*R*,3*S*,5*S*)-2-Methyl-1,3-*O*-(1-methylethylidene)-5-*O*-(trimethylsilyl)-7-octene-1,3,5-triol (12). A solution of 1.26 g (5.89 mmol, 1.0 equiv) of (2*R*,3*S*,5*S*)-2-methyl-1,3-*O*-(1-methylethylidene)-7-octene-1,3,5-triol and 2.19 mL (8.8 mmol, 1.5 equiv) of BSA in 10 mL of CH_3CN was heated to reflux for 2 h. The mixture was concentrated under reduced pressure and purified by chromatography on silica gel, eluting with 3–5% EtOAc/hexanes to give 1.47 g (5.1 mmol, 87%) of the product as a colorless oil: $[\alpha]^{24}_D$ = –25.9° (c = 0.87, $CHCl_3$); IR (neat) 3074, 2992, 2955, 2853, 1640, 1458, 1380, 1367, 1262, 1250, 1200, 1169, 1112, 1069, 1028, 1001, 910, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.80 (1 H, m), 4.98 (2 H, m), 3.90 (1 H, m), 3.64 (1 H, dd, J = 5.3, 11.6 Hz), 3.45 (2 H, m), 2.14 (2 H, m), 1.68 (1 H, m), 1.56 (2 H, m), 1.39 (3 H, s), 1.33 (3 H, s), 0.68 (3 H, d, J = 6.7 Hz), 0.08 (9 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 98.0; *C*H, 135.5, 72.1, 68.6, 34.4; CH_2, 116.7, 66.2, 40.9, 40.8; CH_3, 29.8, 19.1, 12.7, 0.3. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.56. Found: C, 62.93; H, 10.58.

(3*R*,5*S*,6*R*)-6-Methyl-5,7-*O*-(1-methylethylidene)-3-*O*-(trimethylsilyl)-3,5,7-trihydroxyheptanal (13). A solution of 1.25 g (4.37 mmol, 1 equiv) of alkene **13**, 1.46 g (7.49 mmol, 1.7 equiv) of *N*-methylmorpholine *N*-oxide hydrate, and 0.8 mL (0.079 mmol, 1.8%) of OsO_4 solution (2.5% in

(45) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

tert-butyl alcohol) in 20 mL of acetone and 6 mL of H_2O was stirred at room temperature. After 2.5 h, TLC analysis showed complete consumption of the starting alkene. A solution of 1.87 g (8.7 mmol, 2 equiv) of $NaIO_4$ in 10 mL of H_2O was added all at once. A second 0.5-g portion of $NaIO_4$ in water was added after 1 h, and stirring was continued for 30 min. The mixture was diluted with water, extracted (2× Et_2O), washed (Na_2SO_3, brine), and concentrated. The residue was dissolved in CH_2Cl_2, washed (NH_4Cl), dried (Na_2SO_4), and concentrated under reduced pressure to give 1.12 g (3.89 mmol, 89%) of the aldehyde as a tan oil: $[\alpha]^{24}_D = -42.9°$ ($c = 0.75$, $CHCl_3$); IR (neat) 2992, 2956, 2855, 2724, 1727, 1460, 1382, 1368, 1251, 1200, 1113, 1090, 1061, 1009, 842 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.73, (1 H, dd, $J = 2.2$, 2.8 Hz), 4.39 (1 H, m), 3.64 (1 H, dd, $J = 5.2$, 11.7 Hz), 3.45 (2 H, m), 2.51 (2 H, m), 1.65 (3 H, m), 1.38 (3 H, s), 1.32 (3 H, s), 0.69 (3 H, d, $J = 6.7$ Hz). 0.08 (9 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 98.0; *C*H, 202.4, 71.7, 65.0, 34.2; CH_2, 66.0, 50.1, 41.0; CH_3, 29.7, 19.0, 12.6, 0.2. Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.12; H, 9.26.

(2*S*,4*S*,6*S*,7*R*)- and (2*R*,4*S*,6*S*,7*R*)-7-Methyl-2,4:6,8-bis-*O*-(1-methylethylidene)-2,4,6,8-tetrahydroxyoctanenitrile (2). To a solution of 1.12 g (3.89 mmol, 1 equiv) of aldehyde **13** and 0.57 mL (4.3 mmol, 1.1 equiv) of TMSCN in 2 mL of CH_2Cl_2 was added 10 mg of KCN/18-crown-6 complex.[19] After 40 min, the volatiles were removed under reduced pressure, and the residue was treated with 30 mg of CSA, 15 mL of acetone, and 10 mL of 2,2-dimethoxypropane. After 3 h at 22 °C, the reaction was quenched with Et_3N and concentrated under reduced pressure. The crude product was purified by silica gel chromatography, eluting with 25% EtOAc/hexanes to give 1.02 g (3.60 mmol, 93%) of the products as a colorless, viscous oil: IR (neat) 2992, 2940, 1460, 1382, 1264, 1203, 1164, 1112, 1061, 984, 908, 880 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.80 (1 H, m), 4.40 (0.5 H, m) 4.10 (0.5 H, m), 3.68 (1 H, m), 3.47 (2 H, m), 1.90–1.60 (5 H, m), 1.67 (1.5 H, s), 1.44 (1.5 H, s), 1.40 (4.5 H, s), 1.37 (1.5 H, s), 1.35 (3 H, s), 0.72 (3 H, d, $J = 6.6$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 119.7, 118.0, 100.9, 99.9, 98.2, 98.1; *C*H, 71.5, 71.4, 64.7, 62.6, 59.2, 58.8, 34.0 (2); CH_2, 66.2, 66.1, 38.8, 38.5, 34.0, 33.1; CH_3, 29.8 (2), 29.7 (2), 21.9, 19.3 (2), 19.1, 12.6, 12.5. HRMS (CI-NH_3) 284.1835 (M + H). Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89. Found: C, 63.53; H, 8.89.

The C(24) to C(32) Fragment. Methyl 2,4-Dimethyl-3-oxopentanoate (19). A sample of 16.2 g (248 mmol, 1.25 equiv) of activated Zn dust was suspended in 200 mL of THF in a three-neck flask with mechanical stirrer and reflux condenser. The mixture was heated to reflux, and 0.3 mL of methyl 2-bromopropionate was added to initiate the reaction. To the mixture was added 35 mL (385 mmol, 2.0 equiv) of 2-methylpropionitrile followed by the slow addition of 22 mL (0.197 mmol, 1.0 equiv) of methyl 2-bromopropionate over 2 h. The mixture was heated to reflux for another hour, cooled, and then diluted with 400 mL of THF followed by 75 mL of 50% aqueous K_2CO_3. The THF was decanted from the precipitated zinc salts, and the salts were washed with THF (3×). The combined THF layers were stirred with 200 mL of 1 N HCl for 90 min. The mixture was concentrated under reduced pressure, diluted with 400 mL of CH_2Cl_2, separated, and washed with 200 mL of $NaHCO_3$ (2×) and brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure to give 25 g of crude product and a slightly yellow liquid. Distillation (93 °C at 6–10 Torr) gave 16.3 g (103 mmol, 52%) of the product as a colorless liquid: IR (neat) 2977, 2360, 1747, 1715, 1455, 1377, 1331, 1205, 1124, 1014, 857 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.67 (3 H, s), 3.66 (1 H, m), 2.78 (1 H, m), 1.28 (3 H, d, $J = 7.2$ Hz), 1.07 (6 H, d, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 209.7, 171.1; *C*H, 50.6, 40.1; CH_3, 52.3, 19.1, 18.4, 13.1; HRMS (EI) 158.0951. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.50; H, 9.09.

Methyl (2*S*,3*R*)-2,4-Dimethyl-3-hydroxypentanoate (20). A sample of [((*R*)-BINAP)$RuCl_2$]·Et_3N was prepared from 79.3 mg (0.28 mmol) of $RuCl_2$·COD and 198 mg (0.32 mmol) of (*R*)-BINAP as previously described.[13] A degassed solution of 21.7 g (137 mmol) of keto ester **19** in 30 mL of methanol was added to the catalyst in a Schlenk tube and heated to dissolve the catalyst. The orange solution was transferred by cannula to a 125-mL pressure reaction vessel (Parr No. 4751) and pressurized to 1325 psi with H_2. No change was observed after 2 days, so the vessel was heated to 80 °C for 24 h, during which time the pressure dropped by 200 psi. The solution was concentrated under reduced pressure and distilled at 63–66 °C and 1 Torr to give 20.5 g (128 mmol, 94%) of the product as a colorless oil: IR (neat) 3510, 2961, 2877, 1736, 1458, 1436, 1258, 1201, 1170, 1004, 980 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.67 (3 H, s), 3.53 (1 H, ddd, $J = 3.9$, 3.9, 7.9 Hz), 2.62 (1 H, m), 2.55 (1 H, d, $J = 4.2$ Hz), 1.60 (1 H, m), 1.14 (3 H, d, $J = 7.2$ Hz), 0.96 (3 H, d, $J = 6.6$ Hz), 0.83 (3 H, d, $J = 6.8$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 176.9; *C*H, 76.8, 41.9, 30.7; CH_3, 51.8, 19.1, 18.6, 10.3.

(2*R*,3*R*)-2,4-Dimethyl-1,3-pentanediol (21). To a suspension of 6.25 g (164 mmol, 1.55 equiv) of $LiAlH_4$ in 200 mL of ether at 0 °C was added a solution of 17.0 g (106 mmol, 1.0 equiv) of crude hydroxy ester **20** in 75 mL of ether over 40 min. The mixture was slowly warmed to reflux, at which point a very viscous precipitate separated. THF (50 mL) was added to dissolve most of the precipitate, and the mixture was heated at reflux for 16 h. The reaction was quenched by slow addition of 6 mL of H_2O, 6 mL of 15% NaOH, and 18 mL of H_2O. The precipitated alumina was removed by filtration and extracted with hot THF. The combined THF extracts were dried over 4-Å sieves and concentrated under reduced pressure to give 11.27 g (85 mmol, 80%) of the crude diol as a viscous, colorless oil.

