Stereochemical Determination of Roflamycoin: ^{13}C Acetonide Analysis and Synthetic Correlation

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Received August 2, 1994[⊗]

Abstract: The relative configuration of natural roflamycoin (**1**) was determined by ^{13}C acetonide analysis, combined with other supporting spectroscopic data. A previous proposal for the configuration of roflamycoin was shown to be incorrect. The absolute configuration was determined by the advanced Mosher's method. Our proposed structure of natural roflamycoin was confirmed by the synthesis of a degradation fragment that incorporates all of the 11 independent stereogenic centers of roflamycoin. The complete structure of roflamycoin is illustrated in Figure 1.

Complex polyol segments make the stereochemical elucidation of polyene macrolide antibiotics a serious challenge. The most convenient method for determining the structure of a complex organic molecule is X-ray crystallography. Unfortunately, the polyene macrolide antibiotics exhibit poor crystallographic properties. Of the over 200 known polyene macrolide antibiotics, only the structures of amphotericin B and roxaticin have been determined by X-ray crystallography.[2,3] Without crystalline compounds suitable for X-ray analysis, one must rely on spectroscopic analysis, chemical degradation, and synthetic studies to determine the structures of polyene macrolide antibiotics. Schreiber and Goulet determined the stereochemical pattern for mycoticin by synthesizing a compound that matched a degradation product obtained from the natural material.[4] The stereochemical assignments of nystatin A_1[5] and pentamycin,[6] as well as the partial stereochemical assignment of lienomycin,[7] have been determined by NMR analysis of degradation products complemented by synthetic studies. Lancelin and Beau used sophisticated NMR analysis to predict the stereochemical structure of pimaricin,[8] and the structure was later confirmed by the synthesis of pimaricin aglycon.[9] Most recently, the stereochemical structure of candidin was determined by a combination of NMR methods.[10]

Although several approaches have been suggested for determining the configuration of alternating polyol chains,[11] we desired a more convenient method to determine the stereochemical structure of polyene macrolide antibiotics. One powerful tool which may be employed to determine the relative configuration of compounds containing 1,3-polyols is that of ^{13}C NMR acetonide analysis.[12] In general, it has been observed that syn 1,3-diol acetonides have acetal methyl shifts at 19 and 30 ppm, while anti 1,3-diol acetonides have methyl shifts at approximately 25 ppm. The ^{13}C NMR acetonide analysis has proven to be a very reliable indicator of stereochemistry in that syn 1,3-diol acetonides are easily distinguished from anti 1,3-diol acetonides.[13] We report the stereochemical determination of roflamycoin using the ^{13}C NMR analysis of acetonide derivatives along with other spectroscopic investigations.

Roflamycoin (**1**) was isolated over 20 years ago from the mycelium of *Streptomyces roseoflavus* ARIA 1951 var. *jenensis* nov. var. JA 5068 and was originally called flavomycoin (Figure 1).[14] It is a polyene macrolide antibiotic with antifungal activity and has been shown to form sterol dependent ion-channels.[15] The flat structure was determined by careful degradative studies, in addition to NMR and mass spectral analysis.[16] The relative stereochemistry, however remained a mystery. Roflamycoin has 11 independent stereogenic centers leading to 2048 possible

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⊗ Abstract published in *Advance ACS Abstracts,* December 1, 1994.
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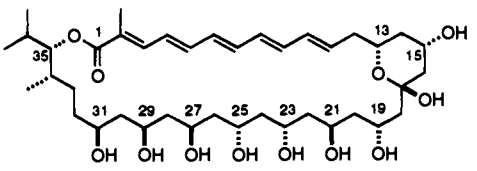
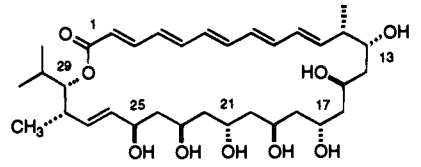
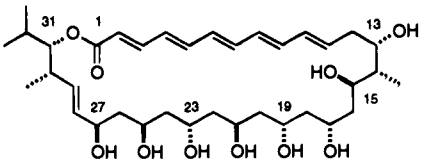


Roflamycoin (1)

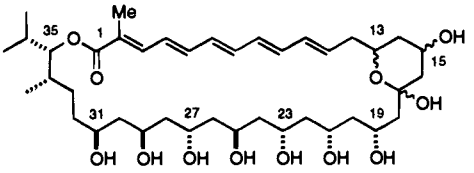
Figure 1. Structure and absolute configuration of natural roflamycoin.



Roxaticin



Mycoticin A



Roflamycoin
(Maehr's Proposed Stereochemistry)

Figure 2. Polyene macrolide antibiotics related to roflamycoin.

stereoisomers.[17] In the structure determination of roxaticin, Maehr's group found that roxaticin and mycoticin shared the same relative and absolute stereochemical configurations and proposed that roflamycoin had the same stereochemical pattern in the analogous C19–C35 region of the chain (Figure 2).[3] Their proposal was based on a presumed common biogenesis, but without access to natural roflamycoin, Maehr's group was unable to test it. We have synthesized a roflamycoin analog based on this stereochemical proposal, but found that the particular isomer we prepared did not have the same stereochemistry as natural roflamycoin.[18,19] When an authentic sample of roflamycoin became available, we set out to investigate its stereochemistry.[20]

The Relative Configuration of Roflamycoin. We set out to prepare suitable derivatives of roflamycoin that would shed light on its configuration. When roflamycoin was treated with Dowex 50W-X1 acid resin in MeOH, it formed spiro acetal **2** in good yield (Scheme 1). Treatment of **2** with Ac_2O and DMAP in THF gave the peracetate **4**. The ^1H NMR and COSY analysis of **4** revealed several proton signals on the spiro acetal portion of the molecule (Figure 3). Of special note were the axial protons at C14 (1.18 ppm, q, J = 11.6 Hz), C18 (1.11 ppm, t, J = 12.2 Hz), and C20 (1.41 ppm, q, J = 11.7 Hz). Each of these protons showed large coupling constants to the adjacent protons on the six membered spiro acetal rings. To account for these observed signals, the protons at C13, C15, C19, and C21 must all be axial. Thus the relative (acyclic) configurations at C13/C15 and C19/C21 must be anti.

If spiro acetal **2** was first subjected to acetonide-forming conditions, followed by acetylation, a mixture of compounds containing two acetonides and three acetates was obtained (Scheme 1). Careful separation by reverse-phase HPLC gave a single, pure compound that was identified as **3**. The ^1H NMR and COSY information allowed us to unambiguously assign nearly every proton signal. This allowed us to perform ^1H NMR and NOE experiments to determine the relative configuration of the spiro acetal portion. There are only two possible combinations for which both C13/C15 and C19/C21 are anti (Figure 4). The first possibility, **A**, has a local meso-type symmetry (i.e. a mirror plane) through the keto center at C17. The second possibility, **B**, has a local C_2-type symmetry through the keto center. If **B** was to form a spiro acetal, it should still exhibit C_2 symmetric properties; however when **A** forms a spiro acetal, the symmetry is lost. The chemical shifts for the protons at C13 and C21 of compound **3** are 3.40 and 4.32 ppm, respectively. This large difference in chemical shift suggests that the spiro acetal formed is the one derived from **A** and that the relative configuration at C15/C19 is syn. This was confirmed by the NOESY spectrum of **3**, which showed cross peaks between the equatorial C18 proton and the axial protons at C13 and C15.

The ^{13}C NMR spectrum of **3** showed acetonide methyl signals in only the 30 and 19 ppm range. The actual positions of the methyl signals were confirmed by removing the acetonides and then reforming them with [1,3-$^{13}C_2$]acetone. The ^{13}C-enriched compound showed methyl doublets at 30.65, 30.48, 19.54, and 19.47 ppm.[21] Thus the relative configurations at C23/C25 and C29/C31 must be syn.

The hemiacetal of roflamycoin could be reduced by treating with $NaBH_4$ in EtOH to give 17-dihydroroflamycoin as a 5:3 mixture of epimers at C17 as determined by HPLC integration (Scheme 2). The structures were confirmed by treating the epimeric mixture with Ac_2O and DMAP to form two peracetates that were easily separated by HPLC. Mass spectral and ^1H NMR analysis were consistent for both epimers having the expected 10 acetates.[22] The dihydroroflamycoin epimers were then separated by reverse-phase HPLC. Each was treated with acetone, 2,2-dimethoxypropane (2,2-DMP), and CSA to give pentaacetonides **5** and **6** (Scheme 2). The ^{13}C NMR spectra showed that **5** had two syn acetonides and three anti acetonides. The same analysis of **6** showed the presence of four anti acetonides and only one syn acetonide. The acetonide formed from C17/C19 must be syn in **5** and anti in **6**. We know that the C29/C31 relationship is syn from compound **3**; therefore the relationships at C13/C15, C21/C23, and C25/C27 must each be anti.

The remaining unknown stereochemical relationships were between C27/C29, C31/C34, and C34/C35. Roflamycoin spiro acetal **2** was silylated and then subjected to ozonolysis followed by treatment with $NaBH_4$ (Scheme 3). This effectively removed the polyene portion. The resulting diol was silylated, and the lactate ester at C35 was cleaved by treatment with LAH. This gave a compound where the only unprotected hydroxyl group was at C35. The alcohol was mesylated to give **7**. Treatment with tetrabutylammonium fluoride (TBAF) removed the silyl protecting groups and was basic enough to promote cyclization. This cyclization should take place with inversion at C35. The

(17) The configuration at C17 is dependent upon the configuration at C13.

(18) Rychnovsky, S. D.; Griesgraber, G.; Kim, J. *J. Am. Chem. Soc.* **1994**, *116*, 2621–2622.

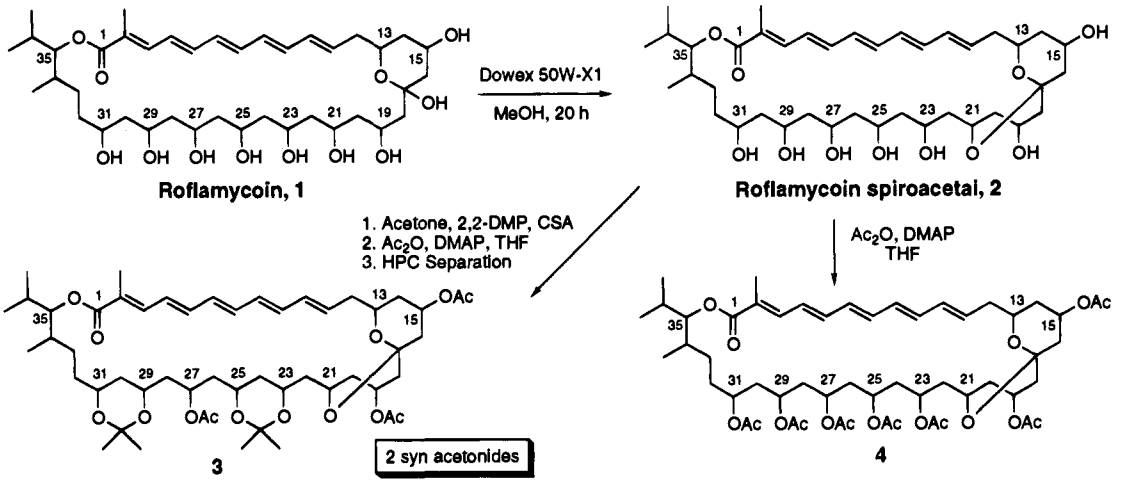
(19) For synthetic work directed toward the hypothetical all syn roflamycoin, see: (a) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15–18. (b) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825–4828.

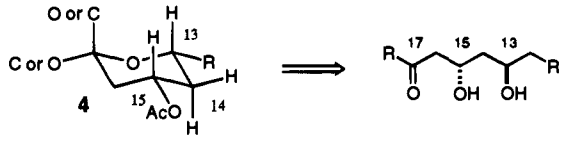
(20) For a preliminary account, see: Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1994**, *116*, 2623–2624.

(21) The signals are doublets ($J \cong 5$ Hz) due to ^{13}C–^{13}C coupling in the isotopically enriched acetonides.

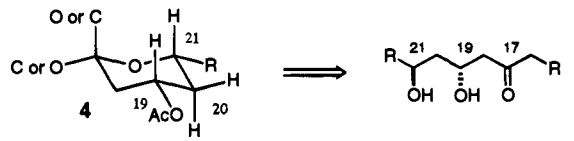
(22) Major isomer: HRMS (FAB) 1161.5768 (M + H), calcd for $C_{60}H_{89}O_{22}$ 1161.5820. Minor isomer: HRMS (FAB) 1161.5854 (M + H), calcd for $C_{60}H_{89}O_{22}$ 1161.5820.

Scheme 1





C_{14} H_{ax}: 1.18 ppm, q, J = 11.6 Hz



C_{20} H_{ax}: 1.41 ppm, q, J = 11.7 Hz

Figure 3. Coupling constants and relative configurations of the spiro acetal portion of **4**.

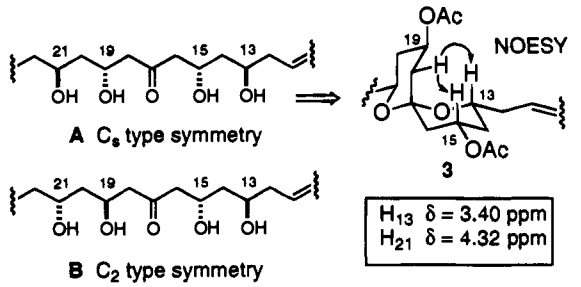


Figure 4. Relative configuration of the spiro acetal portion of **3**.

free alcohols were then acetylated to give **8**. The ^{1}H NMR and COSY spectra of **8** revealed that the proton at C35 was a doublet of doublets at 3.18 ppm with J = 3.9 and 8.0 Hz. Decoupling revealed that J_{34-35} = 8.0 Hz, and J_{35-36} = 3.9 Hz.[23]

There are four possible diastereomeric relationships for the tetrahydropyran portion of compound **8**. Knowing the coupling constants for the C35 proton, we turned to computer modeling to help us determine the configuration of the tetrahydropyran ring. A complete conformational search[24] was carried out on each of the four possible tetrahydropyran diastereomers (**10a**–**d**), and the predicted coupling constants for each conformer within 10 kJ/mol of the minimum were weighted according to a Boltzmann distribution at 25 °C (Figure 5). Only the predicted coupling constants for stereoisomer **10d** are consistent with the observed coupling found in **8**. Because the cyclization occurred with inversion at C35, the relative configurations at C31/C34 and C34/C35 are both syn.

To find the final stereochemical relationship, C27/C29, we prepared compound **9** from mesylate **7** (Scheme 3). The tetrahydropyran ring was formed as before by treating **7** with TBAF. Subsequent treatment with acetone, 2,2-DMP, and PPTS introduced two acetonides. The crude reaction mixture was then benzoylated to give **9** as a UV active compound that was purified by reverse-phase HPLC. The ^{1}H NMR showed that we had formed a tribenzoate with two acetonides, but due to limited material, we did not have enough sample for the important ^{13}C NMR analysis. This problem was solved by removing the acetonides (Dowex 50W-X1, MeOH) and reforming them with acetone that was isotopically enriched with 33% [1,3-$^{13}C_2$]acetone. The ^{13}C NMR of isotopically enriched **9** was easily obtained and revealed methyl signals at 30.74 (overlap), 20.22, and 20.04 ppm.[21] These signals indicate that both acetonides are syn and that the final unassigned relationship, C27/C29, is syn.