The oil was dissolved in 10 mL of acetone and 100 mL of hexanes. Addition of a seed crystal followed by addition of another 50 mL of hexanes after 1 h, cooling to 10 °C, and filtration gave 4.85 g of fluffy white crystals, mp = 78–83 °C. Another 4.96 g of crude diol was recovered from the mother liquors by concentration and bulb-to-bulb distillation (0.25 Torr, 100 °C). The crystalline material was recrystallized from acetone/hexanes to give 4.00 g (two crops, 35% from the crude diol) of diol **21** as colorless needles: mp = 83–85 °C; $[\alpha]^{24}_D = -10.42°$ ($c = 0.96$, $CHCl_3$); IR (KBr) 3316, 2972, 2875, 1466, 1381, 1322, 1283, 1137, 1090, 1067, 1037, 989 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.66 (2 H, m), 3.36 (1 H, m), 3.18 (1 H, t, $J = 5.0$ Hz), 2.86 (1 H, d, $J = 4.6$ Hz), 1.80 (1 H, m), 1.67 (1 H, m), 0.97 (3 H, d, $J = 6.6$ Hz), 0.89 (3 H, d, $J = 7.0$ Hz), 0.82 (3 H, d, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*H, 79.6, 36.3, 31.4; CH_2, 67.7; CH_3, 19.5, 19.0, 9.0. Anal. Calcd for $C_7H_{16}O_2$: C, 63.60; H, 12.20. Found: C, 63.47; H, 11.96.

(2*R*,3*R*)-3-*O*-((1,1-Dimethylethyl)dimethylsilyl)-2,4-dimethyl-1,3-pentanediol (22). To a 0 °C solution of 1.21 g (9.2 mmol, 1.0 equiv) of diol **21** in 30 mL of CH_2Cl_2 were added 3.20 mL (27.5 mmol, 3 equiv) of 2,6-lutidine and 4.64 mL (20.2 mmol, 2.2 equiv) of TBSOTf. After 4 h, the reaction was quenched with H_2O, and the mixture was diluted with ether, washed with $NaHSO_4$ (2×) and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The remaining volatiles were removed under high vacuum to give 3.40 g (9.4 mmol, 102% of theory) of the bis-TBS ether.

A solution of the crude bis-TBS ether (3.16 g, ca. 8.8 mmol) was dissolved in 100 mL of methanol and treated with 2 g of Dowex 50-X4 (H^+) resin for 3 h at 22 °C. The mixture was filtered and concentrated under reduced pressure. Chromatography on SiO_2, eluting with 5–20–50% ethyl acetate/hexanes gave 0.57 g (1.6 mmol, 18%) of recovered bis-TBS ether, 0.22 g (1.7 mmol, 19%) of diol **21**, and 1.29 g (5.2 mmol, 60%) of TBS ether **22** as a colorless oil: $[\alpha]^{22}_D = -2.0°$ ($c = 0.64$, CH_2Cl_2); IR (neat) 3335, 2958, 2930, 1472, 1386, 1252, 1097, 1047, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.55 (1 H, m), 3.48 (2 H, m), 2.03 (1 H, br s), 1.85 (2 H, m), 0.92 (3 H, d, J = ca. 4.4 Hz), 0.90 (9 H, s), 0.88 (3 H, d, J = ca. 5 Hz), 0.84 (3 H, d, $J = 7.0$ Hz), 0.07 (3 H, s), 0.05 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.4; *C*H, 78.3, 39.3, 31.6; CH_2, 66.5; CH_3, 26.1 (3), 20.3, 19.2, 12.0, –3.9, –4.0; HRMS (EI) 231.1763 (M – CH_3). Anal. Calcd for $C_{13}H_{30}O_2Si$: C, 63.35; H, 12.27. Found: C, 63.09; H, 11.99.

(2*R*,3*R*)-3-*O*-((1,1-Dimethylethyl)dimethylsilyl)-2,4-dimethyl-3-hydroxypentanal (17). To a solution of oxalyl chloride (1.93 mL, 22 mmol, 1.1 equiv) in CH_2Cl_2 at –50 °C was added dropwise a solution of DMSO (3.12 mL, 44 mmol, 2.2 equiv) in 6 mL of CH_2Cl_2. Alcohol **22** (4.93 g, 20 mmol, 1 equiv) in 14 mL of CH_2Cl_2 was added by cannula over 5 min. After 15 min, 13.9 mL (100 mmol, 5 equiv) of Et_3N was added, and the mixture was allowed to warm to room temperature. The mixture was diluted with H_2O and extracted twice with CH_2Cl_2. The extracts were washed with brine and a $NaHSO_4$ solution, dried over $MgSO_4$, filtered through a SiO_2 plug with CH_2Cl_2, and concentrated under reduced pressure to give 5.05 g (20.6 mmol, 103% of theory) of aldehyde **17** as a colorless oil: $[\alpha]^{24}_D = +61.7°$ ($c = 0.87$, CH_2Cl_2); IR (neat) 2958, 2930, 2709, 1727, 1472, 1388, 1253, 1100, 1053, 1031, 837, 774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.77 (1 H, d, $J = 0.7$ Hz), 3.88 (1 H, dd, $J = 3.87$, 5.5 Hz), 1.80 (1 H, m), 1.23 (1 H, m), 1.07 (3 H, d, J = 6.9 Hz), 0.88 (15 H, m), 0.00 (3 H, s), –0.10 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.3; *C*H, 205.4, 76.5, 50.7, 32.3; CH_3, 26.0 (3), 19.7, 18.3, 8.7, –4.0, –4.1.

Methyl (2*E*,4*R*,5*R*)-5-*O*-((1,1-Dimethylethyl)dimethylsilyl)-4,6-dimethyl-5-hydroxy-2-heptenoate (18). A mixture of aldehyde **17** (5.05 g, ca. 20 mmol, 1 equiv) and methyl (triphenylphosphoranylidine)acetate (10.66 g, 31.9 mmol, 1.6 equiv) in 80 mL of dry acetonitrile was heated

to reflux for 18 h. The mixture was concentrated, diluted with 50 mL of CH_2Cl_2 and 100 mL of hexanes, and filtered through an SiO_2 plug to remove most of the polar impurities. The solution was concentrated to ca. 75 mL, diluted with 100 mL of hexanes, and cooled to 0 °C. Filtration removed the precipitated PPh_3O, and the resulting solution was concentrated and then chromatographed on SiO_2, eluting with 3–5% ethyl acetate/hexanes to give 5.78 g (19.3 mmol, 96%) of ester **18** as a colorless oil: $[\alpha]^{23}_D = +34.0°$ ($c = 1.48$, CH_2Cl_2); IR (neat) 2957, 2857, 1728, 1658, 1434, 1335, 1254, 1175, 1054, 837, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (1 H, dd, J = 7.8, 15.7 Hz), 5.77 (1 H, dd, J = 1.1, 15.7 Hz), 3.70 (3 H, s), 3.36 (1 H, t, J = 4.8 Hz), 2.48 (1 H, m), 1.71 (1 H, m), 1.03 (3 H, d, J = 6.8 Hz), 0.89 (9 H, s), 0.86 (3 H, d, J = 5.7 Hz), 0.85 (3 H, d, J = 6.7 Hz), 0.03 (3 H, s), 0.01 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 167.2, 18.4; *C*H, 153.2, 119.7, 80.0, 40.9, 32.0; *C*H_3, 51.3, 26.1 (3), 20.3, 17.5, 15.1, –3.7, –3.8; HRMS (CI-CH_4) 301.2175 (M + H). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.75; H, 10.54.

(2*E*,4*R*,5*R*)-5-*O*-((1,1-Dimethylethyl)dimethylsilyl)-4,6-dimethyl-2-heptene-1,5-diol. To a –78 °C solution of 5.78 g (19.3 mmol, 1 equiv) of ester **18** in 100 mL of ether was added 42.5 mL (42.5 mmol, 2.2 equiv) of a 1 M solution of DIBAL-H in cyclohexanes. After 30 min, the mixture was warmed to 0 °C and stirred for an additional 75 min. The solution was slowly added to 200 mL of 10% HOAc in water and stirred for 2 h at 22 °C. The mixture was extracted (2× ether), washed (water, $NaHCO_3$, brine), and dried ($MgSO_4$). The ether solution was filtered through a plug of silica gel with ether and concentrated under reduced pressure to give 5.09 g (18.7 mmol, 97%) of the product as a colorless oil: $[\alpha]^{24}_D = +21.7°$ ($c = 1.18$, CH_2Cl_2); IR (neat) 3317, 2958, 2930, 2856, 1472, 1385, 1252, 1053, 1006, 976, 856, 836, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.62 (2 H, m), 4.08 (2 H, d, J = 4.5 Hz), 3.25 (1 H, dd, J = 4.3, 5.5 Hz), 2.33 (1 H, h, J = 6.3 Hz), 1.73 (1 H, m), 1.37 (1 H, s), 0.98 (3 H, d, J = 6.7 Hz), 0.89 (9 H, s), 0.85 (6 H, t, J = 6.9 Hz), 0.02 (3 H, s), 0.01 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.5; *C*H, 137.3, 127.7, 80.8, 40.6, 31.7; *C*H_2, 64.0; *C*H_3, 26.2 (3), 29.6, 17.6, 16.1, –3.5, –3.7; HRMS (CI-CH_4) 273.2233 (M + H). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 65.83; H, 11.65.

(2*E*,4*R*,5*R*)-5-*O*-((1,1-Dimethylethyl)dimethylsilyl)-4,6-dimethyl-5-hydroxy-2-heptenal (23). A solution of 4.28 g (36.6 mmol, 2.7 equiv) of *N*-methylmorpholine *N*-oxide monohydrate in 70 mL of CH_2Cl_2 was dried over 4-Å molecular sieves. The solution was filtered and added to 5.09 g (18.7 mmol, 1 equiv) of (2*E*,4*R*,5*R*)-5-*O*-((1,1-dimethylethyl)-dimethylsilyl)-4,6-dimethyl-2-heptene-1,5-diol in 50 mL of CH_2Cl_2 with 7 g of powered 4-Å sieves. After 30 min, 180 mg (0.51 mmol, 2.7%) of tetrapropylammonium perruthenate was added with stirring in a water bath to moderate the mildly exothermic reaction. After 90 min, the mixture was filtered through Celite, washed ($NaHSO_4$), and dried (Na_2SO_4). The dark solution was filtered through a silica gel plug with CH_2Cl and concentrated under reduced pressure to give 4.58 g (16.9 mmol, 91%) of the product as a tan oil: $[\alpha]^{24}_D = +47.2°$ ($c = 1.18$, CH_2Cl_2); IR (neat) 2958, 2930, 2857, 1694, 1472, 1387, 1254, 1114, 1081, 1054, 858, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (1 H, d, J = 7.8 Hz), 6.91 (1 H, dd, J = 7.0, 15.8 Hz), 6.09 (1 H, ddd, J = 1.3, 7.8, 15.8 Hz), 3.44 (1 H, t, J = 4.9 Hz), 2.63 (1 H, h, J = 6.8 Hz), 1.73 (1 H, m), 1.08 (3 H, d, J = 6.8 Hz), 0.89 (9 H, s), 0.87 (3 H, d, J = 7 Hz), 0.82 (3 H, d, J = 6.8 Hz), 0.04 (3 H, s), 0.02 (3 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.2; *C*H, 194.2, 162.4, 131.5, 79.8, 41.6, 31.8; *C*H_3, 26.1 (3), 20.5, 17.6, 14.7, –3.6, –3.9; HRMS (CI-CH_4) 271.2073 (M + H).

(3*R*,4*R*,5*E*,7*S*)-3-*O*-((1,1-Dimethylethyl)dimethylsilyl)-2,4-dimethyl-5,9-decadiene-3,7-diol (24). A solution of 4.58 g (16.9 mmol, 1 equiv) of aldehyde **23** in 20 mL ether was added dropwise to 50 mmol (3 equiv) of $Ipc_2BCH_2CH{=}CH_2$ (prepared by Brown's procedure from (*R*)-(+)-α-pinene)[17] in 120 mL of ether at –78 °C. The well-insulated cooling bath was allowed to warm to room temperature overnight, and then the mixture was cooled to 0 °C. The reaction was quenched with 50 mL of 15% NaOH followed by ***dropwise*** addition of 15 mL of 30% H_2O_2. The reaction was refluxed for 1.5 h, cooled to room temperature, and filtered through Celite with ether. The solution was diluted with water, extracted (2× ether), washed (NH_4Cl, brine), dried ($MgSO_4$), and concentrated under reduced pressure (<0.1 Torr, 50 °C) to remove the pinenol. The crude product was purified by chromatography on silica gel, eluting with 5–10% EtOAc/hexanes to give 4.43 g (14.2 mmol, 84%) of the product as a colorless oil: $[\alpha]^{24}_D = +12.1°$ ($c = 0.91$, $CHCl_3$); IR (neat) 3346, 2958, 2930, 2857, 1640, 1472, 1252, 1113, 1053, 1005, 974, 858, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (1 H, m), 5.62 (1 H, dd, J = 8.3, 15.5 Hz), 5.44 (1 H, dd, J = 7.1, 15.5 Hz), 5.12 (2 H, m), 4.12 (1 H, m), 3.25 (1 H, dd, J = 3.9, 6.0 Hz), 2.30 (3 H, m), 1.73 (1 H, m), 1.56 (1 H, d, J = 4.0 Hz), 0.98 (3 H, d, J = 6.7 Hz), 0.89 (9 H, s), 0.87 (1 H, d, J = 6.8 Hz), 0.83 (3 H, d, J = 6.8 Hz), 0.03 (6 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.5; *C*H, 136.1, 134.4, 131.0, 80.9, 72.0, 40.9, 31.7; *C*H_2, 118.0, 42.1; *C*H_3, 26.2 (3), 20.6, 17.3, 16.7, –3.5, –3.7; HRMS (CI-CH_4) 313.2563 (M + H). Anal. Calcd for $C_{18}H_{36}O_2Si$: C, 69.17; H, 11.61. Found: C, 68.89; H, 11.36.

(3*R*,4*R*,5*E*,7*S*)-3-*O*-((1,1-Dimethylethyl)dimethylsilyl)-2,4-dimethyl-7-*O*-(triethylsilyl)-5,9-decadiene-3,7-diol (25). A solution of 4.43 g (14.2 mmol, 1 equiv) of alcohol **24** in 100 mL of CH_2Cl_2 at 0 °C was treated with 2.15 mL (18.5 mmol, 1.3 equiv) of 2,6-lutidine and 3.53 mL (15.6 mmol, 1.1 equiv) of TESOTf. After 2 h, the mixture was diluted with water and ether, washed (H_2O, 2× $NaHSO_4$, brine), dried ($MgSO_4$), and concentrated under reduced pressure to give 6.32 g (theory = 6.05 g) of product as a tan oil: $[\alpha]^{24}_D = +9.36°$ ($c = 0.98$, CH_2Cl_2); IR (neat) 2956, 2876, 1641, 1461, 1252, 1056, 1005, 974, 858, 836, 727, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (1 H, m), 5.43 (2 H, m), 5.01 (2 H, m), 4.05 (1 H, q, J = 6.4 Hz), 3.24 (1 H, dd, J = 3.2, 6.5 Hz), 2.27 (3 H, m), 1.74 (1 H, m), 0.95 (12 H, m), 0.91 (9 H, s), 0.87 (3 H, d, J = 6.9 Hz), 0.82 (3 H, d, J = 6.7 Hz), 0.57 (6 H, q, J = 7.8 Hz), 0.04 (6 H, s); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.3; *C*H, 135.1, 134.4, 132.1, 80.8, 73.6, 41.2, 31.5; *C*H_2, 116.6, 43.2, 5.0; *C*H_3, 26.2 (3), 20.7, 17.3, 16.7, 6.8, –3.5, –3.7; HRMS (CI-CH_4) 427.3400 (M + H). Anal. Calcd for $C_{24}H_{50}O_2Si_2$: C, 67.54; H, 11.81. Found: C, 67.33; H, 11.61.

(2*S*,4*S*,5*E*,7*R*,8*R*)- and (2*R*,4*S*,5*E*,7*R*,8*R*)-8-*O*-((1,1-Dimethylethyl)-dimethylsilyl)-7,9-dimethyl-5-decene-1,2,4,8-tetraol (26). A solution of 6.32 g (14.2 mmol, 1 equiv) of diene **25** and 1.74 g (14.9 mmol, 1.05 equiv) of *N*-methylmorpholine *N*-oxide monohydrate in 12 mL of water and 140 mL of acetone was treated with 1.7 mL (0.17 mmol, 1.2%) of OsO_4 solution (2.5% in *tert*-butyl alcohol). After 51 h at 23 °C, the reaction was quenched by addition of Celite and 190 mg of $Na_2S_2O_4$ in 2 mL of water. The mixture was filtered through Celite after 1 h and concentrated under reduced pressure. The residue was treated with 50 mL of a 2:2:1 mixture of THF/HOAc/H_2O for 3 h at 23 °C to remove the triethylsilyl ether. The mixture was concentrated under reduced pressure and purified by silica gel chromatography, eluting with 70–100% EtOAc/hexanes to give 3.55 g (10.3 mmol, 72%) of the product as a mixture of isomers. Subsequent hydrolysis of the nonpolar fractions followed by chromatography gave another 0.20 g (0.58 mmol, 4%) of the product as a tan oil: IR (neat) 3354, 2957, 2857, 1471, 1385, 1360, 1252, 1114, 1053, 974, 836, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.63 (1 H, dd, J = 7.7, 15.5 Hz), 5.44 (1 H, m), 4.33 (1 H, m), 3.95 (1 H, m), 3.60 (1 H, dd, J = 3.1, 11.2 Hz), 3.47 (2 H, m), 3.25 (1 H, dd, J = 3.8, 5.9 Hz), 3.00 (2 H, br s) 2.28 (1 H, m), 1.61 (3 H, m), 0.97 (3 H, d, J = 6.7 Hz), 0.89 (9 H, s), 0.86 (3 H, d, J = 6.9 Hz), 0.81 (3 H, d, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C*, 18.4 (2); *C*H, 136.0, 135.9, 131.1, 131.0, 80.7 (2), 73.0, 72.0, 70.2, 69.5, 40.9, 40.8, 31.7 (2); *C*H_2, 66.8, 66.7, 39.4, 39.3; *C*H_3, 26.2 (6), 20.5 (2), 17.4 (2), 16.6, 16.5, –3.5 (2), –3.8 (2); HRMS (CI-CH_4) 347.2614 (M + H). Anal. Calcd for $C_{18}H_{38}O_4Si$: C, 62.38; H, 11.05. Found: C, 62.18; H, 10.96.

(2*R*,4*S*,5*E*,7*R*,8*R*)- and (2*R*,4*S*,5*E*,7*R*,8*R*)-8-*O*-((1,1-Dimethylethyl)-dimethylsilyl)-7,9-dimethyl-2,4-*O*-(1-methylethylidene)-2,4,8-trihydroxy-5-decenenitrile (4). A solution of 3.55 g (10.3 mmol, 1 equiv) of triol **26** in 100 mL of MeOH was treated with a solution of 3.32 g (15.5 mmol, 1.5 equiv) of $NaIO_4$ in 20 mL of water. After 25 min, the mixture was concentrated, diluted with NH_4Cl, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated under redueed pressure. The resulting crude aldehyde was treated with 4.7 mL (51.5 mmol, 5 equiv) of acetone cyanohydrin, 50 mL of THF, and 100 mg of powdered K_2CO_3 under N_2. After 25 h at 22 °C, the mixture was diluted with NH_4Cl, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated. The crude product was filtered through a plug of silica gel, eluting with 35% EtOAc/hexanes to give 3.50 g (10.2 mmol, 99%) of the cyanohydrins, which were used without further purification.

The crude cyanohydrins were combined with 25 mL of 2,2-dimethoxypropane and 125 mL of acetone and treated with 80 mg of CSA. After 18 h at 23 °C, the reaction was quenched with Et_3N and the solvent removed under reduced pressure. The crude product was purified by chromatography on silica gel, eluting with 10–50% EtOAc/hexanes to give 0.55 g (1.6 mmol, 16%) of recovered cyanohydrin and 3.04 g (7.97 mmol, 78%) of the product as a colorless oil: IR (neat) 2958, 2931, 2856, 1472, 1462, 1383, 1257, 1203, 1161, 1096, 1055, 1024, 1005, 975, 858, 836, 773 cm^{-1}; ^1H NMR (*syn* isomer, 200 MHz, $CDCl_3$) δ 5.74 (1 H, dd, J = 7.8, 15.6 Hz), 5.40 (1 H, dd, J = 6.3, 15.6 Hz), 4.77 (1 H, dd, J = 3.8, 11.0 Hz), 4.29 (1 H, m), 3.26 (1 H, dd, J = 4.2, 8.8 Hz), 2.31

(1 H, m), 1.6–2.0 (3 H, m), 1.46 (3 H, s), 1.44 (3 H, s), 0.97 (3 H, d, J = 6.8 Hz), 0.89 (9 H, s), 0.86 (3 H, d, J = 7.0 Hz), 0.82 (3 H, d, J = 6.8 Hz), 0.02 (3 H, s), 0.00 (3 H, s); ^{13}C NMR (*syn* isomer, 75 MHz, $CDCl_3$, DEPT) δ *C*, 117.5, 99.8, 18.2; *CH*, 137.8, 127.4, 80.7, 69.0, 59.0, 40.7, 31.6; *CH*$_2$, 34.6; *CH*$_3$, 29.6, 26.2 (3), 20.5, 19.2, 17.8, 15.6, –3.5, –3.7; ^{1}H NMR (*anti* isomer, 200 MHz, $CDCl_3$) δ 5.74 (1 H, dd, J = 7.8, 15.6 Hz), 5.36 (1 H, dd, J = 6.1, 15.6 Hz), 4.84 (1 H, dd, J = 2.2, 6.4 Hz), 4.60 (1 H, ddd, J = 2.5, 6.1, 11.1 Hz), 3.27 (1 H, t, J = 4.8 Hz), 2.33 (1 H, m), 1.97 (1 H, m), 1.80 (2 H, m), 1.70 (3 H, s) 1.39 (3 H, s), 0.98 (3 H, d, J = 6.8 Hz), 0.90 (9 H, s), 0.87 (3 H, d, J = 6.9 Hz), 0.83 (3 H, d, J = 6.8 Hz), 0.02 (6 H, s); ^{13}C NMR (*anti* isomer, 75 MHz, $CDCl_3$, DEPT) δ *C*, 120.1, 101.2, 18.3; *CH*, 137.9, 127.3, 80.7, 66.6, 58.8, 40.7, 31.6; *CH*$_2$, 33.4; *CH*$_3$, 29.9, 26.2 (3), 21.9, 20.5, 17.8, 15.6, –3.5, –3.7; HRMS (CI-CH_4) 427.3400 (M + H). Anal. Calcd for $C_{21}H_{39}NO_3Si$: C, 66.09; H, 10.30. Found: C, 65.95; H, 10.19.