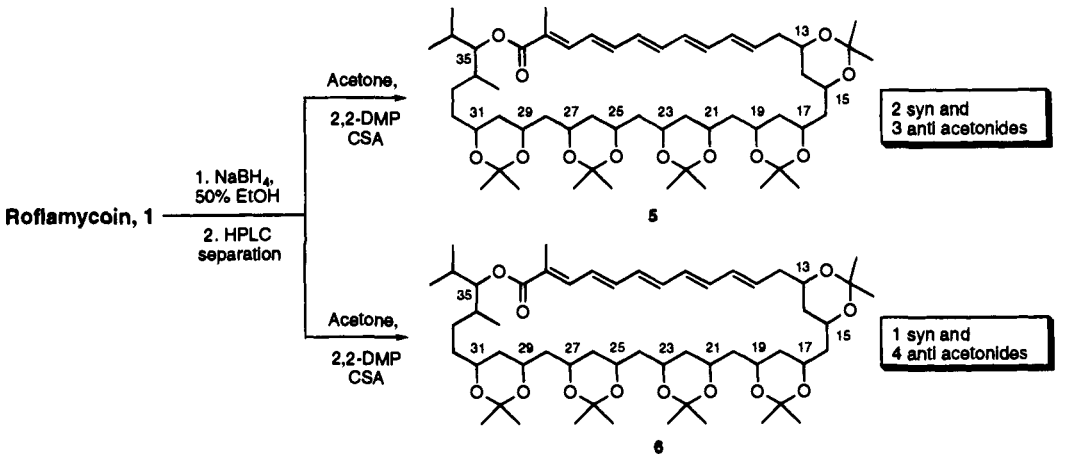
We now have all the information necessary to determine the relative stereochemistry of roflamycoin. We know from spiro acetals **3** and **4** that the relationships C13/C15 and C19/C21 are anti and C15/C19 is syn. In addition, the acetonide information obtained from **3** tells us that the relationships C23/C25 and C29/C31 are syn. The pentaacetonides **5** and **6** revealed that the relationships C21/C23 and C25/C27 are both anti. The relative stereochemistry for C31, C34, and C35 was determined by ^{1}H NMR analysis of the tetrahydropyran portion of **8**, and the final relationship, C27/C29, was shown to be syn by ^{13}C NMR analysis of **9**. The relative configuration of natural roflamycoin is illustrated in Figure 6. It is epimeric with the structure proposed by Maehr at C21, C25, and C27.

To strengthen this conclusion, pentaacetonide **12** was prepared from **5** as described in Scheme 4. Compound **5** was subjected to ozonolysis, silylation, LAH reduction, and mesylation to give the expected C35 mesylate **11**. The acetonides were removed by treatment with acidic Dowex in MeOH, and cyclization was induced by treatment with TBAF. Now that the C31 hydroxyl is tied up in the tetrahydropyran ring, reprotection directs the

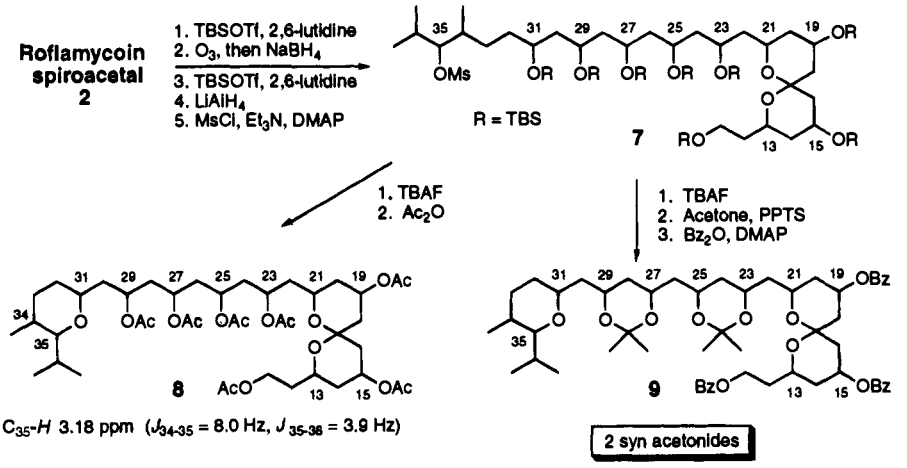
(23) The protons of interest were identified from the COSY spectrum. The C36–H (δ 1.88 ppm) has COSY off-diagonal peaks with the two methyl groups (δ 1.15 ppm, d, J = 6.9 Hz; δ 1.00 ppm, d, J = 6.9 Hz) attached to C36. The C34–H (δ 1.42 ppm) has an off-diagonal peak with the methyl group (δ 0.76 ppm, d, J = 6.7 Hz) attached to C34. The C35–H (δ 3.19 ppm, dd, J = 3.9, 8.0 Hz) has an off-diagonal peak with C34–H, but a weak off-diagonal peak with C36–H. Our assignments were confirmed by the decoupling experiment. When we decoupled at 1.88 ppm, the signals at 1.15 and 1.00 ppm collapsed to singlets, and the signal at 3.19 ppm collapsed to a doublet (J = 8.0 Hz). When we decoupled at 1.42 ppm, the signal at 0.76 ppm collapsed to a singlet, and the signal at 3.19 ppm collapsed to a doublet (J = 3.9 Hz).

(24) A Monte Carlo search with 500 initial structures using the MM2 force field was carried out using Macromodel 3.5 (Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467).

Scheme 2



Scheme 3



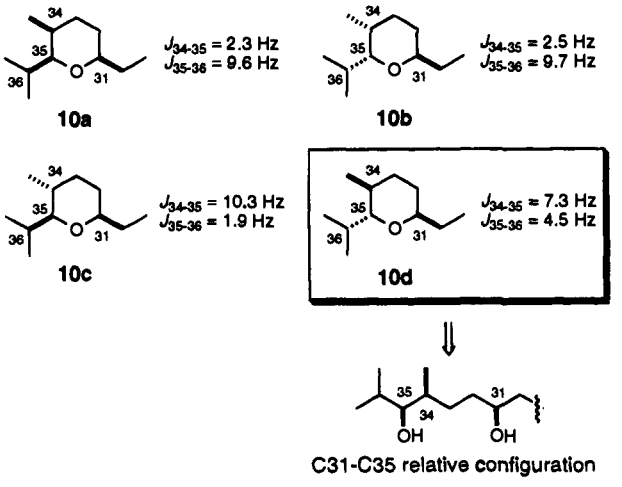


Figure 5. Predicted ^{1}H NMR coupling constants based on molecular modeling.

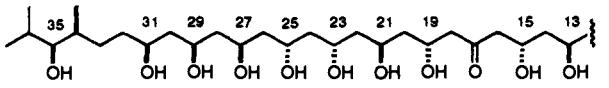


Figure 6. Relative configuration of natural roflamycoin.

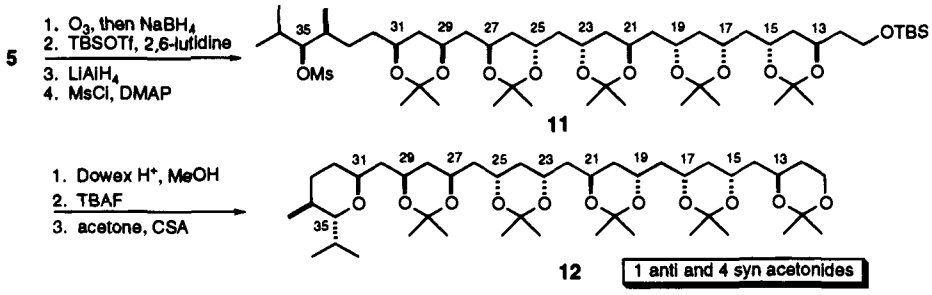
acetonide protecting groups one oxygen to the right with respect to their position in **5** and thus shifts the "reading frame" for the ^{13}C acetonide analysis.[12] The crude polyol was reacted with [1,3-$^{13}C_2$]acetone and CSA to give pentaacetonide **12** that showed the presence of one anti and four syn acetonides by ^{13}C NMR analysis.[21] This result was consistent with the configurational assignment in Figure 6.

Determination of the Absolute Configuration of Roflamycoin. Only the absolute stereochemistry of roflamycoin remained to be determined. We used the advanced Mosher ester technique refined by Kakisawa.[25] The secondary alcohol at C35 is best suited for the Mosher analysis because the three methyl groups and the protons at C34 and C36 are easily identified by ^{1}H NMR. To liberate the alcohol at C35, pentaacetonide **6** was ozonized and treated with $NaBH_4$ to give a diol (Scheme 5). Both of the (*R*)- and (*S*)-MTPA esters, **13R** and **13S**, were prepared. The protons of interest were identified by ^{1}H NMR and COSY analysis, and the $\Delta\delta_H$ values were measured and are listed in Table 1. The configuration at C35 is *S* based on this analysis.

The magnitude of the $\Delta\delta_H$ values were quite small, which led us to question the reliability of the advanced Mosher's method with this type of hindered secondary alcohol. To test its validity, we repeated the advanced Mosher's analysis on synthetic material of known configuration. Compound **14** was an intermediate in our synthesis of a roflamycoin analogue,[18] and the stereochemistry at C35 was known to be *S*. We prepared both MTPA esters of compound **14**, followed by removal of the TBS protecting group, which obscured important proton signals (Scheme 5). The measured $\Delta\delta_H$ values for **15R** and **15S** were in very close agreement to those found for the material derived from natural roflamycoin, lending support to the prediction that C35 has an *S* configuration. The measured

(25) (a) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. (b) Ohtani, I.; Kusumi, T.; Ishitsuka, O. M.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147–3150. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

Scheme 4



Scheme 5

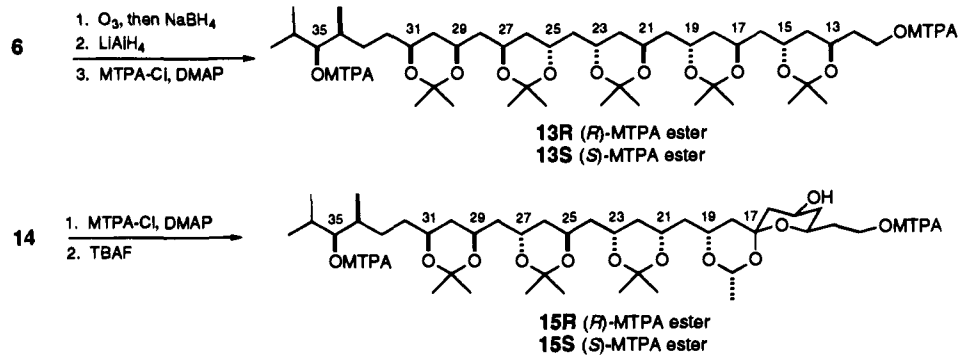
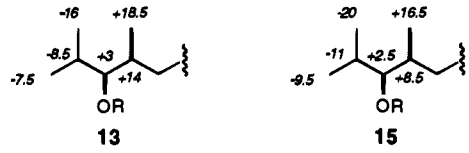


Table 1. Comparison of the $\Delta\delta_H$ ($=\delta_S - \delta_R$) Values for Compounds **13** and **15**



	13(R) δ (ppm)	13(S) δ (ppm)	$\Delta\delta_H$ (Hz)	15(R) δ (ppm)	15(S) δ (ppm)	$\Delta\delta_H$ (Hz)
C34–H	1.742	1.770	+14	1.726	1.743	+8.5
C34–Me	0.794	0.831	+18.5	0.791	0.824	+16.5
C35–H	4.865	4.871	+3	4.863	4.868	+2.5
C36–H	1.945	1.928	−8.5	1.948	1.926	−11
C36–Me(1)	0.867	0.852	−7.5	0.868	0.849	−9.5
C36–Me(2)	0.819	0.787	−16	0.826	0.786	−20

$\Delta\delta_H$ values for the protons of interest are summarized in Table 1. Taken together, the data and analysis presented here are only consistent with roflamycoin having the structure shown in Figure 1.

Synthesis and Correlation of Degradation Fragment 12. We were interested in pursuing a synthesis of natural roflamycoin, but before attempting a revised total synthesis, we considered it prudent to confirm the predicted stereochemical assignment by preparing a less complicated degradation piece. Degradation product **12**, vide infra, was chosen as a synthetic target because it contains all of the independent stereogenic centers of natural roflamycoin. Our methods for the rapid construction of polyol chains allowed us to prepare this molecule in an efficient manner from optically active precursors that we had on hand.

Our synthetic approach to **12** was based on the cyanohydrin acetonide approach for the convergent synthesis of polyol chains.[26] It appeared that **12** could be constructed from four relatively simple optically active precursors (Figure 7). Our strategy involved the coupling of these pieces using standard

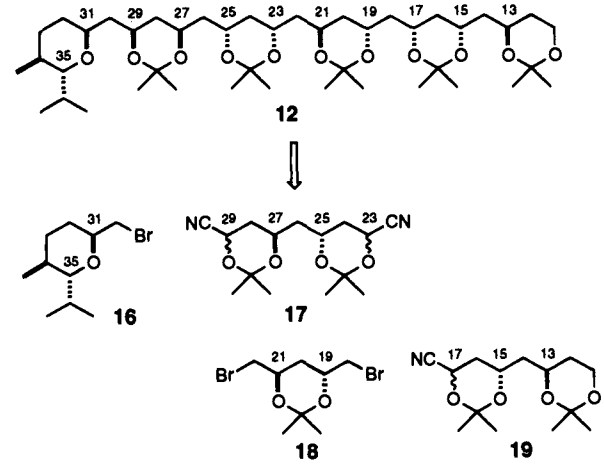


Figure 7. Synthetic analysis of the degradation fragment **12**.

alkylation chemistry followed by a stereoselective reductive decyanation to give pentaacetonide **12**. We have already shown that dibromide **18** is an effective alkylating agent for the construction of polyol chains and its synthesis has been described.[27] This left us with the task of synthesizing bromide **16**, cyanohydrin acetonide **19**, and the C_2 symmetric dinitrile **17**. The preparation of these optically active synthons and the synthesis of the roflamycoin degradation product **12** are described below.

Synthesis of the Pieces. Our strategy for the synthesis of **16** involved the coupling of two optically active fragments, **21** and **22**, followed by an intramolecular cyclization to form the tetrahydropyran ring (Scheme 6). Starting with (2*R*,3*R*)-2,4-dimethyl-1,3-pentanediol,[28] **20**, we could selectively convert the primary alcohol to a phenyl thioether by treatment with tributylphosphine and diphenyl disulfide.[29] The resulting alcohol was protected as its benzyl ether by treatment with KH

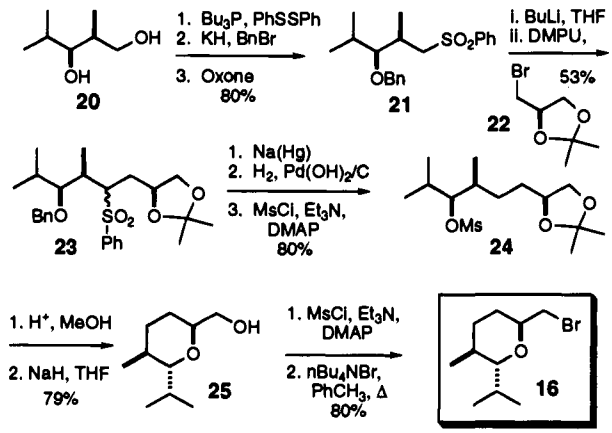
(26) (a) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551. (b) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563.

(27) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161–5169.

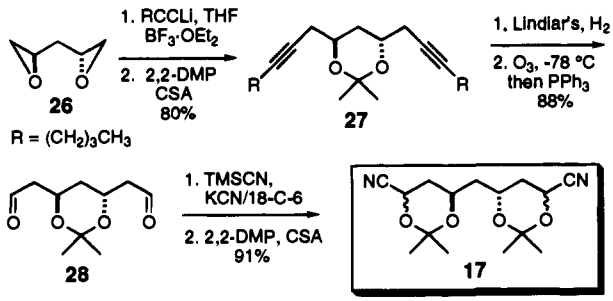
(28) Hoye, R. C.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.

(29) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409–1412.