Assembling the Polyol Chain. (2*R*,3*S*,5*S*,7*R*,9*R*,11*R*)-12-Bromo-7-cyano-1,3:5,7:9,11-tris-*O*-(1-methylethylidene)dodecane-1,3,5,7,9,11-hexol (28). A solution of 787 mg (2.78 mmol, 1 equiv) of nitriles **2** in 5 mL of THF was added dropwise to 3.06 mmol (1.1 equiv) of $LiNEt_2$ in 30 mL of THF at –78 °C. After 1 h, a solution of 1.71 g (5.66 mmol, 2.0 equiv) of dibromide **3** in 3 mL of THF was added by cannula, and the reaction was transferred to a –18 °C ice/MeOH bath. The system was allowed to warm to 10 °C over 13 h. The mixture was diluted with NH_4Cl, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on silica gel, eluting with 10–15–25% EtOAc/hexanes to give 1.00 g (3.31 mmol, 58%) of recovered dibromide and 875 mg (1.74 mmol, 63%) of the coupled product as a colorless oil: $[\alpha]^{24}_D$ = +14.3° (c = 1.58, CH_2Cl_2); IR (neat) 2990, 2939, 2857, 2246, 1460, 1382, 1264, 1224, 1202, 1176, 1122, 1060, 911, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (1 H, m), 4.25 (1 H, dq, J = 5.7, 8.5 Hz), 4.00 (1 H, quintet, J = 6.0 Hz), 3.66 (1 H, dd, J = 5.1, 11.7 Hz), 3.45 (2 H, m), 3.33 (2 H, d, J = 6.2 Hz), 1.6–2.0 (8 H, m), 1.68 (3 H, s), 1.43 (1 H, m), 1.39 (3 H, s), 1.38 (3 H, s), 1.35 (3 H, s), 1.33 (6 H, s), 0.71 (3 H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 121.2, 101.1, 100.9, 98.0, 68.3; *CH*, 71.4, 66.7, 63.0, 62.4, 34.0; *CH*$_2$, 66.1, 47.7, 40.4, 38.5, 37.4, 35.0; *CH*$_3$, 31.0, 29.7, 24.6, 24.4, 21.6, 19.0, 12.6; HRMS (CI-CH_4) 504.1964 (M + H). Anal. Calcd for $C_{23}H_{38}BrNO_6$: C, 54.76; H, 7.59. Found: C, 54.95; H, 7.69.

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-7,13-Di-cyano-19-*O*-((1,1-dimethylethyl)dimethylsilyl)-1,3:5,7:9,11:13,15-tetrakis-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (29). A solution of 1.42 g (3.73 mmol, 2.2 equiv) of nitriles **4** in 5 mL of THF was added dropwise to 3.73 mmol (2.2 equiv) of $LiNEt_2$ in 35 mL of THF at –78 °C. After 1 h, a solution of 855 mg (1.70 mmol, 1 equiv) of bromide **28** in 3 mL of THF was added by cannula, and after another hour the reaction was transferred to a –18 °C ice/MeOH bath. The bath was allowed to warm to 10 °C over 20 h. The mixture was diluted with NH_4Cl, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on silica gel, eluting with 5–10–15% EtOAc/hexanes to give 228 mg (0.60 mmol, 16%) of recovered cyanohydrin **4** and 1.24 g (1.54 mmol, 91%) of the coupled product **29** as a slightly yellow oil: $[\alpha]^{23}_D$ = +24.7° (c = 0.50, CH_2Cl_2); IR (neat) 2957, 2361, 1463, 1383, 1252, 1225, 1204, 1176, 1124, 1058, 836, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (1 H, dd, J = 7.9, 15.6 Hz), 5.36 (1 H, dd, J = 6.3, 15.5 Hz), 4.58 (1 H, m), 4.40 (1 H, m), 4.23 (2 H, m), 3.68 (1 H, dd, J = 5.1, 11.7 Hz), 3.49 (2 H, m), 3.25 (1 H, t, J = 4.7 Hz), 2.32 (1 H, sextet, J = 6.5 Hz), 1.2–2.0 (14 H, m), 1.71 (3 H, s), 1.69 (3 H, s), 1.40 (3 H, s), 1.37 (12 H, s), 1.34 (3 H, s), 0.98 (3 H, d, J = 6.8 Hz), 0.89 (9 H, s), 0.86 (3 H, d, J = 7.0 Hz), 0.82 (3 H, d, J = 6.7 Hz), 0.73 (3 H, d, J = 6.6 Hz), 0.02 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 121.2, 121.0, 100.8, 100.70, 100.67, 97.9, 68.3, 68.2, 18.2; *CH*, 137.7, 127.5, 80.8, 71.4, 67.2, 63.0, 62.4, 62.3, 40.8, 34.1, 31.7; *CH*$_2$, 66.1, 47.9, 47.6, 40.9, 40.4, 39.2, 38.6; *CH*$_3$, 31.0(2), 29.6, 26.1(3), 24.4(2), 21.7(2), 20.4, 19.0, 17.7, 15.8, 12.6, –3.5, –3.7; HRMS (CI-CH_4) 805.5372 (M + H). Anal. Calcd for $C_{44}H_{76}O_9Si$: C, 65.64; H, 9.51; N, 3.48. Found: C, 65.78; H, 9.36; N, 3.45.

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-((1,1-Dimethylethyl)dimethylsilyl)-1,3:5,7:9,11:13,15-tetrakis-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (5). A solution of LiDBB[29] was prepared by cutting 4 cm (180 mg, 26 mmol, 17 equiv) of Li wire into a solution of 4.15 g (15.4 mmol, 10 equiv) of di-*tert*-butylbiphenyl in 80 mL of THF at 0 °C. After 5 h, the dark green solution was transferred to a dry flask by cannula and cooled to –78 °C. A solution of 1.24 g (1.54 mmol, 1 equiv) of the dinitrile **29** in 10 mL of THF was added over 15 min by cannula. After 1 h, the reaction was quenched by addition of 3.1 mL (77 mmol, 50 equiv) of MeOH in 10 mL of THF all at once. The mixture was diluted with NH_4Cl, extracted (3× CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was chromatographed on silica gel, eluting with 25% CH_2Cl_2/hexanes and then 15% EtOAc/hexanes. Further purification by MPLC using a 25-cm × 2.5-cm silica gel column and eluting with 10% EtOAc/hexanes gave 729 mg (0.97 mmol, 63%) of product as a colorless oil: $[\alpha]^{24}_D$ = –14.3° (c = 1.36, CH_2Cl_2); IR (neat) 2989, 2949, 2856, 1462, 1379, 1251, 1224, 1200, 1170, 1127, 1059, 939 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (1 H, dd, J = 7.9, 15.5 Hz), 5.35 (1 H, dd, J = 6.4, 15.5 Hz), 4.26 (1 H, m), 4.03 (5 H, m), 3.63 (1 H, dd, J = 5.2, 11.7 Hz), 3.48 (1 H, m), 3.44 (1 H, t, J = 11.5 Hz), 3.21 (1 H, t, J = 4.8 Hz), 2.27 (1 H, sextet, J = 6.2 Hz), 1.9–1.0 (14 H, m), 1.41 (3 H, s), 1.39 (3 H, s), 1.36 (6 H, s), 1.33 (3 H, s), 1.33 (3 H, s), 1.30 (6 H, s), 0.94 (3 H, d, J = 6.8 Hz), 0.86 (9 H, s), 0.83 (3 H, d, J = 6.9 Hz), 0.79 (3 H, d, J = 6.7 Hz), 0.69 (3 H, d, J = 6.6 Hz), –0.01 (3 H, s), –0.02 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 100.6, 98.6, 98.5, 98.0, 18.5; *CH*, 136.2, 129.5, 80.9, 71.4, 70.4, 65.6, 64.8, 64.7, 62.4 (2), 40.6, 34.3, 31.6; *CH*$_2$, 66.1, 42.4, 42.2, 39.6, 39.0, 37.6, 36.7; *CH*$_3$, 30.3 (2), 29.8, 26.2 (3), 24.4 (2), 20.5, 20.0, 19.8, 19.0, 17.8, 15.7, 12.6, –3.5, –3.7; HRMS (FAB) 777.5303 (M + Na). Anal. Calcd for $C_{42}H_{78}O_9Si$: C, 66.80; H, 10.41. Found: C, 66.85; H, 10.36.

The MCP Ether Approach. (2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-((1,1-Dimethylethyl)dimethylsilyl)-3-*O*-(1-methylcyclopropyl)-1-*O*-(triethylsilyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol. To a solution of **5** (345 mg, 0.457 mmol, 1.0 equiv) in 3 mL of 1,2-dichloroethane in a resealable tube at 0 °C were added 0.75 mL of Hunig's base (4.3 mmol, 9.5 equiv) and 210 mL of triethylsilyl triflate (0.93 mmol, 2.0 equiv). The sealed tube was warmed in a drying pistol over refluxing toluene at ca. 110 °C for 18 h. The tube was cooled to room temperature, and the contents were diluted with 30 mL of hexanes and filtered through a plug of activity III alumina, eluting with 10% ethyl acetate/hexanes. The crude enol silyl ether **30** was isolated by removing the solvent under reduced pressure. To a solution of the crude enol silyl ether in 30 mL of dry Et_2O was added a 1 M solution of Et_2Zn in hexanes (3 mL, 3 mmol, 6.5 equiv) followed by 400 mL of diiodomethane (5.0 mmol, 11 equiv). After 6 h, the reaction was quenched with 2 N NaOH and extracted with Et_2O (3×). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with 5–7–10–15% ethyl acetate/hexanes, gave 30.1 mg (8.7%) of recovered **5** along with 325 mg (0.368 mmol, 80%) of the MCP ether as a colorless oil: IR (neat) 2954, 2876, 1379, 1252, 1224, 1199, 1170, 1094, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (1 H, dd, J = 7.8, 15.6 Hz), 5.35 (1 H, dd, J = 6.8, 15.6 Hz), 4.29 (1 H, m), 4.05 (5 H, m), 3.78 (1 H, m), 3.48 (1 H, m), 3.40 (2 H, d, J = 6.8 Hz), 3.23 (1 H, t, J = 4.9 Hz), 2.30 (1 H, sextet, J = 5.9 Hz), 2.10 (1 H, m), 1.7–1.3 (14 H, m), 1.42 (3 H, s), 1.39 (3 H, s), 1.38 (3 H, s), 1.35 (3 H, s), 1.34 (3 H, s), 1.31 (6 H, s), 1.0–0.7 (13 H, m), 0.94 (9 H, t, J = 7.8 Hz), 0.88 (9 H, s), 0.56 (6 H, q, J = 7.8 Hz), 0.35 (2 H, d, J = 2.0 Hz), 0.01 (3 H, s), 0.00 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 129.4, 100.5, 98.5, 98.4, 80.9, 73.0, 70.5, 66.4, 65.0, 64.9 (2), 64.8, 62.4, 56.4 (2), 42.3, 42.2, 40.6, 39.0, 38.4, 37.5, 37.4, 37.0, 31.6, 30.3 (2), 26.2 (3), 24.4 (2), 20.4, 19.8, 18.4, 17.7, 15.7, 13.9, 13.5, 11.4, 11.3, 6.8 (3), 4.4 (3), –3.5, –3.7; HRMS (FAB) 905.6283 (M + Na).

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-3-*O*-(1-Methylcyclopropyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (31). The MCP ether (588 mg, 0.67 mmol) was dissolved in 15 mL of THF and treated with 5 mL (5 mmol, 7.5 equiv) of a 1 M solution of *n*-Bu_4NF in THF. The mixture was refluxed under N_2 for 7 h and then cooled to room temperature, diluted with brine, and extracted (3× EtOAc). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude diol was purified by SiO_2 chromatography, eluting with 50–70% ethyl acetate/hexanes to give 453 mg (0.69 mmol, 103% of theory) of diol **31** as a colorless, viscous oil: IR (neat) 3443, 2987, 2940, 2874, 1455, 1380, 1253, 1224, 1200, 1169, 1128, 1025, 981, 938 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (1 H, dd, J = 7.3, 15.9 Hz), 5.47 (1 H, dd, J = 6.1, 15.9 Hz), 4.32 (1 H, m), 4.05 (5 H, m), 3.95 (1 H, m), 3.73 (1 H, m), 3.60 (1 H, d, J = 7.3 Hz), 3.45 (1 H, dd, J = 6.1, 9.8 Hz), 3.14 (1 H, s), 2.71 (1 H, s), 2.38 (3 H, m), 1.92 (1 H, m), 1.78 (1 H, m), 1.70 (1 H, m), 1.64 (1 H, m), 1.65–1.10 (8 H, m), 1.43 (3 H, s), 1.39 (6 H, s), 1.37 (3 H, s), 1.34 (3 H, s), 1.31 (6 H, s), 1.01 (3 H, d, J = 6.1 Hz), 0.89 (9 H, m), 0.77 (2 H, s), 0.39 (2 H, d, J = 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.8, 131.0, 100.4, 98.6, 98.4, 79.7, 77.6, 70.2, 66.2, 66.1, 65.0, 64.7, 62.4, 56.8, 53.9, 42.2, 42.1, 39.2, 38.9,

38.5, 37.7, 37.5, 30.5, 30.3, 30.2, 29.1, 24.4 (2), 22.4, 20.7, 19.8, 19.7, 19.6, 17.1, 14.1, 13.7, 13.0; HRMS (FAB) 655.4783 (M + H).

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-(Diethylphosphonoacetyl)-3-*O*-(1-methylcyclopropyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (32). The diol **31** (453 mg, 0.66 mmol, 1.0 equiv) was combined with DMAP (380 mg, 3.1 mmol, 4.5 equiv) and BOP (1.05 g, 2.3 mmol, 3.4 equiv) in 10 mL of CH_2Cl_2. A solution of 446 mg (2.27 mmol, 3.3 equiv) of the diethyl phosphonoacetic acid in 5 mL of CH_2Cl_2 was added dropwise, and the reaction was stirred at 25 °C for 23 h. The mixture was diluted with EtOAc, washed with NH_4Cl and $NaHCO_3$ solutions, dried over Na_2SO_4, and concentrated under reduced pressure. The crude bis ester was treated with 50 mL of NH_3-saturated MeOH for 25 h at 25 °C. The reaction mixture was concentrated and chromatographed on SiO_2, eluting with EtOAc. The resulting oil was dissolved in CH_2Cl_2 and filtered to remove a small amount of solid impurity. The eluant was concentrated to give 499 mg (0.60 mmol, 91%) of the phosphonoacetate **32** as a colorless foam: IR (neat) 3443, 2939, 1732, 1653, 1455, 1380, 1256, 1200, 1170, 1126, 1028, 974, 938 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (2 H, m), 4.70 (1 H, dd, J = 4.9, 7.8 Hz), 4.28 (1 H, d, J = 8.8 Hz), 4.15 (4 H, quintet, J = 7.4 Hz), 4.02 (5 H, m), 3.73 (1 H, m), 3.60 (1 H, m), 3.46 (1 H, m), 2.95 (2 H, d, 22.0 Hz), 2.73 (1 H, t, J = 6.1 Hz), 2.44 (1 H, m), 2.00–1.10 (13 H, m), 1.42 (3 H, s), 1.39 (3 H, s), 1.37 (6 H, s), 1.34 (3 H, m), 1.33 (6 H, t, J = 6.8 Hz), 1.30 (6 H, s), 0.98 (3 H, d, J = 6.3 Hz), 0.88 (10 H, m), 0.76 (2 H, s), 0.39 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 133.2, 131.4, 100.4, 98.6, 98.4, 82.2, 77.6, 70.2, 66.2, 66.1, 65.0, 64.7, 62.5, 62.4, 62.3 (2), 56.8, 42.2 (2), 38.9, 38.4, 37.7, 37.5, 37.4, 35.1, 33.3, 30.2 (2), 29.5, 24.4 (2), 22.3, 19.8, 19.7, 19.6, 16.4, 16.2 (2), 15.6, 14.1, 13.7, 13.0; HRMS (FAB) 833.5151 (M + H). Anal. Calcd for $C_{43}H_{77}O_{13}P$: C, 62.00; H, 9.32. Found: C, 61.78; H, 9.19.

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-(Diethylphosphonoacetyl)-3-*O*-(1-methylcyclopropyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-3,5,7,9,11,13,15,19-octahydroxy-2,18,20-trimethyl-16-heneicosenal (33). A solution of 67.8 mg (81 μmol, 1 equiv) of alcohol **32** and 30 mg of NMO monohydrate (256 μmol, 3.1 equiv) in CH_2Cl_2 was dried with 4-Å molecular sieves. After 30 min, 2.6 mg (7.4 μmol, 9%) of TPAP was added, and the mixture was stirred for 2.5 h. The reaction mixture was filtered through Celite, concentrated, and chromatographed on SiO_2, eluting with 70% EtOAc/hexanes to give 47.0 mg (56 μmol, 70%) of aldehyde **33** as a colorless oil: IR (neat) 2986, 2940, 1380, 1257, 1224, 1200, 1170, 1126, 1027, 971, 938 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (1 H, d, J = 1.8 Hz), 5.47 (2 H, m), 4.70 (1 H, dd, J = 4.9, 7.8 Hz), 4.28 (1 H, d, J = 11.2 Hz), 4.16 (4 H, quintet, J = 7.3 Hz), 4.04 (5 H, m), 3.92 (1 H, m), 2.95 (2 H, d, 22.0 Hz), 2.68 (1 H, m), 2.44 (1 H, m), 1.84 (2 H, m), 1.60–1.10 (11 H, m), 1.42 (3 H, s), 1.37 (9 H, s), 1.33 (6 H, t, J = 7.2 Hz), 1.30 (9 H, s), 1.07 (3 H, d, J = 6.9 Hz), 0.98 (3 H, d, J = 6.9 Hz), 0.87 (6 H, d, J = 6.9 Hz), 0.75 (2 H, s), 0.40 (2 H, m); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 165.6, 100.4, 98.6, 98.4, 56.9; *C*H, 204.6, 133.2, 131.6, 82.2, 73.5, 70.2, 65.6, 65.0, 64.8, 62.4 (2), 49.7, 38.5, 29.6; *C*H_2, 62.6, 42.2 (2), 39.0, 38.9, 37.6, 37.5, 35.1, 33.3, 13.8, 13.1; *C*H_3, 30.3, 30.2, 24.4 (2), 22.2, 19.8, 19.7, 19.6, 16.4, 16.3 (2), 15.6, 9.7.

(6*R*,7*S*,9*R*,11*R*,13*R*,15*R*,17*R*,19*S*,20*E*,22*R*,13*R*)-23-*O*-(Diethylphosphonoacetyl)-7-*O*-(1-methylcyclopropyl)-9,11:13,15:17,19-tris-*O*-(1-methylethylidene)-7,9,11,13,15,17,19,23-octahydroxy-6,22,24-trimethyl-2,4,20-pentacosatrienal. The Grignard reagent **34** was prepared by combining (4-ethoxybutadienyl)tributylstannane[31] (118 mg, 0.30 mmol, 5.4 equiv) and *n*-BuLi (2.11 M in hexanes, 128 μL, 0.27 mmol, 4.8 equiv) at –78 °C in 1.5 mL of THF followed by the addition of a 0.22 M solution of $MgBr_2$ in THF (0.64 mL, 0.14 mmol, 2.5 equiv). A solution of the aldehyde **33** (47.0 mg, 0.056 mmol, 1 equiv) in 0.5 mL of THF was added to the –78 °C Grignard solution by cannula, and the flask was rinsed with another 0.5 mL of THF. After 1 h, the reaction was warmed slowly to 0 °C and then quenched with pH 7 phosphate buffer. The mixture was stirred for 1 h, diluted with NH_4Cl solution, and then extracted (2× CH_2Cl_2). The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure.