Scheme 6



Scheme 7



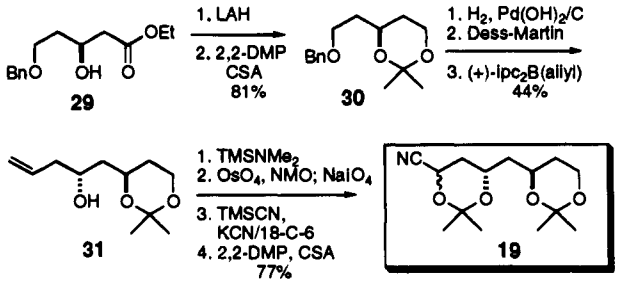
and benzyl bromide, and the thiol was then oxidized with Oxone to give sulfone **21** in 80% overall yield. Deprotonation of the sulfone with butyllithium in THF at 0 °C followed by the addition of DMPU and (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)-methyl bromide (**22**)[30] gave the coupled product **23** in 53% yield. The sulfone was removed by reduction with sodium amalgam, followed by removal of the benzyl protecting group by hydrogenolysis. Mesylation of the resulting C35 alcohol gave the mesylate **24** in 80% yield from **23**. Removal of the acetonide was accomplished by treatment with Dowex 50W-X1 acid resin in MeOH to give a diol which was treated with NaH in THF to give the cyclized product, tetrahydropyranyl-methanol **25**, in 79% yield for the two steps. The free alcohol was converted to its mesylate, followed by displacement with tetrabutylammonium bromide, to give **16** in 80% yield for the two steps. The synthesis of **16** was completed in a straightforward manner from diol **20** in 22% overall yield.

The C_2 symmetric dinitrile **17** appeared to be a useful synthon for the synthesis of alternating polyol chains. Sequential alkylation of **17** with different electrophiles, followed by reductive decyanation, would introduce four new stereogenic centers into a chain. Dinitrile **17** was prepared from the optically active diepoxide **26** (Scheme 7).[26a] The inexpensive alkyne 1-hexyne was chosen as the nucleophile because it could be easily converted to an aldehyde by the two-step process of hydrogenation and ozonolysis. Deprotonation of 1-hexyne with butyllithium, followed by addition to the diepoxide **26** with BF_3·OEt_2 catalysis, gave the expected diol in excellent yield.[31] The diol was protected as an acetonide to give the C_2 symmetric dialkyne **27** in 80% overall yield. Acetonide **27** was then hydrogenated with 5% Pd/$BaSO_4$ and quinoline to give the *Z,Z*-diene, which was cleaved by treatment with ozone to give the unstable dialdehyde **28** in 88% yield over the two steps.

(30) Prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol by the following sequence: (i) $Pb(OAc)_4$; (ii) $NaBH_4$; (iii) TsCl, Pyr; (iv) Bu_4NBr, Δ. Kawakami, Y.; Asai, T.; Umeyama, K.; Yamashita, Y. *J. Org. Chem.* **1982**, *47*, 3585–3587.

(31) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.

Scheme 8



Dialdehyde **28** was immediately treated with 2 equiv of TMSCN and catalytic KCN/18-crown-6 complex followed by acetone, 2,2-dimethoxypropane and CSA to give nitriles **17** as a 1:2:1 mixture of isomers in 91% yield. This mixture of isomers was of no consequence as the cyanohydrin stereogenic centers are set during a subsequent reductive decyanation step. The transformation of diepoxide **26** into diacetonide **17** in 64% overall yield is one example of the potentially important conversion of an epoxide into a chain extended cyanohydrin acetonide.

The final fragment needed for the preparation of pentaacetonide **12** was prepared from hydroxy ester **29** by a procedure similar to that used to synthesize a piece of roxaticin.[28] Hydroxy ester **29** was prepared in optically active form by a Noyori enantioselective hydrogenation of the corresponding β-keto ester.[32,33] Reduction of **29** with LAH followed by treatment with acetone, 2,2-dimethoxypropane, and catalytic CSA gave acetonide **30** in 81% yield (Scheme 8). The next steps were carried out carefully to avoid possible epimerization that could occur by migration of the acetonide group. Hydrogenolysis of the benzyl ether was accomplished with Pearlman's catalyst in the presence of H_2. The crude alcohol was immediately oxidized with Dess–Martin reagent to give an aldehyde which was treated with Brown's (+)-Ipc_2B(allyl) reagent[34] to give **31** as a single homoallylic alcohol in 44% overall yield for the three-step sequence. Silylation of the free hydroxyl group and stepwise oxidation of the terminal alkene (OsO_4, NMO, $NaIO_4$) gave the intermediate aldehyde. The aldehyde was treated with TMSCN and catalytic KCN/18-crown-6 followed by addition of acetone, 2,2-dimethoxypropane and CSA to give cyanohydrin acetonide **19** in 77% yield from alcohol **31**.

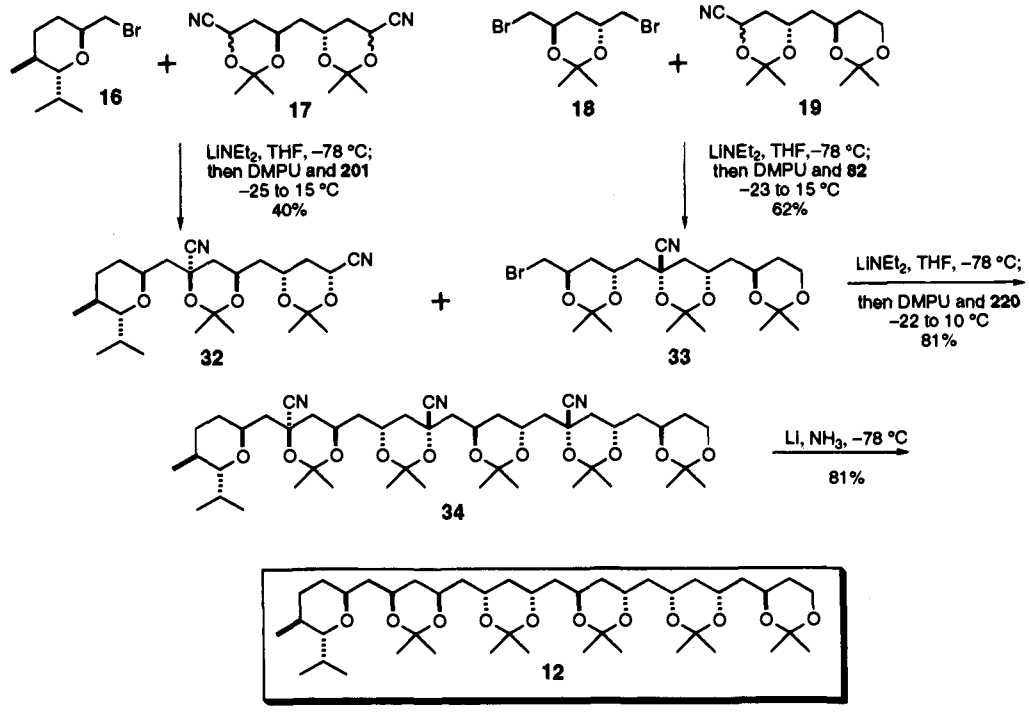
Preparation of Pentaacetonide 12. The four fragments were assembled to give pentaacetonide **12** using our alkylation and reductive decyanation protocol (Scheme 9). Dinitrile **17** has effective C_2 symmetry, so only one monoalkylation product is possible in the coupling to give the left-hand fragment **32**. Overalkylation could have been a problem, but it was avoided by using the monoanion of **17** in excess. Dinitrile **17** (1.9 equiv) was deprotonated with $LiNEt_2$ (1.1 equiv) in THF at −78 °C followed by addition of 1.0 equiv of bromide **16**. The reaction vessel was then transferred to a −25 °C MeOH/ice bath, and the reaction mixture was allowed to slowly warm to 15 °C overnight. The monoalkylated product was isolated in 40% yield, and 28% of the unreacted bromide was also recovered. The alkylation of **17** proceeds in only moderate yield, but it is the linchpin for this convergent synthesis and dramatically

(32) We thank Dr. Daniel E. Mickus for preparing hydroxy ester **29**.

(33) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631. (b) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.

(34) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

Scheme 9



simplifies the route. We will continue to investigate dinitrile **17** as a polyol synthon.

For the preparation of **33**, dibromide **18** is now the C_2 symmetric piece, and again only one monoalkylation product is possible. To avoid overalkylation, an excess of **18** was used in the alkylation. Cyanohydrin acetonide **19** (1.0 equiv) was deprotonated with $LiNEt_2$ (1.2 equiv) in THF at −78 °C followed by addition of 2.5 equiv of dibromide **18**. The reaction vessel was then transferred to a −23 °C MeOH/ice bath, and the reaction mixture was allowed to slowly warm to 15 °C overnight. The monoalkylated product was isolated in 62% yield, and 68% of the unreacted dibromide was recovered.

Fragments **32** and **33** were then assembled to give the complete carbon skeleton of our target molecule. Deprotonation of **32** (1.0 equiv) and alkylation with **33** (1.3 equiv) was carried out as described for the first two coupling reactions to give adduct **34** in 81% yield. Reductive decyanation of **34** with lithium in ammonia cleanly gave pentaacetonide **12** in 81% yield.

Comparison of Synthetically and Naturally Derived Pentaacetonide 12. The synthetic pentaacetonide **12** was identical to the compound obtained by the degradation of natural roflamycoin by ^1H NMR, ^{13}C NMR, HRMS, and TLC.[35] Especially convincing was the comparison of ^1H NMR spectra shown in Figure 8. The two spectra were identical except for a few small peaks observed at approximately 1.7 ppm in the spectrum of the material derived from natural roflamycoin. These peaks are the result of using 20% enriched [1,3-$^{13}C_2$]-acetone in the preparation of pentaacetonide **12**. The extra signals in the NMR are due to $^{13}C-^1H$ coupling. The comparison of our synthetic material with that obtained from the natural product confirms the configurational assignment of roflamycoin (**1**) based on our ^{13}C acetonide analysis. Direct comparison of natural and synthetic samples can provide a valuable check on NMR based structural assignments.

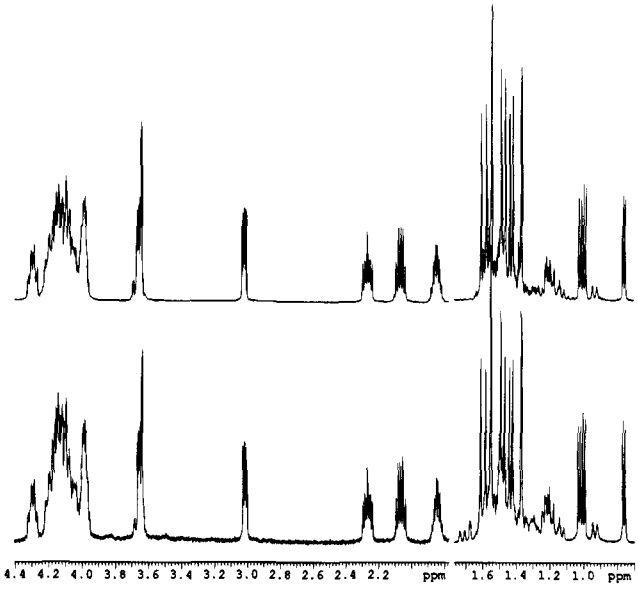


Figure 8. The ^1H NMR spectrum of synthetic **12** (top) and the roflamycoin degradation product **12** (bottom). Note: the 4.40−1.77 ppm region is shown at 5× the intensity of the 1.77−0.70 ppm region.

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).[36] HPLC purifications were performed on a reverse-phase column (Spherisorb S5 ODS2, 25-cm × 10-mm) eluting with H_2O/MeOH mixtures. Commercial CH_2Cl_2 was distilled from CaH_2 under N_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 are given in parentheses.

Degradation and NMR Analysis of Roflamycoin. Roflamycoin (1): ^1H NMR (500 MHz, CD_3OD) δ 7.175 (dd, J = 1.2, 11.1 Hz, 1

(35) The optical rotation of synthetic **12** is $[\alpha]^{27}_D = +20.5°$ (*c* 0.85, $CHCl_3$). The optical rotation of naturally derived **12** was not measured due to insufficient material.

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

H), 6.577 (dd, J = 10.3, 14.6 Hz, 1 H), 6.509 (dd, J = 11.3, 14.6 Hz, 1 H), 6.403 (dd, J = 10.6, 14.7 Hz, 1 H), 6.324 (dd, J = 10.3, 14.7 Hz, 1 H), 6.284 (dd, J = 10.6, 14.7 Hz, 1 H), 6.173 (dd, J = 10.6, 14.7 Hz, 1 H), 6.108 (dd, J = 10.7, 15.0 Hz, 1 H), 5.746 (ddd, J = 5.5, 8.7, 15.0 Hz, 1 H), 4.728 (dd, J = 2.3, 9.9 Hz, 1 H), 4.219 (m, 1 H), 4.00–3.85 (m, 7 H), 3.528 (m, 1 H), 2.311 (dt, J = 2.2, 15.2 Hz, 1 H), 2.130 (dt, J = 9.3, 15.1 Hz, 1 H), 1.896 (s, 3 H), 1.88–1.81 (m, 3 H), 1.72 (m, 1 H), 1.704 (dd, J = 7.8, 14.0 Hz, 1 H), 1.63–1.57 (m, 2 H), 1.50–1.24 (m, 13 H), 1.150 (t, J = 11.7 Hz, 1 H), 1.143 (m, 1 H), 1.048 (q, J = 11.8 Hz, 1 H), 1.020 (m, 1 H), 0.881 (d, J = 6.7 Hz, 3 H), 0.849 (d, J = 6.7 Hz, 3 H), 0.795 (d, J = 6.6 Hz, 3 H); HRMS (FAB) 739.4611 (M + H), calcd for $C_{40}H_{67}O_{12}$ 739.4634.

Roflamycoin Spiro Acetal (2). Roflamycoin (100 mg) was dissolved in 20 mL of MeOH and treated with Dowex 50W-X1 acid resin. The reaction was kept in the dark and stirred for 20 h under Ar. The reaction was then filtered and concentrated under reduced pressure. Chromatography (SiO_2, 15%–20% MeOH/ethyl acetate) gave the product (58 mg) as a yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.17 (dd, J = 1.3, 10.9 Hz, 1 H), 6.58 (dd, J = 9.4, 14.7 Hz, 1 H), 6.52 (dd, J = 10.9, 14.4 Hz, 1 H), 6.41–6.38 (m, 2 H), 6.29 (dd, J = 10.0, 14.7 Hz, 1 H), 6.22 (dd, J = 9.4, 14.7 Hz, 1 H), 6.16 (dd, J = 10.0, 14.7 Hz, 1 H), 5.68 (ddd, J = 5.9, 9.1, 14.7 Hz, 1 H), 4.70 (dd, J = 2.2, 9.7 Hz, 1 H), 3.98 (m, 1 H), 3.91–3.78 (m, 4 H), 3.74 (m, 1 H), 3.63 (m, 1 H), 3.61 (m, 1 H), 3.47 (m, 1 H), 2.35 (m, 1 H), 2.31 (dd, J = 4.0, 13.1 Hz, 1 H), 2.10 (dt, J = 14.1, 9.0 Hz, 1 H), 1.90 (d, J = 1.3 Hz, 3 H), 1.88 (m, 1 H), 1.87 (dd, J = 3.4, 13.1 Hz, 1 H), 1.82 (m, 1 H), 1.79–1.75 (m, 2 H), 1.67 (ddd, J = 5.9, 7.8, 13.4 Hz, 1 H), 1.54 (ddd, J = 5.3, 8.1, 13.4 Hz, 1 H), 1.47 (m, 1 H), 1.38–1.17 (m, 11 H), 1.12–0.98 (m, 4 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); HRMS (FAB) 721.4540 (M + H), calcd for $C_{40}H_{65}O_{11}$ 721.4528.