The crude adduct was dissolved in 3 mL of CH_2Cl_2, cooled to –40 °C, and treated with Et_3N (72 mL, 0.52 mmol) followed by MsCl (20 mL, 0.26 mmol). After 30 min, the reaction was quenched with pH 7 phosphate buffer, and the mixture was diluted with NH_4Cl solution, extracted (2× CH_2Cl_2), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography on SiO_2, eluting with 70% ethyl acetate/hexanes, gave 43.7 mg (0.049 mmol, 88%) of the dienal as a slightly yellow oil: IR (neat) 2986, 1731, 1681, 1640, 1455, 1380, 1256, 1224, 1200, 1169, 1115, 1026, 972, 938 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.52 (1 H, d, J = 8.3 Hz), 7.05 (1 H, dd, J = 10.2, 15.1 Hz), 6.30 (1 H, dd, J = 10.2, 15 Hz), 6.18 (1 H, dd, J = 7.3, 15 Hz), 6.08 (1 H, dd, J = 8.3, 15.6), 5.47 (2 H, m), 4.70 (1 H, dd, J = 4.9, 7.8 Hz), 4.28 (1 H, m), 4.15 (4 H, quintet, J = 7.3 Hz), 4.03 (4 H, m), 3.90 (1 H, m), 3.66 (1 H, m), 2.95 (2 H, d, 22.0 Hz), 2.65 (1 H, m), 2.44 (1 H, m), 1.90–1.00 (13 H, m), 1.42 (3 H, s), 1.39 (3 H, s), 1.37 (6 H, s), 1.35 (3 H, s), 1.33 (6 H, t, J = 6.8 Hz), 1.31 (6 H, s), 1.04 (3 H, d, J = 6.9 Hz), 0.98 (3 H, d, J = 6.3 Hz), 0.87 (6 H, d, J = 6.9 Hz), 0.76 (2 H, s), 0.40 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 165.6, 152.5, 148.8, 133.2, 131.5, 130.5, 128.7, 100.5, 98.6, 98.4, 82.2, 75.9, 70.2, 66.2, 65.9, 64.9, 64.7, 62.5, 62.4, 62.3, 57.1, 42.2 (2), 40.2, 38.9, 38.8, 38.5, 37.6, 35.1, 33.3, 30.2 (2), 29.5, 24.4 (2), 22.6, 19.8 (2), 19.6, 16.4, 16.2 (2), 15.6, 15.2, 13.7, 13.5.

(10*R*,11*S*,13*R*,15*R*,17*R*,19*R*,21*R*,23*S*,24*E*,26*R*,27*R*)-27-*O*-(Diethylphosphonoacetyl)-11-*O*-(1-methylcyclopropyl)-13,15:17,19:21,23-tris-*O*-(1-methylethylidene)-11,13,15,17,19,21,23,27-octahydroxy-10,26,28-trimethyl-2,4,6,8,24-nonacosapentaenal (35). A solution of Grignard reagent **34** was prepared as described above. A solution of 43 mg of the dienal (0.049 mmol, 1 equiv) was added as before at –78 °C. After 1 h, the reaction flask was warmed to 0 °C, and the mixture was then quenched and extracted as in the previous procedure. Elimination using Et_3N and MsCl as before followed by chromatography on SiO_2, eluting with 50–70% ethyl acetate/hexanes, gave 30.1 mg (0.032 mmol, 66%) of tetraenal **35** as a bright yellow oil: IR (neat) 2986, 1731, 1681, 1590, 1455, 1380, 1258, 1224, 1200, 1168, 1025, 972, 938, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 (1 H, d, J = 8.0 Hz), 7.10 (1 H, dd, J = 11.2, 15.1 Hz), 6.67 (1 H, dd, J = 10.8, 15.4 Hz), 6.42 (2 H, m), 6.30–6.05 (3 H, m), 5.80 (1 H, dd, J = 8.0, 15.5 Hz), 5.48 (2 H, m), 4.69 (1 H, dd, J = 4.8, 7.8 Hz), 4.28 (1 H, d, J = 12 Hz), 4.15 (4 H, quintet, J = 7.5 Hz), 4.03 (4 H, m), 3.89 (1 H, m), 3.62 (1 H, m), 2.95 (2 H, d, 22.0 Hz), 2.58 (1 H, m), 2.44 (1 H, m), 1.90–1.00 (13 H, m), 1.42 (3 H, s), 1.38 (3 H, s), 1.37 (3 H, s), 1.36 (3 H, s), 1.35 (3 H, s), 1.32 (6 H, m), 1.30 (6 H, s), 1.00 (3 H, d, J = 6.9 Hz), 0.97 (3 H, d, J = 6.9 Hz), 0.86 (6 H, d, J = 6.6 Hz), 0.76 (2 H, s), 0.38 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 165.6, 152.0, 142.9, 141.3, 139.0, 133.2, 130.7, 130.3, 130.2, 129.9, 129.2, 100.4, 98.6, 98.4, 82.2, 76.0, 70.2, 66.3, 64.8, 64.7, 62.5, 62.4, 62.3, 57.0, 42.2 (2), 39.9, 38.9, 38.5, 37.5 (2), 35.1, 33.3, 30.2 (2), 29.5, 24.4 (2), 22.7, 19.8 (2), 19.6, 16.4, 16.2 (2), 15.6, 15.0, 14.1, 13.7, 13.5.

14-*O*-(1-Methylcyclopropyl)-16,18:20,22:24,26-tris-*O*-(1-methylethylidene)roxaticin (36). A mixture of 52 mg (376 mmol, 32 equiv) of K_2CO_3, 57 mg (215 mmol, 18 equiv) of 18-crown-6, and 20 mL of benzene was heated to reflux under N_2. A solution of 11.0 mg (11.7 μmol, 1 equiv) of the tetraenal **35** in 4 mL of benzene was added over ca. 10 h using a syringe pump. After a total of 18 h, the reaction mixture was cooled and diluted with 50 mL of Et_2O, washed with $NaHCO_3$ and brine solutions, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography on SiO_2, eluting with 20% ethyl acetate/hexanes, gave 1.1 mg of a less polar macrocycle and 4.1 mg (5.2 μmol, 45%) of the macrocyclic lactone **36** as a yellow oil: IR (neat) 2940, 1706, 1621, 1579, 1379, 1256, 1226, 1200, 170, 1126, 1009, 938 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (1 H, dd, J = 11.0, 14.7 Hz), 6.50 (1 H, dd, J = 11.0, 14.7 Hz), 6.38 (1 H, dd, J = 9.8, 14.7 Hz), 6.26 (4 H, m), 6.09 (1 H, dd, J = 11.0, 15.8 Hz), 5.80 (2 H, m), 5.63 (1 H, dd, J = 6.1, 15.8 Hz), 5.33 (1 H, dd, J = 6.1, 15.8 Hz), 4.75 (1 H, dd, J = 3.7, 7.3 Hz), 4.26 (1 H, dd, J = 4.9, 9.8 Hz), 3.96 (2 H, m), 3.80 (2 H, m), 3.70 (2 H, m), 2.65 (2 H, m), 2.00–0.85 (13 H, m), 1.53 (3 H, s), 1.39 (3 H, s), 1.38 (3 H, s), 1.35 (6 H, s), 1.28 (3 H, s), 1.27 (3 H, s), 1.05 (3 H, d, J = 7.3 Hz), 1.00 (3 H, d, J = 6.1 Hz), 0.93 (3 H, d, J = 7.3 Hz), 0.91 (3 H, d, J = 6.1 Hz), 0.79 (2 H, s), 0.39 (2 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 144.2, 140.5, 139.6, 137.1, 135.4, 132.4, 131.3, 131.2, 131.1, 130.8, 129.8, 121.1, 100.3, 98.5, 98.4, 80.0, 76.1, 69.8, 66.9, 65.4, 64.9, 62.8, 62.0, 57.6, 42.6, 41.9, 40.6, 38.9 (2), 37.3, 36.7, 35.1, 30.2 (2), 28.8, 24.6, 24.5, 22.4, 19.9 (2), 19.7, 19.2, 13.5 (2), 13.2, 12.7; HRMS (FAB) 781.5306 (M + H).

The BDT Ether Approach. (2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-((1,1-Dimethylethyl)dimethylsilyl)-1-*O*-(triethylsilyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (47). A solution of 40.6 mg (53 μmol, 1 equiv) of tetraacetonide **5** in 0.5 mL of 1,2-dichloromethane in a resealable tube was cooled to 0 °C and treated with 92 μL (530 μmol, 10 equiv) of Hunig's base and 72 μL (318 μmol, 6 equiv) of TESOTf. The reaction vessel was heated at 110 °C for 20 h. The mixture was diluted with ether, washed with $NaHCO_3$ (2×) and brine, and dried over Na_2SO_4.

Concentration under reduced pressure gave 67.4 mg of the crude enol ether **30** as a red-orange oil.

The enol ether **30** was dissolved in 2.5 mL of $CDCl_3$ and treated with 20 μL of pyridine and 30 μL of a 2.5% OsO_4 solution in *t*-BuOH. After 24 h, an NMR spectrum of the reaction showed that the reaction was almost complete. The mixture was concentrated under reduced pressure and purified by SiO_2 chromatography, eluting with 10% ethyl acetate/hexanes to give 5.8 mg of recovered enol ether, 12.7 mg of what appears to be an acetonide isomer, and 26.1 mg (31.5 μmol, 60%) of the alcohol **47** as a colorless oil: IR (neat) 3650, 2988, 2954, 2877, 1462, 1380, 1250, 1224, 1200, 1170, 1094, 1018, 970, 938, 858, 836, 773, 744, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (1 H, dd, *J* = 7.3, 15.9 Hz), 5.36 (1 H, dd, *J* = 6.1, 15.9 Hz), 4.27 (1 H, m), 4.13 (1 H, m), 4.03 (4 H, m), 3.99 (1 H, s), 3.67 (1 H, m), 3.61 (2 H, m), 3.23 (1 H, t, *J* = 4.9 Hz), 2.28 (1 H, sextet, *J* = 6.1 Hz), 1.80–1.10 (14 H, m), 1.44 (6 H, s), 1.41 (3 H, s), 1.35 (3 H, s), 1.30 (6 H, s), 0.95 (3 H, d, *J* = 7.3 Hz), 0.93 (9 H, t, *J* = 8.6 Hz), 0.89 (9 H, s), 0.85 (3 H, d, *J* = 8.9 Hz), 0.84 (3 H, d, *J* = 7.3 Hz), 0.81 (3 H, d, *J* = 7.3 Hz), 0.58 (6 H, q, *J* = 8.6 Hz), 0.01 (3 H, s), –0.01 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 100.4, 98.5 (2), 18.4; *CH*, 136.2, 129.5, 81.0, 73.9, 70.4, 69.1, 65.1, 64.9, 62.4 (2), 40.8, 40.6, 31.7; *CH_2*, 66.7, 42.2 (2), 40.5, 38.9, 37.3, 37.2, 4.3 (3); *CH_3*, 30.3 (2), 26.2 (3), 24.4 (2), 20.4, 19.9, 19.8, 17.8, 15.8, 13.0, 6.7 (3), –3.5, –3.8; HRMS (FAB) 813.5668 (M – CH_3).

The recovered enol ether and acetonide isomer were dissolved in 4 mL of acetone with 1.5 mL of 2,2-dimethoxypropane and ca. 10 mg of CSA. After 40 h, the reaction was quenched with Et_3N, concentrated, and purified by SiO_2 chromatography, eluting with 10% ethyl acetate/hexanes to give 7.9 mg (10.5 μmol, 20%) of recovered tetraacetonide **5** as a colorless oil.

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-3-*O*-(1,3-Benzodithiolan-2-yl)-19-*O*-((1,1-dimethylethyl)dimethylsilyl)-1-*O*-(triethylsilyl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (48). A solution of 28.1 mg (34 μmol, 1 equiv) of alcohol **47** in 1.0 mL of CH_2Cl_2 was treated with 53 μL (680 μmol, 20 equiv) of pyridine and 25 mg (102 μmol, 3 equiv) of 1,3-benzodithiolyl tetrafluoroborate. After 24 h at 25 °C, the reaction was quenched by addition of Et_3N. The mixture was poured into pH 7 phosphate buffer and extracted with CH_2Cl_2 (3×). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography, eluting with 5% ethyl acetate/hexanes to give 24.1 mg (24.6 μmol, 72%) of BDT ether **48** as a light yellow oil: IR (neat) 2987, 2953, 1458, 1445, 1379, 1250, 1224, 1199, 1170, 1093, 1024, 938, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (2 H, m), 7.08 (2 H, m), 6.47 (1 H, s), 5.61 (1 H, dd, *J* = 8.6, 15.9 Hz), 5.37 (1 H, dd, *J* = 6.1, 15.9 Hz), 4.29 (1 H, m), 4.04 (3 H, m), 3.94 (1 H, m), 3.82 (2 H, m), 3.48 (1 H, dd, *J* = 4.9, 9.8 Hz), 3.38 (1 H, dd, *J* = 7.3, 9,8 Hz), 3.23 (1 H, t, *J* = 6.1 Hz), 2.29 (1 H, m), 1.96 (1 H, septet, *J* = 6.1 Hz), 1.80–1.10 (13 H, m), 1.44 (3 H, s), 1.39 (3 H, s), 1.36 (3 H, s), 1.33 (3 H, s), 1.31 (3 H, s), 1.21 (3 H, s), 0.96 (3 H, d, *J* = 6.1 Hz), 0.93 (9 H, t, *J* = 8.5 Hz), 0.89 (9 H, s), 0.85 (3 H, d, *J* = 6.1 Hz), 0.83 (3 H, d, *J* = 6.1 Hz), 0.81 (3 H, d, *J* = 6.1 Hz), 0.55 (6 H, q, *J* = 8.5 Hz), 0.01 (3 H, s), 0.00 (3 H, s); HRMS (FAB) 979.5660 (M – H).

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-3-*O*-(1,3-Benzodithiolan-2-yl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol. A sample of 12.5 mg (13 μmol) of silyl ether **48** in 1 mL of THF was treated with 130 mL of Bu_4NF solution (1 M in THF) at 80 °C for 2 h. The solution was diluted with brine and extracted with ethyl acetate (3×). The organic layers were dried with Na_2SO_4, concentrated under reduced pressure, and purified by SiO_2 chromatography, eluting with 50% ethyl acetate/hexanes to give 10.2 mg (13 μmol, quantitative) of BDT ether diol as a colorless oil: IR (neat) 3423, 2986, 2939, 1445, 1379, 1249, 1223, 1199, 1169, 1127, 1025, 982, 936, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (2 H, m), 7.10 (2 H, m), 6.55 (1 H, s), 5.61 (1 H, dd, *J* = 7.3, 15.9 Hz), 5.48 (1 H, dd, *J* = 6.1, 15.9 Hz), 4.31 (1 H, m), 4.03 (4 H, m), 3.85 (1 H, m), 3.74 (1 H, dd, *J* = 4.9, 11.0 Hz), 3.55 (1 H, dd, *J* = 2.4, 9.8 Hz), 3.40 (1 H, dd, *J* = 6.1, 11.0 Hz), 3.13 (1 H, m), 2.36 (3 H, m), 1.86 (1 H, m), 1.76–1.20 (13 H, m), 1.43 (3 H, s), 1.39 (3 H, s), 1.36 (3 H, s), 1.34 (3 H, s), 1.32 (3 H, s), 1.31 (3 H, s), 1.00 (3 H, d, *J* = 7.3 Hz), 0.91 (3 H, d, *J* = 6.1 Hz), 0.88 (6 H, d, *J* = 7.3 Hz); HRMS (FAB) 753.4052 (M + H).

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-(Diethylphosphonoacetyl)-3-*O*-(1,3-benzodithiolan-2-yl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-2,18,20-trimethyl-16-heneicosene-1,3,5,7,9,11,13,15,19-nonol (49). To a solution of BDT ether diol (11 mg, 14.6 μmol, 1 equiv) in 1 mL of CH_2Cl_2 was added 10 mg of DMAP (80 μmol, 5.5 equiv) and 26 mg of BOP (60 μmol, 4 equiv). A solution of 11.5 mg (60 μmol, 4 equiv) of the diethyl phosphonoacetic acid in 0.5 mL of CH_2Cl_2 was added dropwise. After 12 h, the mixture was diluted with ethyl acetate, washed with $NaHCO_3$ (2×) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was dissolved in 4 mL of NH_3 saturated MeOH and stirred for 4 h. The mixture was concentrated and purified by chromatography on SiO_2, eluting with ethyl acetate to give 11.7 mg (13.6 μmol, 93%) of phosphonoacetate **49** as a colorless oil: IR (neat) 3447, 2985, 2938, 1734, 1380, 1252, 1223, 1200, 1169, 1120, 1024, 978, 937, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (2 H, m), 7.09 (2 H, m), 6.55 (1 H, s), 5.47 (2 H, m), 4.69 (1 H, dd, *J* = 4.9, 7.3 Hz), 4.28 (1 H, m), 4.15 (4 H, quintet, *J* = 7.5 Hz), 4.01 (4 H, m), 3.85 (1 H, m), 3.74 (1 H, m), 3.72 (1 H, s), 3.59 (1 H, m), 3.40 (1 H, ddd, *J* = 6.1, 6.1, 11.0 Hz), 2.95 (2 H, d, *J* = 22.0 Hz), 2.44 (1 H, m), 1.95–1.05 (15 H, m), 1.42 (3 H, s), 1.37 (3 H, s), 1.36 (3 H, s), 1.34 (3 H, s), 1.32 (3 H, s), 1.32 (6 H, t, *J* = 7.3 Hz), 1.31 (3 H, s), 0.97 (3 H, d, *J* = 7.3 Hz), 0.87 (3 H, d, *J* = 6 Hz), 0.86 (6 H, d, *J* = 6.1 Hz); HRMS (FAB) 953.4331 (M + Na).

(2*R*,3*S*,5*R*,7*R*,9*R*,11*R*,13*R*,15*S*,16*E*,18*R*,19*R*)-19-*O*-(Diethylphosphonoacetyl)-3-*O*-(1,3-benzodithiolan-2-yl)-5,7:9,11:13,15-tris-*O*-(1-methylethylidene)-3,5,7,9,11,13,15,19-octahydroxy-2,18,20-trimethyl-16-heneicosenal. A solution of alcohol **49** (20 mg, 23 μmol, 1 equiv) in 2 mL of CH_2Cl_2 was cooled to 0 °C and treated with solid $NaHCO_3$ (50 mg) and Dess–Martin reagent (14.6 mg, 35 μmol, 1.5 equiv). After 60 min, the mixture was diluted with Et_2O, washed sequentially with $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 18.1 mg (21 μmol, 91%) of the aldehyde as a colorless foam: IR (neat) 3440, 2985, 2938, 1731, 1445, 1380, 1265, 1224, 1200, 1169, 1119, 1025, 972, 937, 744 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.38 (1 H, s), 7.09 (2 H, m), 6.75 (2 H, m), 6.36 (1 H, s), 5.57 (2 H, dd, *J* = 3.7, 7.3 Hz), 4.93 (1 H, dd, *J* = 3.7, 7.3 Hz), 4.24 (3 H, m), 4.15 (1 H, m), 3.98 (6 H, m), 3.74 (1 H, m), 2.82 (2 H, d, *J* = 21 Hz), 2.43 (1 H, m), 1.86 (1 H, m), 1.76 (1 H, m), 1.70–1.30 (13 H, m), 1.57 (3 H, s), 1.50 (3 H, s), 1.48 (3 H, s), 1.46 (3 H, s), 1.42 (3 H, s), 1.29 (3 H, s), 1.07 (6 H, t, *J* = 7.3 Hz), 1.05 (3 H, d, *J* = 7.3 Hz), 0.94 (3 H, d, *J* = 7.3 Hz), 0.88 (3 H, d, *J* = 7.3 Hz), 0.86 (3 H, d, *J* = 7.3 Hz).