15,19,23,25,27,29,31-Hepta-*O*-acetylroflamycoin Spiro Acetal (4). A suspension of roflamycoin spiro acetal **2** (2 mg, 0.3 μmol, 1 equiv) in 1.5 mL of THF was treated with DMAP (24 mg, 0.20 mmol, 67 equiv) and Ac_2O (18 μL, 0.19 mmol, 63 equiv). The reaction was kept in the dark, under Ar. After 18 h, the reaction was quenched by adding a drop of MeOH. The reaction mixture was then diluted in 20 mL of ethyl acetate and washed with 0.05 M H_2SO_4 (2 × 5 mL) and brine (5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude yellow solid was passed through a SiO_2 column eluting with 30–50% ethyl acetate/hexanes and then purified by reverse-phase HPLC (12% H_2O/MeOH) to give **4** (1.5 mg) as a yellow solid: ^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (d, J = 9.4 Hz, 1 H), 6.52 (dd, J = 11.2, 14.6 Hz, 1 H), 6.50–6.40 (m, 2 H), 6.33–6.25 (m, 3 H), 6.23 (dd, J = 10.9, 14.9 Hz, 1 H), 5.85 (ddd, J = 5.7, 9.5, 14.6 Hz, 1 H), 5.21–5.13 (m, 4 H), 5.05 (m, 1 H), 5.02 (m, 1 H), 4.97 (m, 1 H), 4.95 (m, 1 H), 4.24 (m, 1 H), 3.21 (m, 1 H), 2.35 (dd, J = 3.4, 12.3 Hz, 1 H), 2.09 (dd, J = 4.9, 12.3 Hz, 1 H), 2.042 (s, 3 H), 1.904 (s, 3 H), 1.846 (s, 3 H), 1.833 (s, 3 H), 1.785 (s, 3 H), 1.744 (s, 3 H), 1.689 (s, 3 H), 1.645 (s, 3 H), 2.02–1.52 (m, 18 H), 1.41 (q, J = 11.7 Hz, 1 H), 1.35–1.25 (m, 3 H), 1.18 (q, J = 11.7 Hz, 1 H), 1.11 (t, J = 12.2 Hz, 1 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.9 Hz, 3 H), 0.73 (d, J = 6.9 Hz, 3 H); HRMS (FAB) 1015.5259 (M + H), calcd for $C_{54}H_{79}O_{18}$ 1015.5267.

15,19,27-Tri-*O*-acetyl-23,25:29,31-bis-*O*-(1-methylethylidene)-roflamycoin Spiro Acetal (3). A solution of roflamycoin spiro acetal **2** (22.0 mg) dissolved in 4 mL of a 4:1 mixture of acetone and 2,2-DMP was treated with 2 mg of CSA. The reaction was stirred under N_2, in the dark, for 1 h. The reaction was then quenched by addition of 5 μL of Et_3N and concentrated under a stream of N_2. Chromatography (SiO_2, 50% acetone/hexanes) gave 16.7 mg of a yellow solid.

The resulting yellow solid was dissolved in 5 mL of THF and treated with DMAP (30.2 mg, 0.248 mmol) and Ac_2O (21 μL, 0.22 mmol). The reaction was kept under N_2, in the dark, for 20 h. The reaction was then quenched by addition of 3 drops of MeOH. The reaction mixture was then diluted in 20 mL of ethyl acetate and washed with H_2O (5 mL), 0.05 M H_2SO_4 (2 × 5 mL), and brine (5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude yellow solid was passed through a SiO_2 column eluting with 40% ethyl acetate/hexanes and then purified by reverse-phase HPLC (4% H_2O/MeOH) to give **3** (5.4 mg) as a yellow glass: ^{1}H NMR (500 MHz, C_6D_6) δ 7.51 (d, J = 11.7 Hz, 1 H), 6.29 (dd, J = 12.0, 14.4 Hz, 1 H), 6.24 (m, 1 H), 6.17–6.06 (m, 5 H), 5.79 (ddd, J = 5.0, 10.0, 14.9 Hz, 1 H), 5.67 (m, 1 H), 5.07 (m, 1 H), 5.06 (dd, J = 2.9, 9.5 Hz, 1 H), 5.00 (m, 1 H), 4.32 (m, 1 H), 3.95 (m, 1 H), 3.88 (m, 1 H), 3.79 (m, 1 H), 3.59 (m, 1 H), 3.40 (m, 1 H), 2.51 (dd, J = 2.9, 12.9 Hz, 1 H), 2.11 (dd, J = 4.4, 12.9 Hz, 1 H), 2.10 (m, 1 H), 2.05 (m, 1 H), 1.99 (m, 1 H), 1.946 (s, 3 H), 1.926 (s, 3 H), 1.749 (s, 3 H), 1.638 (s, 3 H), 1.522 (s, 3 H), 1.514 (s, 3 H), 1.467 (s, 3 H), 1.443 (s, 3 H), 1.96–1.74 (m, 6 H), 1.70 (t, J = 11.9 Hz, 1 H), 1.66–1.41 (m, 5 H), 1.31 (q, J = 11.8 Hz, 1 H), 1.21–0.98 (m, 6 H), 1.16 (q, J = 11.6 Hz, 1 H), 1.13 (t, J = 12.2 Hz, 1 H), 1.02 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H); HRMS (FAB) 926.5369 calcd for $C_{52}H_{78}O_{14}$ 926.5393.

A portion of **3** (4 mg) was treated with Dowex 50W-X1 resin in methanol to remove the acetonides. The resulting material was treated with [1,3-$^{13}C_2$]acetone (10% in toluene) and CSA. After stirring for 18 h in the dark, the reaction mixture was filtered through a SiO_2 plug eluting with 40% ethyl acetate/hexanes. Purification by reverse-phase HPLC (5% H_2O/MeOH) gave 1.5 mg of **3** with isotopically enriched acetonides: ^{13}C NMR (75 MHz, C_6D_6) δ 30.66 (d, J = 4.7 Hz), 30.48 (d, J = 4.8 Hz), 19.54 (d, J = 5.9 Hz), 19.47 (d, J = 5.0 Hz).

16,17-Dihydro-13,15:17,19:21,23:25,27:29,31-pentakis-*O*-(1-methylethylidene)roflamycoin (5). A solution of roflamycoin (50 mg, 0.068 mmol) dissolved in 3 mL of 50% aqueous EtOH was treated with $NaBH_4$ (10 mg, 0.26 mmol, 4 equiv) and stirred under N_2, in the dark, for 16 h. The reaction was then quenched with 15 mL of pH 7 phosphate buffer solution. The reaction mixture was then extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 30% MeOH/ethyl acetate) gave 42 mg of an epimeric mixture of reduced roflamycoin. Separation of these epimers was achieved by reverse-phase HPLC (25% H_2O/MeOH) to give 18.4 mg of the major isomer and 12.9 mg of the minor isomer, both as yellow solids.

The major isomer (14.7 mg) was dissolved in 4 mL of acetone and 0.5 mL of 2,2-DMP and treated with 3 mg of CSA. The reaction was heated to 50 °C and stirred in the dark, under Ar, for 16 h. The reaction appeared to reach an equilibrium at this point as indicated by TLC. The reaction was quenched with 10 μL of Et_3N and concentrated under a stream of Ar. Chromatography (SiO_2, 50–100% ethyl acetate/hexanes) gave 3.6 mg of the desired pentaacetonide and 12.7 mg of more polar compounds. The more polar material was resubjected to the reaction conditions to give another 10.4 mg of desired material and 4 mg of polar material. Again, the more polar material was resubjected to the reaction conditions. The desired material from all of the reactions was combined for a final purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) to give **5** (17.0 mg) as a yellow solid: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.64 (d, J = 11.1 Hz, 1 H), 6.37–6.04 (m, 7 H), 5.91 (m, 1 H), 5.10 (dd, J = 2.1, 9.3 Hz, 1 H), 4.32–3.82 (m, 9 H), 3.69 (m, 1 H), 2.50 (m, 1 H), 2.15–2.00 (m, 3 H), 1.998 (s, 3 H), 1.90–1.10 (m, 22 H), 1.556 (s, 3 H), 1.535 (s, 3 H), 1.420 (s, 12 H), 1.398 (s, 3 H), 1.384 (s, 3 H), 1.350 (s, 3 H), 1.342 (s, 3 H), 0.99 (d, J = 6.1 Hz, 3 H), 0.97 (d, J = 6.0 Hz, 3 H), 0.74 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (C_6D_6, 75 MHz, DEPT) *C* 168.0, 100.3 (2), 100.1, 98.6, 98.5; *C*H 140.1, 139.2, 136.8, 135.5, 134.1, 132.3, 131.6, 131.3, 127.6, 80.3, 69.4, 66.3, 65.9, 65.7, 65.6, 63.9, 63.5, 63.4, 63.3, 62.9, 34.9, 30.1; *C*H_2 43.2, 43.1, 42.8, 42.4, 39.2, 39.1, 38.4, 37.9, 37.5, 36.1, 34.6, 29.8; *C*H_3 30.7, 30.6, 26.3, 25.4, 25.1 (3), 24.9, 19.9, 19.9, 19.8, 19.0, 14.2, 13.1; HRMS (FAB) 925.6064 (M − CH_3), calcd for $C_{54}H_{85}O_{12}$ 925.6044.

16,17-Dihydro-13,15:17,19:21,23:25,27:29,31-pentakis-*O*-(1-methylethylidene)roflamycoin (6). Compound **6** was prepared from the minor isomer of reduced roflamycoin (12.9 mg) using the procedure described above for the preparation of **5**. We obtained 10.6 mg of **6** as a yellow solid: ^{1}H NMR (C_6D_6, 300 MHz) δ 7.64 (d, J = 11.7 Hz, 1 H), 6.36 (dd, J = 11.3, 14.3 Hz, 1 H), 6.27–5.88 (m, 7 H), 5.12 (dd, J = 2.1, 9.2 Hz, 1 H), 4.25–3.90 (m, 9 H), 3.77 (m, 1 H), 2.56 (m, 1 H), 2.13–1.87 (m, 8 H), 2.022 (s, 3 H), 1.76–1.20 (m, 17 H), 1.570 (s, 3 H), 1.465 (s, 3 H), 1.415 (s, 6 H), 1.406 (s, 6 H), 1.380 (s, 6 H), 1.359 (s, 6 H), 0.98 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.72 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (C_6D_6, 75 MHz, signals for acetonide methyls) 30.66, 26.43, 25.36, 25.30, 25.14 (2), 25.08 (2), 25.00, 19.96; HRMS (FAB) 925.5988 (M − CH_3), calcd for $C_{54}H_{85}O_{12}$ 925.6044.

[2*S*,2(2*S*,4*S*,6*S*,8*S*,10*S*,13*S*,14*S*),4*R*,6*R*,8*R*,10*S*]-4,10-Bis((1,1-dimethylethyl)dimethylsiloxy)-8-(2-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-2-(13,15-dimethyl-2,4,6,8,10,14-hexakis((1,1-dimethylethyl)dimethylsiloxy)-14-hydroxyhexadecanyl)-1,7-dioxaspiro[5.5]undecane (7 [Ms = H]). A solution of roflamycoin spiro acetal **2** (38.2 mg, 0.053 mmol) was dissolved in 5 mL of CH_2Cl_2 and treated with 2,6-lutidine (109 μL, 0.532 mmol, 10 equiv) and TBSOTf (62 μL, 0.475 mmol, 9 equiv) at 0 °C, under N_2. The reaction was allowed to warm to room temperature and stirred in the dark for 16 h. The reaction was quenched by addition of 3 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into CH_2Cl_2 (20 mL) and the organic layer was washed with H_2O, followed by brine. The organic layer was then dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography (SiO_2, 3% ethyl acetate/hexanes) gave 58.4 mg of a yellow solid.

The yellow solid was dissolved in 9 mL of a 2:1 mixture of MeOH and CH_2Cl_2 and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Nitrogen was then bubbled through the solution until it was colorless, then $NaBH_4$ (32 mg) was added and the reaction mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was diluted with Et_2O (30 mL) and quenched with 3 mL of saturated $NaHCO_3$ solution. The organic portion was decanted and the aqueous portion was washed with Et_2O (2 × 10 mL). The combined organic portions were then washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 56.2 mg of a colorless syrup.

The syrup was dissolved in 5 mL of CH_2Cl_2 and treated with 2,6-lutidine (25 μL) and TBSOTf (42 μL) at 0 °C, under N_2. The reaction was allowed to warm to room temperature. After stirring overnight, the reaction was quenched by addition of 3 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into CH_2Cl_2 (20 mL) and the organic layer was washed with H_2O, followed by brine. The organic layer was then dried with Na_2SO_4 and concentrated under reduced pressure to give 45 mg of a colorless oil.

This colorless oil (40 mg) was dissolved in 4 mL of THF and treated with LAH (10 mg). After stirring for 1 h, the reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$. The reaction mixture was filtered through a small column of Na_2SO_4, eluting with Et_2O, and concentrated under reduced pressure. Chromatography (3% ethyl acetate/hexanes) gave alcohol **7** [Ms = H] (21.7 mg) as a colorless syrup: ^{1}H NMR (C_6D_6, 500 MHz) δ 4.51 (t, J = 10.9 Hz, 1 H), 4.46 (dd, J = 8.7, 9.9 Hz, 1 H), 4.18−4.13 (m, 3 H), 3.99−3.90 (m, 3 H), 3.89 (dt, J = 10.0, 6.6 Hz, 1 H), 3.79 (dt, J = 10.0, 6.6 Hz, 1 H), 3.14 (dd, J = 6.0, 11.2 Hz, 1 H), 2.49 (dd, J = 3.0, 12.7 Hz, 1 H), 2.11 (dd, J = 3.3, 12.7 Hz, 1 H), 2.08−1.53 (m, 22 H), 1.52 (q, J = 11.9 Hz, 1 H), 1.41 (q, J = 11.1 Hz, 1 H), 1.38 (t, J = 11.9 Hz, 1 H), 1.118 (s, 9 H), 1.103 (s, 9 H), 1.065 (s, 9 H), 1.034 (s, 9 H), 1.027 (s, 9 H), 1.019 (s, 18 H), 1.01 (d, J = 6.5 Hz, 3 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.979 (s, 9 H), 0.86 (d, J = 6.9 Hz, 3 H), 0.402 (s, 3 H), 0.352 (s, 3 H), 0.293 (s, 3 H), 0.279 (s, 3 H), 0.249 (s, 3 H), 0.238 (s, 3 H), 0.213 (s, 3 H), 0.201 (s, 3 H), 0.190 (s, 3 H), 0.175 (s, 3 H), 0.170 (s, 3 H), 0.158 (s, 3 H), 0.140 (s, 3 H), 0.135 (s, 3 H), 0.067 (s, 3 H), 0.056 (s, 3 H).

[2*S*,2(2*S*,4*S*,6*S*,8*S*,10*S*,13*S*,14*S*),4*R*,6*R*,8*R*,10*S*]-4,10-Bis((1,1-dimethylethyl)dimethylsiloxy)-8-(2-((1,1-dimethylethyl)dimethylsiloxy)ethyl)-2-(13,15-dimethyl-2,4,6,8,10-hexakis((1,1-dimethylethyl)dimethylsiloxy)-14-*O*-(methylsulfonyl)hexadecanyl)-1,7-dioxaspiro[5.5]undecane (7). Alcohol **7** [Ms = H] (21.7 mg) was dissolved in 4 mL of CH_2Cl_2 and treated with DMAP (40 mg, 0.328 mmol), Et_3N (45 μL, 0.323 mmol), and MsCl (25 μL, 0.323 mmol). After stirring under N_2 for 18 h, the reaction was quenched with 3 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into Et_2O (20 mL), and the organic layer was washed with $NaHCO_3$, H_2O, and brine. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (3% ethyl acetate/hexanes) gave mesylate **7** as a colorless syrup: ^{1}H NMR (C_6D_6, 500 MHz) δ 4.63 (br t, J = 5.3 Hz, 1 H), 4.52 (m, 1 H), 4.46 (m, 1 H), 4.19−4.12 (m, 3 H), 3.98−3.91 (m, 3 H), 3.89 (dt, J = 9.8, 6.8 Hz, 1 H), 3.79 (dt, J = 9.8, 6.5 Hz, 1 H), 3.64 (m, 1 H), 2.49 (dd, J = 3.6, 13.0 Hz, 1 H), 2.326 (s, 3 H), 2.11 (dd, J = 3.9, 13.0 Hz, 1 H), 2.09−1.35 (m, 24 H), 1.119 (s, 9 H), 1.107 (s, 9 H), 1.09 (d, J = 6.5 Hz, 3 H), 1.069 (s, 9 H), 1.045 (s, 9 H), 1.037 (s, 9 H), 1.028 (s, 9 H), 1.019 (s, 9 H), 1.00 (d, J = 7.1 Hz, 3 H), 0.980 (s, 9 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.406 (s, 3 H), 0.354 (s, 3 H), 0.308 (s, 3 H), 0.283 (s, 3 H), 0.274 (s, 3 H), 0.259 (s, 3 H), 0.241 (s, 3 H), 0.205 (s, 3 H), 0.191 (s, 3 H), 0.175 (s, 9 H), 0.140 (s, 3 H), 0.135 (s, 3 H), 0.066 (s, 3 H), 0.054 (s, 3 H).