(6*R*,7*S*,9*R*,11*R*,13*R*,15*R*,17*R*,19*S*,20*E*,22*R*,13*R*)-23-*O*-(Diethylphosphonoacetyl)-7-*O*-(1,3-benzodithiolan-2-yl)-9,11:13,15:17,19-tris-*O*-(1-methylethylidene)-7,9,11,13,15,17,19,23-octahydroxy-6,22,24-trimethyl-2,4,20-pentacosatrienal. A solution of 92 μmol of Grignard reagent **34** in THF was prepared at –78 °C as described above. The aldehyde (18.1 mg, 21 μmol) was added in 0.5 mL of THF, and the reaction was stirred for 1.5 h at –78 °C. The reaction was quenched, and the resulting alcohol was dehydrated and purified as previously described to give 17.5 mg (19 μmol, 90%) of the expected dienal as a light yellow oil: IR (neat) 2985, 2939, 1732, 1681, 1639, 1445, 1380, 1267, 1223, 1199, 1169, 1117, 1024, 971, 938 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.39 (1 H, d, *J* = 8.5 Hz), 7.12 (2 H, m), 6.75 (2 H, m), 6.38 (1 H, s), 6.28 (1 H, dd, *J* = 9.8, 15.9 Hz), 5.88 (1 H, dd, *J* = 8.5, 15.9 Hz), 5.75 (2 H, m), 5.57 (2 H, m), 4.92 (1 H, dd, *J* = 4.9, 7.3 Hz), 4.26 (3 H, m), 4.11 (1 H, m), 3.99 (1 H, m), 3.98 (4 H, quintet, *J* = 7.5 Hz), 3.77 (1 H, m), 3.65 (1 H, q, *J* = 4.9 Hz), 2.81 (2 H, d, *J* = 22.0 Hz), 2.43 (1 H, m), 2.30 (1 H, m), 1.85 (1 H, m), 1.76 (1 H, septet, *J* = 7.3 Hz), 1.60–1.10 (11 H, m), 1.56 (3 H, s), 1.53 (3 H, s), 1.51 (3 H, s), 1.50 (3 H, s), 1.42 (3 H, s), 1.35 (3 H, s), 1.05 (6 H, m), 0.94 (3 H, d, *J* = 6.1 Hz), 0.91 (3 H, d, *J* = 6.3 Hz), 0.90 (3 H, d, *J* = 7.3 Hz), 0.86 (3 H, d, *J* = 6.1, 7.3 Hz).

(10*R*,11*S*,13*R*,15*R*,17*R*,19*R*,21*R*,23*S*,24*E*,26*R*,27*R*)-27-*O*-(Diethylphosphonoacetyl)-11-*O*-(1,3-benzodithiolan-2-yl)-13,15:17,19:21,23-tris-*O*-(1-methylethylidene)-11,13,15,17,19,21,23,27-octahydroxy-10,-26,28-trimethyl-2,4,6,8,24-nonacosapentaenal (50). The same procedure was repeated using the 17.5 mg (19 μmol, 1 equiv) of the dienal and 76 μmol of the Grignard reagent **34** to give 10.0 mg (10.4 μmol, 55%) of tetraenal **50** as a bright yellow glass: IR (neat) 2985, 2938, 1733, 1675, 1598, 1445, 1380, 1267, 1223, 1199, 1169, 1117, 1024, 972, 937 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.44 (1 H, d, *J* = 7.3 Hz), 7.13 (2 H, m), 6.78 (2 H, m), 6.45 (1 H, dd, *J* = 11.0, 14.6 Hz), 6.43 (1 H, s), 6.15 (1 H, dd, *J* = 11.0, 14.6 Hz), 6.10 (1 H, dd, *J* = 11.0, 14.6 Hz), 5.95 (4 H, m), 5.70 (1 H, dd, *J* = 7.3, 14.6 Hz), 5.58 (2 H, m), 4.92 (1 H, dd, *J* = 4.9, 7.3 Hz), 4.27 (3 H, m), 4.11 (2 H, m), 3.98 (4 H, quintet, *J* = 7.5 Hz), 3.85 (1 H, m), 3.75 (1 H, q, *J* = 4.9 Hz), 2.81 (2 H, d, *J* = 22.0 Hz), 2.43 (2 H, m), 1.85 (2 H, m), 1.55–1.10 (11 H, m), 1.56 (3 H, s), 1.54 (3 H, s), 1.50 (6 H, s), 1.42 (3 H, s), 1.36 (3 H, s), 1.05 (12 H, m), 0.94 (3 H, d, *J* = 7.3 Hz), 0.86 (3 H, d, *J* = 7.3 Hz).

14-*O*-(1,3-Benzodithiolan-2-yl)-16,18:20,22:24,26-tris-*O*-(1-methylethylidene)roxaticin (51). To 42.4 mg of LiCl (208 μmol, 100 equiv) under N_2 was added 10 mg (10.4 μmol, 1 equiv) of the tetraenal **50** in 10 mL of dry CH_3CN, followed by 106 μL of DBU (156 μmol, 75 equiv). The solution was stirred for 13 h and then diluted with pH 7 phosphate buffer and extracted with Et_2O (2×). The extract was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography to give 1.9 mg (2.1 μmol, 20%) of the macrocyclic lactone **51** as a bright yellow oil: IR (neat) 2984, 2939, 2874, 1704, 1620, 1579, 1379, 1256, 1225, 1199, 1168, 1122, 1010 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.44 (1 H, dd, J = 12.2, 15.9 Hz), 7.09 (2 H, m), 6.72 (2 H, m), 6.42 (1 H, s), 6.14 (1 H, dd, J = 11.0, 14.6 Hz), 5.95 (8 H, m), 5.50 (2 H, m), 5.03 (1 H, dd, J = 3.6, 8.5 Hz), 4.23 (2 H, m), 4.08 (1 H, m), 4.04 (2 H, m), 3.85 (2 H, m), 3.75 (1 H, ddd, J = 3.7, 3.7, 6.1 Hz), 2.72 (1 H, m), 2.61 (1 H, m), 1.90–0.90 (12 H, m), 1.57 (3 H, s), 1.53 (3 H, s), 1.47 (3 H, s), 1.43 (3 H, s), 1.39 (3 H, s), 1.37 (3 H, s), 1.03 (3 H, d, J = 6.1 Hz), 1.02 (3 H, d, J = 6.1 Hz), 1.01 (3 H, d, J = 7.3 Hz), 0.75 (3 H, d, J = 7.3 Hz); HRMS (FAB) 879.4511 (M + H).

(−)-Roxaticin. A solution of 1.3 mg (1.5 μmol) of protected roxaticin **51** in 2 mL of MeOH was treated with 10 mg of Dowex W50-1× acidic resin in the dark under N_2. After 1.5 h, the mixture was filtered with MeOH and concentrated. The oil was redissolved in 1 mL of MeOH and again treated with 10 mg of Dowex resin. After 2 h, the mixture was filtered with MeOH and concentrated under reduced pressure to give 1.3 mg of crude roxaticin. It was purified by reverse-phase HPLC (Spherisorb S5 ODS2 25-cm × 10-mm C18 reverse-phase column), eluting with 84:16 MeOH/H_2O to give ca. 0.5 mg (0.8 μmol, 50%) of (−)-roxaticin as a slightly yellow solid: ^1H NMR (500 MHz, DMSO) δ 7.11 (1 H, dd, J = 12.2, 15.9 Hz), 6.69 (1 H, dd, J = 11.0, 14.6 Hz), 6.47 (1 H, dd, J = 11.0, 14.6 Hz), 6.41–6.25 (4 H, m); 6.10 (1 H, dd, J = 11.0, 14.6 Hz), 5.87 (1 H, dd, J = 6.1, 14.6 Hz), 5.81 (1 H, d, J = 14.6 Hz), 5.50 (1 H, dd, J = 3.7, 15.9 Hz), 5.34 (1 H, d, J = 15.9 Hz), 4.98 (1 H, s), 4.64 (1 H, d, J = 7.3 Hz), 4.58 (1 H, d, J = 3.7 Hz), 4.35 (1 H, d, J = 3.7 Hz), 4.20 (1 H, d, J = 4.9 Hz), 4.15 (1 H, m), 4.11 (1 H, d, J = 4.9 Hz), 3.93 (1 H, d, J = 6.1 Hz), 3.83 (5 H, m), 3.73 (1 H, s), 3.42 (1 H, m, obscured by HOD peak), 2.55 (2 H, m, obscured by DMSO peak) 1.86 (1 H, m), 1.49 (2 H, m), 1.30–1.00 (10 H, m), 1.00 (3 H, d, J = 6.1 Hz), 0.97 (3 H, d, J = 7.3 Hz), 0.92 (3 H, d, J = 7.3 Hz), 0.83 (3 H, d, J = 6.1 Hz); HRMS (FAB) 629.3691 (M + Na), 607.3826 (M + H).

(+)-13,15,17,19,21,23,25-Hepta-*O*-acetylroxaticin.[46] A sample of synthetic (−)-roxaticin (ca. 0.2 mg, 0.3 μmol, 1 equiv) was treated with 10 mg (82 μmol, 100 equiv) of DMAP and 7.0 mL (74 μmol, 90 equiv) of acetic anhydride in 400 μL of THF. The solution was sealed under Ar and stored in the dark for 13 h. The reaction was quenched with 10 mL of methanol, and the mixture was diluted with 10 mL of ethyl acetate and washed with H_2O, 0.05 M H_2SO_4 (2×), and brine. The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by reverse-phase HPLC (Spherisorb S5 ODS2 25-cm × 10-mm C18 reverse-phase column), eluting with 90:10 MeOH/H_2O to give ca. 0.1 mg (0.1 μmol, 30%) of roxaticin heptaacetate as a yellow solid: $[\alpha]^{24}_D$ = +169° (c = 0.083, dioxane); ^1H NMR (500 MHz, $CDCl_3$)[47] δ 7.19 (1 H, dd, J = 3.5, 11.5 Hz, obscured by $CHCl_3$ peak), 6.58 (1 H, dd, J = 11.5, 14.5 Hz), 6.48–6.28 (5 H, m); 6.22 (1 H, dd, J = 11.0, 15.5 Hz), 5.91 (1 H, dd, J = 7.0, 15.5 Hz), 5.83 (1 H, d, J = 15.5 Hz), 5.52 (1 H, dd, J = 4.5, 16.0 Hz), 5.34 (1 H, dd, J = 4.0, 16.0 Hz), 5.13 (1 H, m), 4.90 (4 H, m), 4.80 (1 H, m), 4.76 (1 H, dd, J = 2.5, 9.5 Hz); 4.53 (1 H, m), 2.64 (1 H, m), 2.60 (1 H, m), 2.06 (3 H, s), 2.04, (3 H, s) 2.00 (3 H, s), 1.99 (3 H, s), 1.98 (3 H, s), 1.96 (3 H, s), 1.95 (3 H, s), 1.90–1.20 (13 H, m), 1.02 (6 H, d, J = 6.5 Hz), 0.93 (3 H, d, J = 6.5 Hz), 0.91 (3 H, d, J = 7.0 Hz); HRMS (FAB) 923.4434 (M + Na), 901.4584 (M + H).

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Supplementary Material Available: ^1H NMR spectra for synthetic (−)-roxaticin and natural (+)-roxaticin (provided by Dr. H. Maehr) (2 pages). This material is contained in many 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.

(46) We thank George Griesgraber for carrying out this reaction.

(47) Referenced to $CHCl_3$ at 7.25 ppm. ^1H NMR matches that previously reported (ref 7) when $CHCl_3$ is referenced to 7.31 ppm.