[2*S*,2(2*S*,4*S*,6*S*,8*S*,10(2*R*,3*S*,6*S*)),4*R*,6*S*,8*R*,10*S*]-4,10-Di-*O*-acetyl-8-(2-*O*-acetyl-2-hydroxyethyl)-2-(2,4,6,8-tetra-*O*-acetyl-2,4,6,8-tetrahydroxy-9-(3-methyl-2-(1-methylethyl)tetrahydropyran-6-yl)nonanyl)-4,10-dihydroxy-1,7-dioxaspiro[5.5]undecane (8). Mesylate **7** (1.7 mg) was dissolved in 1 mL of THF and treated with 50 μL of a 1.0 M solution of TBAF in THF. After stirring at 50 °C for 3 h, the reaction mixture was concentrated under a stream of N_2 and purified by column chromatography (SiO_2, 20% MeOH/ethyl acetate) to give 1.0 mg of a white solid. The white solid was dissolved in 1.5 mL of THF and treated with DMAP (12 mg) and Ac_2O (9 μL). After stirring overnight, the reaction was quenched with a drop of MeOH. The reaction mixture was then diluted in 10 mL of ethyl acetate and washed with 0.05 M H_2SO_4 (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography (SiO_2, 50% ethyl acetate/hexanes) gave the product (0.7 mg) as a colorless solid: ^{1}H NMR (C_6D_6, 500 MHz) δ 5.41 (m, 1 H), 5.36−5.20 (m, 3 H), 4.97 (m, 1 H), 4.89 (m, 1 H), 4.32 (m, 1 H), 4.19−4.12 (m, 2 H), 3.87 (m, 1 H), 3.43 (m, 1 H), 3.19 (dd, J = 3.9, 8.0 Hz, 1 H), 2.43 (dd, J = 4.1, 12.7 Hz, 1 H), 2.25 (m, 1 H), 2.08 (dd, J = 4.7, 12.4 Hz, 1 H), 2.05−1.35 (m, 17 H), 1.956 (s, 3 H), 1.912 (s, 3 H), 1.880 (s, 3 H), 1.835 (s, 3 H), 1.778 (s, 3 H), 1.681 (s, 3 H), 1.637 (s, 3 H), 1.29−1.19 (m, 3 H), 1.15 (d, J = 6.9 Hz, 3 H), 1.12−0.94 (m, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.76 (d, J = 6.7 Hz, 3 H); HRMS (FAB) 857.4534 (M + H), calcd for $C_{43}H_{69}O_{17}$ 857.4536.

[2*S*,2(2*R*,4*S*,6*S*,8*S*,10(2*R*,3*S*,6*S*)),4*R*,6*S*,8*R*,10*S*]-4,10-Di-*O*-benzoyl-8-(2-*O*-benzoyl-2-hydroxyethyl)-2-(2,4:6,8-bis-*O*-(1-methylethylidene)-2,4,6,8-tetrahydroxy-9-(3-methyl-2-(1-methylethyl)tetrahydropyran-6-yl)nonanyl)-4,10-dihydroxy-1,7-dioxaspiro[5.5]undecane (9). Mesylate **7** (22.3 mg) was dissolved in 4 mL of THF and treated with 300 μL of a 1.0 M solution of TBAF in THF. After stirring at 50 °C for 3 h, the reaction mixture was concentrated under a stream of N_2 and purified by column chromatography (SiO_2, 20% MeOH/ethyl acetate) to give 10.0 mg of a white solid.

The white solid was then dissolved in 4 mL of acetone and 0.4 mL of 2,2-DMP and treated with 5 mg of PPTS. After stirring at 50 °C for 8 h, the reaction was cooled and the acid quenched with a few drops of Et_3N. The reaction was concentrated under a stream of N_2 and purified by column chromatography (SiO_2, 75% acetone/hexanes) to give 3.5 mg of a colorless syrup.

The syrup was then dissolved in 1.5 mL of THF and treated with DMAP (17 mg) and Bz_2O (30 mg). After stirring overnight, the reaction was quenched with 2 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into CH_2Cl_2 (10 mL) and the organic layer was then washed with saturated $NaHCO_3$, H_2O, and brine. The organic portion was dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 3.0 mg of crude **9** as a colorless oil. The product was further purified by reverse-phase HPLC (MeOH) to give 2.9 mg of **9**: ^{1}H NMR (C_6D_6, 500 MHz) δ 8.36−8.12 (m, 6 H), 7.20−7.05 (m, 9 H), 5.38 (m, 1 H), 5.19 (m, 1 H), 4.62 (m, 1 H), 4.57−4.45 (m, 3 H), 4.22−4.10 (m, 2 H), 4.05−3.96 (m, 2 H), 3.60 (m, 1 H), 3.01 (dd, J = 4.1, 7.9 Hz, 1 H), 2.55 (dd, J = 4.4, 12.6 Hz, 1 H), 2.28−2.22 (m, 2 H), 1.93−1.14 (m, 23 H), 1.616 (s, 3 H), 1.578 (s, 3 H), 1.510 (s, 3 H), 1.488 (s, 3 H), 1.015 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.76 (d, J = 6.8 Hz, 3 H); HRMS (FAB) 955.5207 (M + H), calcd for $C_{56}H_{75}O_{13}$ 955.5209.

In order to get better ^{13}C NMR data in the acetonide region, **9** (2.9 mg) was dissolved in 2 mL of MeOH and treated with a small amount of Dowex 50W-X1 acid resin to remove the acetonides. After 1.5 h, the reaction was filtered and concentrated under reduced pressure to give 2.1 mg of a white solid. This was dissolved in 200 μL of acetone which was 33% enriched with [1,3-$^{13}C_2$]acetone and treated with approximately 0.1 mg of PPTS. After stirring overnight, the acid was quenched with 10 μL of Et_3N and the reaction mixture was subjected to column chromatography (20% ethyl acetate/hexanes) to give 2.0 mg of product which had acetonides 33% ^{13}C-enriched at the methyl positions: ^{13}C NMR (signals for 1,3-^{13}C-acetone enriched acetonides, C_6D_6, 125 MHz) δ 30.746 (2) (d, J = 4.8 Hz), 20.217 (d, J = 3.2 Hz), 20.045 (d, J = 4.8 Hz).

(3*R*,5*S*,7*R*,9*S*,11*S*,13*S*,15*R*,17*R*,19*S*,21*S*,24*S*,25*S*)-1-*O*-((1,1-Dimethylethyl)dimethylsilyl)-3,5:7,9:11,13:15,17:19,21-pentakis-*O*-(1-

methylethylidene)-24,26-dimethylheptacosane-1,3,5,7,9,11,13,15,-17,19,21,25-dodecol (11 [Ms = H]). Pentaacetonide **5** (17.0 mg) was dissolved in 7.5 mL of a 2:1 mixture of MeOH and CH_2Cl_2 and cooled to −78 °C. Solid $NaHCO_3$ (10 mg) was added and then ozone was bubbled through the solution until a blue color persisted. Nitrogen was then bubbled through the solution until it was colorless, followed by addition of $NaBH_4$ (15 mg). The reaction mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was diluted with Et_2O (30 mL) and quenched with 3 mL of saturated $NaHCO_3$ solution. The organic portion was decanted and the aqueous portion was washed with Et_2O (2 × 10 mL). The combined organic portions were then washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 15.2 mg of a colorless syrup.

This syrup was dissolved in 3 mL of CH_2Cl_2 and treated with 2,6-lutidine (15 μL) and TBSOTf (25 μL) at 0 °C, under N_2. The reaction was allowed to warm to room temperature. After stirring overnight, the reaction was quenched by addition of 3 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into CH_2Cl_2 (10 mL) and the organic layer was washed with H_2O and brine. The organic layer was then dried with Na_2SO_4 and concentrated under reduced pressure to give 17.2 mg of a colorless syrup.

The syrup was dissolved in 3 mL of THF and treated with LAH (10 mg). After stirring for 1 h, the reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$. The reaction mixture was filtered through a small column of Na_2SO_4, eluting with Et_2O, and concentrated under reduced pressure. Chromatography (30% ethyl acetate/hexanes) gave alcohol **11** [Ms = H] (8.6 mg) as a colorless syrup: ^1H NMR (300 MHz, C_6D_6) δ 4.35−3.98 (m, 9 H), 3.83−3.64 (m, 3 H), 2.98 (m, 1 H), 2.13−2.00 (m, 3 H), 1.84−1.20 (m, 27 H), 1.555 (s, 3 H), 1.546 (s, 3 H), 1.463 (s, 3 H), 1.444 (s, 6 H), 1.412 (s, 6 H), 1.370 (s, 6 H), 1.356 (s, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.5 Hz, 3 H), 0.77 (d, J = 6.7 Hz, 3 H), 0.079 (s, 3 H), 0.072 (s, 3 H); ^{13}C NMR (C_6D_6, 75 MHz, DEPT) *C* 100.6, 100.4 (2), 98.7, 98.7, 18.6; *CH* 79.7, 69.4, 66.2, 66.1, 65.5, 63.7, 63.5 (2), 63.3 (2), 62.7, 35.4; CH_2 59.7, 43.3 (2), 43.2, 42.7, 39.8, 39.3, 39.2, 39.0, 37.9, 37.5, 34.6, 29.8; CH_3 31.3, 30.8, 26.3 (3), 25.3 (3), 25.2 (2), 25.1, 20.1, 20.0, 19.7, 18.8, 13.5, −5.1 (2).

(3*R*,5*S*,7*R*,9*S*,11*S*,13*S*,15*R*,17*R*,19*S*,21*S*,24*S*,25*S*)-1-*O*-((1,1-Dimethylethyl)dimethylsilyl)-3,5:7,9:11,13:15,17:19,21-pentakis-*O*-(1-methylethylidene)-25-*O*-(methylsulfonyl)-24,26-dimethylheptacosane-1,3,5,7,9,11,13,15,17,19,21,25-dodecol (11). Alcohol **11** [Ms = H] (8.6 mg) was dissolved in 3 mL of CH_2Cl_2 and treated with DMAP (8 mg), Et_3N (9 μL), and MsCl (5 μL). After stirring under N_2 for 18 h, the reaction was quenched with 2 mL of saturated $NaHCO_3$ solution. The reaction mixture was extracted into Et_2O (20 mL), and the organic layer was washed with saturated $NaHCO_3$, H_2O, and brine. The organic layer was then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (30% ethyl acetate/hexanes) gave mesylate **11** (8.5 mg) as a colorless syrup: ^1H NMR (C_6D_6, 500 MHz) δ 4.52 (dd, J = 3.1, 7.5 Hz, 1 H), 4.31 (m, 1 H), 4.21−4.10 (m, 6 H), 4.10−4.00 (m, 2 H), 3.78 (m, 1 H), 3.71 (m, 1 H), 3.68 (m, 1 H), 2.229 (s, 3 H), 2.12−2.03 (m, 3 H), 1.81−1.20 (m, 23 H), 1.534 (s, 3 H), 1.525 (s, 3 H), 1.454 (s, 3 H), 1.433 (s, 6 H), 1.427 (s, 3 H), 1.402 (s, 3 H), 1.366 (s, 3 H), 1.359 (s, 3 H), 1.325 (s, 3 H), 0.985 (s, 9 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.72 (d, J = 6.9 Hz, 3 H), 0.069 (s, 3 H), 0.062 (s, 3 H).

[3*R*,5*S*,7*S*,9*R*,11*R*,13*R*,15*S*,17*S*,19*S*,20(2*R*,3*S*,6*S*)]-20-(3-Methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-1,3:5,7:9,11:13,15:17,19-pentakis-*O*-(1-methylethylidene)eicosane-1,3,5,7,9,11,13,15,17,19-decol (12). Mesylate **11** (8.5 mg) was dissolved in 4 mL of MeOH and treated with Dowex 50W-X1 acid resin. After stirring for 2.5 h, the reaction was filtered and concentrated under reduced pressure. The resulting white solid was resubjected to the reaction conditions to ensure complete removal of the acetonide protecting groups.

The resulting polyol was then suspended in 3 mL of THF and treated with 100 μL of a 1.0 M solution of TBAF in THF. After stirring at 50 °C for 3 h, the reaction was concentrated under reduced pressure. Chromatography (SiO_2, 25% MeOH/ethyl acetate) gave 3.7 mg of a white solid.

The white solid was dissolved in 250 μL of acetone which was 20% enriched with [1,3-$^{13}C_2$]acetone and treated with approximately 1 mg of CSA. After stirring overnight, the acid was quenched with 10 μL of Et_3N and the reaction mixture was subjected to column chromatography (SiO_2, 50% ethyl acetate/hexanes) to give 1.0 mg of the desired product which had acetonides 20% ^{13}C-enriched at the methyl positions: ^1H NMR (C_6D_6, 500 MHz) δ 4.30 (m, 1 H), 4.22−3.95 (m, 9 H), 3.66−3.64 (m, 2 H), 3.01 (dd, J = 4.2, 7.8 Hz, 1 H), 2.27 (ddd, J = 5.3, 9.2, 13.8 Hz, 1 H), 2.07 (quintet, J = 7.1 Hz, 1 H), 1.84 (m, 1 H), 1.67−1.12 (m, 22 H), 1.609 (s, 3 H), 1.580 (s, 3 H), 1.549 (s, 6 H), 1.491 (s, 3 H), 1.466 (s, 3 H), 1.439 (s, 3 H), 1.420 (s, 3 H), 1.369 (s, 6 H), 1.02 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.93 (m, 1 H), 0.76 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (signals for 1,3-^{13}C-acetone enriched acetonides, C_6D_6, 125 MHz) δ 30.729 (2) (d, J = 4.8 Hz), 30.673 (d, J = 4.8 Hz), 30.448 (d, J = 4.6 Hz), 24.963 (2) (d, J = 4.8 Hz), 20.107 (d, J = 4.8 Hz), 20.041 (d, J = 4.8 Hz), 19.938 (d, J = 4.8 Hz), 19.488 (d, J = 4.6 Hz); HRMS (FAB) 767.5366 (M − CH_3), calcd for $C_{43}H_{75}O_{11}$ 767.5311. The ^{13}C-enriched compounds were also observed in the FABMS as (M − CH_3) 767 (30%), 769 (40%), 771 (20%).

(3*R*,5*S*,7*S*,9*S*,11*S*,13*S*,15*R*,17*R*,19*S*,21*S*,24*S*,25*S*)-1,25-Bis-*O*-((*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl)-3,5:7,9:11,13:15,17:19,21-pentakis-*O*-(1-methylethylidene)-24,26-dimethylheptacosane-1,3,5,7,9,11,13,15,17,19,21,25-dodecol (13R). Pentaacetonide **6** (10.6 mg) was dissolved in 6 mL of a 2:1 mixture of MeOH and CH_2Cl_2 and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted. Nitrogen was then bubbled through the solution until it was colorless, followed by addition of $NaBH_4$ (10 mg). The reaction mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was diluted with Et_2O (20 mL) and quenched with 2 mL of saturated $NaHCO_3$ solution. The organic portion was decanted and the aqueous portion was washed with Et_2O (2 × 10 mL). The combined organic portions were then washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 10.3 mg of a colorless syrup.

The syrup was dissolved in 3 mL of THF and treated with LAH (10 mg). After stirring for 1 h, the reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$. The reaction mixture was filtered through a small column of Na_2SO_4, eluting with Et_2O, and concentrated under reduced pressure to give 9.3 mg of a diol as a colorless syrup.

A 2.3 mg portion of the diol was dissolved in 2 mL of CH_2Cl_2 and treated with DMAP (14 mg) and (*S*)-MTPA-Cl (17 μL).[19] After stirring overnight, the reaction was quenched with saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($NaSO_4$), and concentrated under reduced pressure. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the bis ester **13R** (3.5 mg) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.34 (m, 10 H), 4.86 (dd, J = 3.9, 7.5 Hz, 1 H), 4.38−4.36 (m, 2 H), 3.99−3.88 (m, 8 H), 3.80 (m, 1 H), 3.65 (m, 1 H), 3.52 (s, 6 H), 1.95 (m, 1 H), 1.87−1.78 (m, 3 H), 1.74 (m, 1 H), 1.62−1.07 (m, 21 H), 1.359 (s, 3 H), 1.325 (s, 3 H), 1.309 (s, 6 H), 1.300 (s, 6 H), 1.294 (s, 6 H), 1.289 (s, 3 H), 1.275 (s, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.82 (d, J = 6.4 Hz, 3 H), 0.79 (d, J = 6.7 Hz, 3 H); HRMS (FAB) 1217.6188 (M − CH_3), calcd for $C_{63}H_{91}O_{16}F_6$ 1217.6213.

(3*R*,5*S*,7*S*,9*S*,11*S*,13*S*,15*R*,17*R*,19*S*,21*S*,24*S*,25*S*)-1,25-Bis-*O*-((*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl)-3,5:7,9:11,13:15,17:19,21-pentakis-*O*-(1-methylethylidene)-24,26-dimethylheptacosane-1,3,5,7,9,11,13,15,17,19,21,25-dodecol (13S). The (*S*)-MTPA ester was prepared from the intermediate diol (4.2 mg) following the same procedure used to prepare the (*R*)-MPTA ester **13R** described above. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the bis ester **13S** (3.5 mg) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.35 (m, 10 H), 4.87 (dd, J = 3.8, 8.0 Hz, 1 H), 4.42 (m, 1 H), 4.34 (dt, J = 10.7, 7.2 Hz, 1 H), 3.99−3.82 (m, 8 H), 3.80 (m, 1 H), 3.66 (m, 1 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 1.93 (m, 1 H), 1.85−1.74 (m, 4 H), 1.61−1.07 (m, 21 H), 1.367 (s, 3 H), 1.332 (s, 3 H), 1.305 (s, 6 H), 1.300 (s, 6 H), 1.292 (s, 6 H), 1.281 (s, 3 H), 1.236 (s, 3 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.9 Hz, 3 H), 0.79 (d, J = 6.6 Hz, 3 H); HRMS (FAB) 1217.6224 (M − CH_3), calcd for $C_{63}H_{91}O_{16}F_6$ 1217.6213.

[2*R*,4*R*,4(2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,15*S*,16*S*),6*S*,8*R*,10*S*]-4-(2,4,6,8,10,-12,16-Heptahydroxy-16-*O*-((*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl)-15,17-dimethyl-2,4:6,8:10,12-tris-*O*-(1-methylethylidene)-octadecanyl)-8-(2-*O*-((*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)-acetyl)-2-hydroxyethyl)-2-methyl-10-hydroxy-1,3,7-trioxaspiro[5.5]-undecane (15R). A 3.9 mg sample of diol **14** was dissolved in 2 mL of CH_2Cl_2 and treated with DMAP (14 mg) and (*S*)-MTPA-Cl (14 μL).[19] After stirring overnight, the reaction was concentrated and then

dissolved in THF. This was treated with 200 μL of a 1.0 M solution of TBAF in THF. After stirring for 3 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted into CH_2Cl_2. The organic layer was washed with H_2O and brine, dried ($NaSO_4$), and concentrated under reduced pressure. Chromatography (SiO_2, 50% ethyl acetate/hexanes) gave the bis ester **15R** (4.7 mg) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.59−7.35 (m, 10 H), 4.86 (dd, *J* = 4.1, 7.9 Hz, 1 H), 4.76 (q, *J* = 5.1 Hz, 1 H), 4.50 (dt, *J* = 10.9, 5.8 Hz, 1 H), 4.41 (dt, *J* = 10.9, 7.2 Hz, 1 H), 4.12−3.96 (m, 7 H), 3.73−3.64 (m, 2 H), 3.52 (s, 3 H), 3.51 (s, 3 H), 2.37 (br t, *J* = 7.5 Hz, 1 H), 2.01 (m, 1 H), 1.95 (m, 1 H), 1.90−1.86 (m, 4 H), 1.80−1.71 (m, 2 H), 1.58−1.04 (m, 18 H), 1.394 (s, 3 H), 1.357 (s, 3 H), 1.339 (s, 3 H), 1.328 (s, 3 H), 1.306 (s, 3 H), 1.302 (s, 3 H), 1.15 (d, *J* = 5.1 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H); HRMS (FAB) 1161.5554, (M − CH_3) calcd for $C_{59}H_{83}O_{16}F_6$ 1161.5587.

[2*R*,4*R*,4(2*S*,4*S*,6*S*,8*S*,10*S*,12*S*,15*S*,16*S*),6*S*,8*R*,10*S*]-4-(2,4,6,8,10,-12,16-Heptahydroxy-16-*O*-((*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl)-15,17-dimethyl-2,4:6,8:10,12-tris-*O*-(1-methylethylidene)-octadecanyl)-8-(2-*O*-((*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)-acetyl)-2-hydroxyethyl)-2-methyl-10-hydroxy-1,3,7-trioxaspiro[5.5]-undecane (15S). The (*S*)-MTPA ester was prepared from diol **14** (4.0 mg) by following the same procedure used to prepare the (*R*)-MTPA ester described above. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave the bis ester **15S** (4.7 mg) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.36 (m, 10 H), 4.87 (dd, *J* = 3.7, 7.7 Hz, 1 H), 4.77 (q, *J* = 5.1 Hz, 1 H), 4.57 (dt, *J* = 5.6, 10.6 Hz, 1 H), 4.36 (dt, *J* = 10.6, 7.0 Hz, 1 H), 4.07−3.96 (m, 7 H), 3.68 (m, 1 H), 3.61 (m, 1 H), 3.53 (s, 3 H), 3.51 (s, 3 H), 2.38 (m, 1 H), 2.00 (m, 1 H), 1.93 (m, 1 H), 1.88−1.83 (m, 4 H), 1.80−1.73 (m, 2 H), 1.53−1.04 (m, 18 H), 1.393 (s, 3 H), 1.365 (s, 3 H), 1.335 (s, 6 H), 1.300 (s, 6 H), 1.131 (d, *J* = 5.1 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H); HRMS (FAB) 1161.5564 (M − CH_3), calcd for $C_{59}H_{83}O_{16}F_6$ 1161.5587.

Synthesis of Degradation Fragment 12. (2*R*,3*S*)-2,4-Dimethyl-1-(phenylthio)-3-pentanol. A solution of (2*R*,3*R*)-2,4-dimethyl-1,3-pentanediol[28] (**20**) (584 mg, 4.42 mmol, 1.00 equiv) in 20 mL of dry acetonitrile was treated with tributylphosphine (1.10 mL, 4.42 mmol, 1.00 equiv) followed by the addition of diphenyl disulfide (1.00 g, 4.59 mmol, 1.04 equiv). After stirring under N_2 for 20 h, a 40 mL portion of 1 N NaOH was added. The reaction mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with 1 N NaOH and H_2O. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 815 mg of the product (3.84 mmol, 87%) as a colorless oil: IR (neat) 3425, 3074, 3058, 2963, 2930, 2873, 1584, 1480, 1438, 1382, 1246, 1091, 1065, 1026, 980, 952, 737, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.13 (m, 10 H), 3.37 (m, 1 H), 3.05 (dd, *J* = 7.4, 12.7 Hz, 1 H), 2.89 (dd, *J* = 6.6, 12.7 Hz, 1 H), 1.93 (m, 1 H), 1.68 (m, 1 H), 1.51 (d, *J* = 4.8 Hz, 1 H), 0.98 (d, *J* = 6.7 Hz, 6 H), 0.80 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 137.1; *C*H 129.3, 129.1, 126.0, 78.6, 34.9, 31.5; CH_2 38.8; CH_3 19.4, 19.3, 12.8. Anal. Calcd for $C_{13}H_{20}OS$: C, 69.59; H, 8.98. Found: C, 69.62; H, 8.83.

(2*R*,3*S*)-2,4-Dimethyl-3-*O*-(phenylmethyl)-1-(phenylthio)-3-pentanol. A solution of (2*R*,3*S*)-2,4-dimethyl-1-(phenylthio)-3-pentanol (815 mg, 3.84 mmol, 1.0 equiv) in 8 mL of THF was added via cannula to a suspension of KH (300 mg, 7.50 mmol, 2.0 equiv) in 10 mL of THF. After stirring for 15 min, the reaction mixture was cooled to 0 °C and benzyl bromide (500 μL, 4.20 mmol, 1.1 equiv) was added dropwise. After stirring for 18 h, the reaction was quenched with 20 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (2×), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 1% ethyl acetate/hexanes) gave 1.210 g (3.84 mmol, 100%) of the product as a colorless liquid: IR (neat) 3062, 3028, 2962, 2930, 2872, 1716, 1584, 1496, 1479, 1454, 1438, 1383, 1270, 1092, 1068, 1026, 966, 736, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.14 (m, 5 H), 4.67 (d, *J* = 11.3 Hz, 1 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 3.28 (dd, *J* = 3.0, 7.8 Hz, 1 H), 3.01 (dd, *J* = 7.3, 12.6 Hz, 1 H), 2.86 (dd, *J* = 6.8, 12.6 Hz, 1 H), 2.00 (m, 1 H), 1.89 (m, 1 H), 1.05 (d, *J* = 7.0 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 139.2, 136.9; *C*H 129.0, 128.8, 128.2, 127.4, 127.3, 125.7, 86.6, 35.2, 31.2; CH_2 75.1, 38.7; CH_3 19.7, 19.4, 14.0. Anal. Calcd for $C_{20}H_{26}OS$: C, 76.39; H, 8.33. Found: C, 76.50; H, 8.38.

(2*R*,3*S*)-2,4-Dimethyl-3-*O*-(phenylmethyl)-1-(phenylsulfonyl)-3-pentanol (21). (2*R*,3*S*)-2,4-Dimethyl-3-*O*-(phenylmethyl)-1-(phenylthio)-3-pentanol (1.210 g, 3.85 mmol, 1.0 equiv) was dissolved in 20 mL of MeOH and treated with a solution of Oxone (3.22 g, 5.24 mmol, 1.4 equiv) dissolved in 20 mL of H_2O. After stirring for 1 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$ (4 × 30 mL). The combined organic layers were washed with H_2O and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 16% ethyl acetate/hexanes) gave 1.232 g (3.56 mmol, 92%) of the product as a slightly yellow oil: $[\alpha]^{27}_D$ = +9.0° (*c* 1.10, $CHCl_3$); IR (neat) 3062, 3030, 2964, 2873, 1497, 1447, 1403, 1385, 1349, 1305, 1244, 1206, 1147, 1086, 1070, 1027, 999, 963, 927, 869, 856, 839, 785, 739, 722, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.19 (m, 10 H), 4.61 (d, *J* = 11.7 Hz, 1 H), 4.49 (d, *J* = 11.7 Hz, 1 H), 3.25−3.19 (m, 2 H), 2.90 (dd, *J* = 6.9, 14.2 Hz, 1 H), 2.45 (dq, *J* = 3.1, 6.9 Hz, 1 H), 1.85 (m, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 140.0, 138.7; *C*H 133.5, 129.2, 128.2, 127.7, 127.4, 127.3, 86.7, 30.8, 30.7; CH_2 74.4, 60.2; CH_3 19.9, 19.3, 14.4. Anal. Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56. Found: C, 69.49; H, 7.31.

(2*S*,4*R*,5*R*,6*S*)- and (2*S*,4*S*,5*R*,6*S*)-5,7-Dimethyl-1,2-*O*-(1-methylethylidene)-6-*O*-(phenylmethyl)-4-(phenylsulfonyl)-1,2,6-octanetriol (23). A solution of sulfone **21** (2.137 g, 6.18 mmol, 1.00 equiv) dissolved in 30 mL of THF was cooled to 0 °C under N_2 and treated with 2.50 mL of butyllithium (2.47 M in hexanes, 6.18 mmol, 1.00 equiv). After 1.5 h, a solution of (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl bromide[30] (**22**) (1.279 g, 6.56 mmol, 1.06 equiv) and DMPU (3.75 mL, 5 equiv) dissolved in 5 mL of THF was added dropwise via cannula. The reaction mixture was allowed to warm slowly to room temperature over 24 h followed by quenching with saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 (3 × 75 mL), and the combined organic layers were washed with H_2O and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 15−25% ethyl acetate/hexanes) gave 916 mg of unreacted sulfone (43%) and 1.506 g (3.27 mmol, 53%) of the product as a colorless oil: IR (neat) 3088, 3062, 3028, 2963, 2937, 1605, 1585, 1496, 1447, 1380, 1370, 1345, 1305, 1251, 1216, 1147, 1084, 1066, 1029, 998, 966, 924, 881, 866, 832, 731, 695, 606 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.83−7.76 (m, 2 H), 7.33−6.91 (m, 8 H), 4.62−4.46 (m, 2.3 H), 4.34 (d, *J* = 11.3 Hz, 0.7 H), 4.17 (dd, *J* = 3.4, 6.8 Hz, 0.3 H), 3.80 (dd, *J* = 6.3, 8.1 Hz, 1.0 H), 3.56−3.48 (m, 1.0 H), 3.27 (dd, *J* = 6.7, 8.1 Hz, 0.7 H), 3.09 (dd, *J* = 5.3, 8.2 Hz, 0.3 H), 2.93 (dd, *J* = 3.6, 7.4 Hz, 0.7 H), 2.50 (m, 0.3 H), 2.38−2.22 (m, 1.7 H), 1.89−1.76 (m, 2.0 H), 1.46 (d, *J* = 7.0 Hz, 0.9 H), 1.33 (s, 2.1 H), 1.23 (d, *J* = 6.7 Hz, 2.1 H), 1.22 (s, 2.1 H), 1.13 (dd, *J* = 6.8 Hz, 0.9 H), 1.07 (d, *J* = 6.8 Hz, 0.9 H), 1.06 (s, 0.9 H), 0.81 (s, 0.9 H), 0.80 (d, *J* = 7.0 Hz, 2.1 H), 0.50 (d, *J* = 6.7 Hz, 2.1 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 140.5, 139.8, 139.7, 139.3, 109.1; *C*H 133.3, 133.1, 129.3, 129.1, 128.9, 128.7, 128.5, 127.6, 127.5, 86.9, 85.2, 74.6, 72.5, 63.5, 63.2, 35.9, 35.3, 31.0, 30.3; CH_2 75.4, 74.7, 69.9, 69.4, 32.1, 29.4; CH_3 27.4, 26.9, 25.6, 25.5, 20.6, 20.4, 16.4, 15.7, 13.7, 10.4. Anal. Calcd for $C_{26}H_{36}O_5S$: C, 67.80; H, 7.88. Found: C, 68.00; H, 8.08.

(2*S*,5*S*,6*S*)-5,7-Dimethyl-1,2-*O*-(1-methylethylidene)-6-*O*-(phenylmethyl)-1,2,6-octanetriol. A solution of sulfone **23** (794 mg, 1.73 mmol, 1.0 equiv) dissolved in 20 mL of MeOH was treated with Na_2HPO_4 (1.56 g, 10.1 mmol, 6.4 equiv) and sodium amalgam (6% sodium content, 4.21 g, 10.5 mmol, 6.1 equiv). After stirring for 2.5 h, the reaction mixture was filtered through a Celite pad and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 511 mg (1.60 mmol, 93%) of the product as a colorless oil: $[\alpha]^{27}_D$ = +18.1° (*c* 0.93, $CHCl_3$); IR (neat) 3062, 3028, 2965, 2939, 2874, 1718, 1602, 1496, 1454, 1378, 1344, 1273, 1216, 1160, 1096, 1067, 1028, 976, 854, 806, 791, 753, 714, 699 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.35−7.08 (m, 5 H), 4.48−4.42 (m, 2 H), 3.87 (m, 1 H), 3.79 (dd, *J* = 5.9, 7.5 Hz, 1 H), 3.35 (t, *J* = 7.5 Hz, 1 H), 2.80 (dd, *J* = 4.0, 6.5 Hz, 1 H), 1.85 (m, 1 H), 1.66−1.54 (m, 2 H), 1.45 (s, 3 H), 1.44−1.27 (m, 3 H), 1.35 (s, 3 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7

Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 140.0, 108.9; *C*H 128.6, 127.6, 127.5, 76.5, 36.0, 31.4; *C*H$_2$ 75.3, 69.8, 31.9, 31.0; *C*H$_3$ 27.5, 26.1, 20.4, 19.0, 14.8. Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.17; H, 9.88.

(2*S*,5*S*,6*S*)-5,7-Dimethyl-1,2-*O*-(1-methylethylidene)-1,2,6-octanetriol. A suspension of 675 mg (2.11 mmol) of (2*S*,5*S*,6*S*)-5,7-dimethyl-1,2-*O*-(1-methylethylidene)-6-*O*-(phenylmethyl)-1,2,6-octanetriol and 60 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 4 h the mixture was filtered through a Celite pad which had been moistened with MeOH and Et_3N. The resulting filtrate was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 20–25% ethyl acetate/hexanes) to give 436 mg (1.90 mmol, 90%) of the product as a colorless oil: IR (neat) 3498, 2959, 2871, 1457, 1370, 1218, 1160, 1095, 1060, 981, 851, 792 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.87 (m, 1 H), 3.81 (m, 1 H), 3.37 (t, J = 7.3 Hz, 1 H), 2.93 (m, 1 H), 1.66–1.42 (m, 3 H), 1.43 (s, 3 H), 1.40–1.26 (m, 3 H), 1.34 (s, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.82 (d, J = 6.6 Hz, 3 H), 0.76 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 108.7; *C*H 79.3, 76.5, 35.3, 31.2; *C*H$_2$ 69.6, 31.4, 30.4; *C*H$_3$ 27.2, 25.9, 19.5, 18.8, 13.2. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 68.02; H, 11.48.

(2*S*,5*S*,6*S*)-5,7-Dimethyl-6-*O*-(methylsulfonyl)-1,2-*O*-(1-methylethylidene)-1,2,6-octanetriol (24). A solution of (2*S*,5*S*,6*S*)-5,7-dimethyl-1,2-*O*-(1-methylethylidene)-1,2,6-octanetriol (460 mg, 2.00 mmol, 1.0 equiv) and DMAP (244 mg, 2.00 mmol, 1.0 equiv) dissolved in 20 mL of CH_2Cl_2 was cooled to 0 °C under N_2 and treated with Et_3N (668 μL, 4.80 mmol, 2.4 equiv) and mesyl chloride (185 μL, 2.39 mmol, 1.2 equiv). After stirring for 15 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) gave 594 mg (1.93 mmol, 96%) of the product as a colorless oil: IR (neat) 2938, 2876, 1464, 1418, 1369, 1337, 1215, 1172, 1059, 973, 906, 848, 810, 764, 668 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 4.47 (dd, J = 3.5, 7.4 Hz, 1 H), 3.87 (m, 1 H), 3.80 (dd, J = 6.0, 7.5 Hz, 1 H), 3.41 (t, J = 7.5 Hz, 1 H), 2.30 (s, 3 H), 1.75 (m, 1 H), 1.59 (m, 1 H), 1.51–1.31 (m, 4 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 108.8; *C*H 90.8, 76.3, 35.1, 30.4; *C*H$_2$ 69.6, 31.4, 30.5; *C*H$_3$ 38.2, 27.2, 26.0, 19.7, 19.0, 14.4. Anal. Calcd for $C_{14}H_{28}O_5S$: C, 54.52; H, 9.15. Found: C, 54.32; H, 9.27.

(2*R*,3*S*,6*S*)-(3-Methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-methanol (25). Mesylate **24** (584 mg, 1.90 mmol, 1.0 equiv) was dissolved in 20 mL of MeOH and treated with Dowex 50W-X1 acid resin. After stirring for 2 h, the reaction was filtered and concentrated under reduced pressure to give 508 mg of a yellow oil which was dissolved in 15 mL of THF and treated with 250 mg of NaH (10.4 mmol, 5.5 equiv). After stirring for 2 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with H_2O and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) gave 257 mg (1.50 mmol, 79%) of the product as a slightly yellow oil: IR (neat) 3428, 2957, 2931, 2872, 1461, 1384, 1367, 1238, 1207, 1173, 1156, 1141, 1107, 1054, 985, 905, 881, 856, 819 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.63–3.58 (m, 2 H), 3.34 (m, 1 H), 2.89 (t, J = 5.9 Hz, 1 H), 2.28 (m, 1 H), 1.80 (m, 1 H), 1.51–1.23 (m, 4 H), 0.94 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C*H 81.7, 71.5, 29.9, 27.8; *C*H$_2$ 63.4, 26.6, 23.7; *C*H$_3$ 23.7, 20.2, 18.2.

(2*R*,3*S*,6*S*)-(3-Methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-*O*-(methylsulfonyl)methanol. A solution of alcohol **25** (250 mg, 1.45 mmol, 1.0 equiv) and DMAP (177 mg, 1.45 mmol, 1.0 equiv) dissolved in 15 mL of CH_2Cl_2 was cooled to 0 °C under N_2 and treated with Et_3N (484 μL, 3.84 mmol, 2.4 equiv) and mesyl chloride (135 μL, 1.74 mmol, 1.2 equiv). After stirring for 17 h, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) gave 340 mg (1.36 mmol, 94%) of the product as a colorless oil: IR (neat) 2959, 2934, 2873, 1462, 1355, 1176, 1119, 1093, 1059, 1031, 961, 886, 823, 747 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 4.06 (dd, J = 7.7, 10.6 Hz, 1 H), 3.78 (dd, J = 4.3, 10.6 Hz, 1 H), 3.64 (m, 1 H), 2.82 (t, J = 6.0 Hz, 1 H), 2.27 (s, 3 H), 1.74 (m, 1 H), 1.40 (m, 1 H), 1.26 (m, 1 H), 1.15–1.08 (m, 2 H), 0.94 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.74 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C*H 82.0, 68.7, 29.7, 27.7; *C*H$_2$ 69.9, 26.2, 23.5; *C*H$_3$ 37.0, 20.1, 18.0, 16.7. Anal. Calcd for $C_{11}H_{22}O_4S$: C, 52.77; H, 8.85. Found: C, 52.75; H, 8.95.

(2*R*,3*S*,6*S*)-6-(Bromomethyl)-3-methyl-2-(1-methylethyl)tetrahydropyran (16). A solution of (2*R*,3*S*,6*S*)-(3-methyl-2-(1-methylethyl)-tetrahydropyran-6-yl)-*O*-(methylsulfonyl)methanol (325 mg, 1.30 mmol, 1.00 equiv) and nBu$_4$NBr (425 mg, 1.32 mmol, 1.02 equiv) in 10 mL of dry toluene was heated to reflux under N_2. After 24 h, an additional 100 mg of nBu$_4$NBr was added and the reaction was refluxed for an additional 2 h. The reaction mixture was then cooled, diluted with 100 mL of Et_2O, and washed with H_2O (2×) and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 3% ethyl acetate/hexanes) gave 259 mg (1.10 mmol, 85%) of the product as a colorless liquid: IR (neat) 2959, 2931, 2872, 1460, 1384, 1222, 1155, 1114, 1078, 1062, 1027, 969 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.74 (m, 1 H), 3.22 (dd, J = 7.5, 10.3 Hz, 1 H), 2.97 (dd, J = 6.1, 10.3 Hz, 1 H), 2.78 (dd, J = 5.3, 6.7 Hz, 1 H), 1.74 (m, 1 H), 1.44–1.31 (m, 3 H), 1.26 (m, 1 H), 0.96 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.91 (m, 1 H), 0.71 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C*H 80.9, 71.1, 30.3, 28.0; *C*H$_2$ 33.6, 26.5, 25.8; *C*H$_3$ 20.3, 17.7, 16.0. Anal. Calcd for $C_{10}H_{19}BrO$: C, 51.08; H, 8.14. Found: C, 51.16; H, 8.24.

(8*S*,10*S*)-5,12-Heptadecadiyne-8,10-diol. A solution of 1-hexyne (2.85 mL, 24.8 mmol, 4.0 equiv) in 50 mL of THF under N_2, cooled to −78 °C, was treated with 9.7 mL (23.7 mmol, 3.8 equiv) of a 2.44 M solution of butyllithium. After 20 min, (2*R*,4*R*)-1,2:4,5-dianhydro-3-deoxypentitol[26a] (**26**) (622 mg, 6.22 mmol, 1.0 equiv), dissolved in 10 mL of THF, was added via cannula followed by dropwise addition of BF_3·OEt_2 (3.00 mL, 24.4 mmol, 3.9 equiv). After 30 min, the reaction was quenched with 40 mL of saturated $NaHCO_3$, and the solution was warmed to room temperature. The reaction mixture was diluted with Et_2O (75 mL), and the layers were separated. The aqueous layer was treated with 40 mL of 1 N NaOH solution and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 1 N NaOH, H_2O, and brine. The organic portion was then dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 20–40% ethyl acetate/hexanes) gave the product (1.541 g, 94%) as a colorless syrup: $[\alpha]^{27}_D$ = +17.7° (c = 1.18, CH_2Cl_2); IR (neat) 3285, 2930, 2872, 1599, 1466, 1428, 1343, 1252, 1232, 1192, 1087, 1057, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (m, 2 H), 2.60 (br s, 2 H), 2.35 (m, 4 H), 2.13 (m, 4 H), 1.72 (t, J = 5.8 Hz, 2 H), 1.49–1.32 (m, 8 H), 0.87 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 83.5, 76.1; *C*H 67.9; *C*H$_2$ 41.0, 31.3, 28.0, 22.2, 18.6; *C*H$_3$ 13.8. Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.13; H, 10.56.

(8*S*,10*S*)-8,10-*O*-(1-Methylethylidene)-5,12-heptadecadiyne-8,10-diol (27). (8*S*,10*S*)-5,12-Heptadecadiyne-8,10-diol (1.541 g, 5.83 mmol) was dissolved in 40 mL of a mixture of acetone and 2,2-dimethoxypropane (3:1) and treated with 12 mg of CSA. After stirring for 18 h, 0.25 mL of Et_3N was added and the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 4% ethyl acetate/hexanes) gave 1.503 g (4.94 mmol, 85%) of the product as a colorless liquid: IR (neat) 2987, 2957, 2932, 2872, 1468, 1434, 1379, 1329, 1303, 1225, 1170, 1111, 1094, 1022, 992, 940, 904, 842, 815, 728 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.98 (m, 2 H), 2.47 (ddt, J = 5.6, 16.3, 2.7 Hz, 2 H), 2.32 (ddt, J = 7.3, 16.3, 2.3 Hz, 2 H), 2.07 (m, 4 H), 1.85 (t, J = 7.5 Hz, 2 H), 1.43–1.32 (m, 8 H), 1.34 (s, 6 H), 0.81 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 100.5, 81.9, 76.8; *C*H 66.2; *C*H$_2$ 37.2, 31.5, 26.6, 22.2, 18.8; *C*H$_3$ 25.3, 13.8. Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 78.83; H, 10.50.

(8*S*,10*S*)-8,10-*O*-(1-Methylethylidene)-5,12-heptadecadiene-8,10-diol. A suspension of 93 mg of 5% Pd on $BaSO_4$ and 930 μL of quinoline in 80 mL of ethyl acetate was stirred under H_2 (balloon pressure) for 1 h followed by the addition of acetonide **27** (1.460 g, 4.80 mmol) dissolved in 10 mL of ethyl acetate. After stirring for 1 h,

the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 2% ethyl acetate/hexanes) gave 1.430 g (4.64 mmol, 97%) of the product as a colorless liquid: IR (neat) 2986, 2957, 2930, 2873, 2859, 1657, 1548, 1512, 1459, 1404, 1378, 1224, 1169, 1107, 1022, 992, 942, 904, 836, 724 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.60−5.47 (m, 4 H), 3.88 (m, 2 H), 2.38 (dt, J = 13.8, 6.6 Hz, 2 H), 2.25 (dt, J = 13.8, 5.7 Hz, 2 H), 2.06−2.00 (m, 4 H), 1.56 (t, J = 7.6 Hz, 2 H), 1.48 (s, 6 H), 1.36−1.21 (m, 8 H), 0.87 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 100.2; *C*H 131.9, 125.7, 66.8; *C*H_2 38.0, 34.2, 32.1, 27.5, 27.5, 22.6; *C*H_3 25.1, 14.1. Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.87; H, 11.76. Found: C, 78.00; H, 11.83.

(3*R*,5*R*)-3,5-Dihydroxy-3,5-*O*-(1-methylethylidene)-1,7-heptanedialdehyde (28). (8*S*,10*S*)-8,10-*O*-(1-Methylethylidene)-5,12-heptadecadiene-8,10-diol (1.40 g, 4.55 mmol, 1.00 equiv) was dissolved in 50 mL of dry CH_2Cl_2 and cooled to −78 °C. Ozone was then bubbled through the solution until a slight blue color persisted. Nitrogen was then bubbled through the solution until it was colorless. Triphenylphosphine (2.45 g, 9.35 mmol, 2.06 equiv) was then added and the reaction was warmed to room temperature. After stirring for 24 h, the reaction was concentrated under a stream of N_2. Purification by flash chromatography (SiO_2, 33% ethyl acetate/hexanes) gave 828 mg (4.14 mmol, 91%) of the unstable dialdehyde as a colorless liquid: IR (neat) 2988, 2938, 2834, 2732, 1726, 1447, 1382, 1224, 1167, 1128, 1031, 1003, 899, 735 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 9.37 (dd, J = 1.0, 2.5 Hz, 2 H), 4.00 (ddt, J = 4.6, 8.3, 7.8 Hz, 2 H), 2.18 (ddd, J = 2.5, 8.3, 16.6 Hz, 2 H), 1.89 (ddd, J = 1.0, 4.6, 16.6 Hz, 2 H), 1.21 (s, 6 H), 1.18 (t, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 100.7; *C*H 199.2, 61.9; *C*H_2 49.0, 37.3; *C*H_3 24.5.

(2*R*,4*R*,6*R*,8*R*)-, (2*R*,4*R*,6*R*,8*S*)-, and (2*S*,4*R*,6*R*,8*S*)-2,4:6,8-Bis-*O*-(1-methylethylidene)-2,4,6,8-tetrahydroxynonane-1,9-dinitrile (17). A solution of dialdehyde **28** (818 mg, 4.09 mmol, 1.00 equiv) dissolved in 2 mL of CH_2Cl_2 was cooled to 0 °C and treated with TMSCN (1.12 mL, 8.40 mmol, 2.05 equiv) and a catalytic amount of KCN/18-crown-6 complex (**caution**: highly exothermic). After stirring for 90 min, the CH_2Cl_2 was evaporated under a stream of N_2, and the resulting oil was treated with 50 mg of CSA and 50 mL of a mixture of acetone and 2,2-dimethoxypropane (4:1). After stirring for 3 h, an additional 50 mg of CSA was added and the reaction was stirred overnight. The reaction was quenched with 0.5 mL of Et_3N and the reaction was concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) gave 1.091 g (3.71 mmol, 91%) of the product as a colorless syrup which was a 1:2:1 mixture of the three possible diastereomers: ^1H NMR (300 MHz, C_6D_6) δ 4.22−4.09 (m, 2 H), 4.04−3.98 (m, 1 H), 3.56−3.45 (m, 1 H), 1.41−0.85 (m, 6 H), 1.53 (s, 1.5 H), 1.52 (s, 1.5 H), 1.32 (s, 1.5 H), 1.29 (s, 1.5 H), 1.27 (s, 1.5 H), 1.24 (s, 1.5 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 119.9, 118.0, 118.0, 100.8, 100.6, 99.8, 99.7; *C*H 63.4, 63.1, 61.2, 59.1, 58.5; *C*H_2 41.2, 41.1, 34.6, 34.4, 33.3, 33.2; *C*H_3 29.5, 29.5, 21.7, 21.7, 18.9, 18.9. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53. Found: C, 61.37; H, 7.59.

(3*S*)-1,3-*O*-(1-Methylethylidene)-5-*O*-(phenylmethyl)-1,3,5-pentanetriol (30). A solution of ethyl (3*S*)-3-hydroxy-5-(phenylmethoxy)-pentanoate[32,33] (**29**) (5.20 g, 20.6 mmol, 1 equiv) dissolved in 50 mL of Et_2O was added dropwise via cannula (over a 30 min period) to a suspension of LAH in 100 mL of Et_2O at 0 °C. After stirring for 60 min, the reaction mixture was warmed to room temperature and stirred an additional 60 min. The reaction was then cooled to 0 °C and quenched by slow addition of H_2O (2.9 mL), 15% NaOH (2.9 mL), and H_2O (12 mL). The aluminum salts were removed by filtration, and the filtrate was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting colorless oil was treated with 30 mg of CSA and 80 mL of a mixture of acetone and 2,2-dimethoxypropane (3:1). After stirring for 2 h, the reaction was quenched with 1 mL of Et_3N and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 12% ethyl acetate/hexanes) gave 4.19 g (16.7 mmol, 81%) of the product as a colorless syrup: IR (neat) 3063, 3029, 2991, 2946, 2866, 1496, 1454, 1380, 1369, 1272, 1238, 1202, 1168, 1135, 1100, 1057, 1028, 997, 969, 870, 860, 797, 738, 698 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.30−7.07 (m, 5 H), 4.33 (d, J = 12.2 Hz, 1 H), 4.31 (d, J = 12.2 Hz, 1 H), 3.91 (dddd, J = 2.6, 4.5, 7.4, 11.9 Hz, 1 H), 3.65−3.61 (m, 2 H), 3.52 (ddd, J = 5.6, 8.0, 9.0 Hz, 1 H), 3.40 (ddd, J = 5.7, 5.8, 9.1 Hz, 1 H), 1.83−1.60 (m, 2 H), 1.49 (s, 3 H), 1.48−1.38 (m, 1 H), 1.30 (s, 3 H), 0.97 (ddd, J = 2.3, 4.6, 12.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 139.4, 98.2; *C*H 128.4, 127.5, 66.1; *C*H_2 73.0, 66.4, 59.8, 37.2, 31.7; *C*H_3 30.3, 19.3. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.76; H, 8.60.

(3*R*,5*R*)-1,3-*O*-(1-Methylethylidene)-7-octene-1,3,5-triol (31). A suspension of 1.03 g (3.96 mmol) of benzyl ether **30** and 20 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 24 h the mixture was filtered through a Celite pad which had been moistened with MeOH and Et_3N. The resulting filtrate was concentrated under reduced pressure and purified by flash chromatography (SiO_2, 50% ethyl acetate/hexanes) to give 580 mg of a colorless oil which was immediately dissolved in 40 mL of CH_2Cl_2 and treated with $NaHCO_3$ (4.53 g, 53.9 mmol) and Dess−Martin reagent (2.03 g, 4.79 mmol). After stirring for 40 min, the reaction mixture was diluted with 200 mL of Et_2O followed by the addition of 80 mL of saturated $NaHCO_3$ solution and 80 mL of 0.5 M $Na_2S_2O_3$ solution. The layers were separated, and the organic portion was washed sequentially with $NaHCO_3$, H_2O and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde as a light brown liquid.

The aldehyde was dissolved in 5 mL of Et_2O and added via cannula to a cooled (−78 °C), stirred solution of (+)-Ipc_2B(allyl)[34] (2.5 mmol) in 12 mL of Et_2O. The reaction mixture was allowed to warm to room temperature overnight followed by the addition of 2 mL of 15% NaOH and 4 mL of 30% H_2O_2. The reaction mixture was refluxed for 2 h and then cooled and diluted with Et_2O. The reaction mixture was then washed sequentially with H_2O (2×), $NaHCO_3$, and brine. The organic layer was dried with $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (20−30% ethyl acetate/hexanes) to give the product (348 mg, 1.74 mmol, 44%) as a colorless oil: IR (neat) 3454, 3075, 2993, 2944, 2918, 2870, 1641, 1460, 1430, 1381, 1272, 1240, 1201, 1164, 1138, 1100, 1051, 998, 968, 936, 914, 884, 870, 813, 747 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 5.80 (m, 1 H), 5.05−5.00 (m, 2 H), 4.00 (m, 1 H), 3.92 (m, 1 H), 3.68−3.53 (m, 2 H), 2.30 (d, J = 3.6 Hz, 1 H), 2.16 (dd, J = 6.8, 13.7 Hz, 1 H), 2.09 (dd, J = 5.7, 13.7 Hz, 1 H), 1.59−1.32 (m, 3 H), 1.43 (s, 3 H), 1.29 (s, 3 H), 0.88 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 98.2; *C*H 135.4, 67.0, 66.4; *C*H_2 117.0, 59.7, 42.9, 42.7, 31.3; *C*H_3 30.1, 19.1. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.07; H, 10.25.

(2*R*,4*S*,6*R*)- and (2*S*,4*S*,6*R*)-2,4:6,8-Bis-*O*-(1-methylethylidene)-2,4,6,8-tetrahydroxyoctanenitrile (19). A solution of alcohol **31** (336 mg, 1.68 mmol, 1.00 equiv) and $TMSNMe_2$ (330 μL, 2.06 mmol, 1.23 equiv) in 10 mL of CH_3CN was heated to reflux for 3 h. The reaction was then cooled and concentrated under reduced pressure to give 440 mg of a colorless liquid which was dissolved in 9 mL of acetone and 3 mL of H_2O. To this solution were added *N*-methylmorpholine *N*-oxide (270 mg, 2.31 mmol, 1.4 equiv) and 0.5 mL of OsO_4 solution (2.5% in *tert*-butyl alcohol). After stirring for 90 min, TLC analysis showed complete consumption of the alkene. A solution of $NaIO_4$ (740 mg, 3.45 mmol, 2.1 equiv) in 3 mL of H_2O was added all at once. After stirring for 60 min, the reaction mixture was diluted with H_2O, extracted (2 × Et_2O), washed (Na_2SO_3, brine), and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 and washed with saturated NH_4Cl solution. The organic layer was then dried with Na_2SO_4 and concentrated under reduced pressure to give 396 mg of the aldehyde as a colorless oil.

The aldehyde was dissolved in 3 mL of CH_2Cl_2, cooled to 0 °C, and treated with TMSCN (200 μL, 1.50 mmol, 1.04 equiv) and a catalytic amount of KCN/18-crown-6 complex. After stirring for 15 min, the CH_2Cl_2 was evaporated under a stream of N_2, and the resulting oil was treated with 15 mg of CSA and 10 mL of a mixture of acetone and 2,2-dimethoxypropane (3:1). After stirring overnight, the reaction was quenched with 0.2 mL of Et_3N and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 346 mg (1.28 mmol, 77% overall yield from alcohol **31**) of the product as a colorless syrup which was a 1:1 epimeric mixture at the cyanohydrin center: IR (neat) 2992, 2943, 2870, 1462, 1431, 1382, 1270, 1240, 1199, 1160, 1105, 1047, 1002, 970, 946, 912, 871, 819, 805 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.29 (m, 0.5 H), 4.19 (m, 0.5 H), 4.01 (m, 0.5 H), 3.93−3.81 (m, 1 H), 3.66−3.57 (m, 2.5 H), 1.59 (s, 1.5 H), 1.45 (s, 1.5 H), 1.43 (s, 1.5 H), 1.34 (s, 1.5 H), 1.29 (s, 1.5 H), 1.26 (s, 3 H), 1.03 (s, 1.5 H), 1.53−1.13 (m, 4.5 H),

0.97−0.79 (m, 1.5 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 120.0, 118.1, 100.8, 99.8, 98.3, 98.2; *C*H 64.5, 64.2, 63.8, 61.8, 59.3, 58.8; *C*H$_2$ 59.8, 42.6, 42.5, 34.9, 33.7, 31.9, 31.8; *C*H$_3$ 30.2, 30.2, 29.7, 21.9, 19.4, 19.3, 19.1. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61. Found: C, 62.13; H, 8.79.

[2*R*,4*S*,6*R*,8*S*,9(2*R*,3*S*,6*S*)]-8-Cyano-2,4:6,8-bis-*O*-(1-methylethylidene)-9-(3-methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-2,4,6,8-tetrahydroxynonanenitrile (32). A solution of nitriles **17** (370 mg, 1.26 mmol, 1.88 equiv) in 8 mL of THF was added dropwise via cannula to a solution of LiNEt$_2$ (0.74 mmol, 1.1 equiv) in 8 mL of THF at −78 °C under argon. After 1 h, DMPU (660 μL, 8 equiv) was added followed by the dropwise addition of a solution of bromide **16** (158 mg, 0.672 mmol, 1.00 equiv) in 2 mL of THF. The reaction mixture was then transferred to a −25 °C ice/MeOH bath. The system was allowed to slowly warm to 15 °C over 15 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted into CH_2Cl_2 (3×). The combined organic layers were washed sequentially with H_2O and brine (2×), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10−20% ethyl acetate/hexanes) gave 45 mg of the unreacted bromide (28%) and 121 mg (0.270 mmol, 40%) of the desired product as a colorless syrup: IR (neat) 2993, 2932, 2873, 1460, 1433, 1384, 1330, 1262, 1206, 1163, 1124, 1060, 1024, 1002, 976, 944, 920, 877, 814, 672 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.35 (dddd, *J* = 2.3, 4.8, 6.9, 12.1 Hz, 1 H), 4.24 (m, 1 H), 3.89 (dd, *J* = 2.8, 11.9 Hz, 1 H), 3.55 (dddd, *J* = 2.5, 5.0, 6.8, 11.8 Hz, 1 H), 2.82 (dd, *J* = 4.9, 7.0 Hz, 1 H), 2.10 (dd, *J* = 7.5, 14.7 Hz, 1 H), 1.92−1.80 (m, 2 H), 1.72 (dd, *J* = 3.3, 14.7 Hz, 1 H), 1.70 (s, 3 H), 1.50 (m, 1 H), 1.43−1.28 (m, 5 H), 1.37 (s, 3 H), 1.30 (s, 3 H), 1.19 (m, 1 H), 1.09 (ddd, *J* = 2.6, 9.5, 13.7 Hz, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.98 (m, 1 H), 0.94 (s, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H), 0.80 (dt, *J* = 12.9, 2.5 Hz, 1 H), 0.77 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 122.5, 117.9, 100.9, 99.9, 69.1; *C*H 80.8, 66.6, 63.6, 62.4, 59.1, 30.8, 28.1; *C*H$_2$ 44.3, 41.5, 38.1, 34.7, 29.6, 26.8; *C*H$_3$ 30.7, 29.5, 21.5, 20.5, 18.9, 18.0, 16.5; HRMS (FAB) 449.3037 (M + H). Anal. Calcd for $C_{25}H_{40}N_2O_5$: C, 66.94; H, 8.99. Found: C, 67.04; H, 8.86.

(3*R*,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 (33). A solution of nitriles **19** (283 mg, 1.05 mmol, 1.00 equiv) in 3 mL of THF was cooled to −78 °C and added dropwise via cannula to a solution of LiNEt$_2$ (1.20 mmol, 1.2 equiv) in 8 mL of THF at −78 °C under argon. After 1 h, a solution of dibromide **18** (800 mg, 2.65 mmol, 2.52 equiv) in 2 mL of THF, cooled to −78 °C, was added dropwise via cannula. The reaction mixture was then transferred to a −23 °C ice/MeOH bath. The system was allowed to slowly warm to 15 °C over 15 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted into CH_2Cl_2 (3×), dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10−20% ethyl acetate/hexanes) gave 540 mg of the unreacted dibromide (68%) and 319 mg (0.651 mmol, 62%) of the desired product as a colorless syrup: IR (neat) 2990, 2942, 2870, 1496, 1461, 1432, 1382, 1262, 1224, 1197, 1160, 1124, 1049, 988, 971, 955, 942, 909, 870, 850, 808, 733, 696, 651 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 4.44 (m, 1 H), 4.05 (m, 1 H), 3.92 (m, 1 H), 3.72 (m, 1 H), 3.63−3.60 (m, 2 H), 3.01 (dd, *J* = 6.5, 10.5 Hz, 1 H), 2.93 (dd, *J* = 5.0, 10.5 Hz, 1 H), 1.88 (dd, *J* = 8.3, 14.6 Hz, 1 H), 1.74−1.63 (m, 3 H), 1.72 (s, 3 H), 1.49−1.20 (m, 5 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.24 (s, 3 H), 0.90 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 122.3, 101.1, 101.0, 98.3, 68.5; *C*H 66.8, 64.6, 62.6, 62.0; *C*H$_2$ 59.8, 46.8, 42.8, 38.6, 37.5, 25.2, 32.0; *C*H$_3$ 31.1, 30.2, 24.7, 24.6, 21.7, 19.4; HRMS (FAB) 490.1795 (M + H). Anal. Calcd for $C_{22}H_{36}BrNO_6$: C, 53.88; H, 7.40. Found: C, 54.04; H, 7.24.

[3*R*,5*S*,7*R*,9*R*,11*R*,13*S*,15*R*,17*R*,19*S*,20(2*R*,3*S*,6*S*)]-7,13,19-Tricyano-20-(3-methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-1,3:5,7:9,11:13,15:17,19-pentakis-*O*-(1-methylethylidene)eicosane-1,3,5,7,9,11,13,15,17,19-decol (34). A solution of nitrile **32** (120 mg, 0.268 mmol, 1.00 equiv) in 1.7 mL of THF was added dropwise via cannula to a solution of LiNEt$_2$ (0.322 mmol, 1.2 equiv) in 2 mL of THF at −78 °C under argon. After 1 h, DMPU (160 μL, 4 equiv) was added followed by the dropwise addition of a solution of bromide **33** (174 mg, 0.355 mmol, 1.33 equiv) in 1.3 mL of THF. The reaction mixture was then transferred to a −22 °C ice/MeOH bath. The system was allowed to slowly warm to 10 °C over 14 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted into CH_2Cl_2 (3×). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 15 → 20 → 25% ethyl acetate/hexanes) gave 187 mg (0.218 mmol, 81%) of the desired product as a colorless syrup: $[\alpha]^{27}_D$ = +13.8° (*c* 0.70, $CHCl_3$); IR (neat) 2990, 2939, 2871, 1462, 1434, 1383, 1262, 1208, 1161, 1026, 955, 871, 807, 680 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.58−4.50 (m, 3 H), 4.33 (m, 1 H), 4.26 (m, 1 H), 3.95 (m, 2 H), 3.63−3.61 (m, 2 H), 2.82 (dd, *J* = 4.9, 7.1 Hz, 1 H), 2.13 (dd, *J* = 7.3, 14.6 Hz, 1 H), 1.97−1.92 (m, 2 H), 1.84−1.79 (m, 2 H), 1.78 (s, 3 H), 1.77 (s, 3 H), 1.76−1.64 (m, 5 H), 1.75 (s, 3 H), 1.54−1.28 (m, 15 H), 1.48 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 0.99 (m, 1 H), 0.99 (d, *J* = 6.7 Hz, 3 H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.86 (m, 1 H), 0.76 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, DEPT) *C* 122.7, 122.5, 121.6, 101.3, 101.3, 101.2, 100.9, 69.3, 68.9, 68.7; *C*H 80.9, 66.9, 64.7, 63.0, 62.7, 62.4, 62.0, 30.9, 28.3; *C*H$_2$ 59.9, 48.1, 47.1, 44.4, 42.9, 41.7, 41.6, 39.5, 38.4, 32.0, 29.9, 27.1; *C*H$_3$ 31.2, 31.0, 30.3, 24.6, 24.6, 21.8, 21.7, 21.7, 20.7, 19.4, 18.1, 16.6; HRMS (FAB) 858.5540 (M + H). Anal. Calcd for $C_{47}H_{75}N_3O_{11}$: C, 65.79; H, 8.81. Found: C, 65.68; H, 8.66.

[3*R*,5*S*,7*S*,9*R*,11*R*,13*R*,15*S*,17*S*,19*S*,20(2*R*,3*S*,6*S*)]-20-(3-Methyl-2-(1-methylethyl)tetrahydropyran-6-yl)-1,3:5,7:9,11:13,15:17,19-pentakis-*O*-(1-methylethylidene)eicosane-1,3,5,7,9,11,13,15,17,19-decol (12). Lithium metal (80 mg, 11.5 mmol, 112 equiv) was dissolved in 15 mL of ammonia to give a bright blue solution which was cooled to −78 °C. Pentaacetonide nitrile **34** (88.0 mg, 0.103 mmol, 1 equiv) was dissolved in 5 mL of THF and added to the Li/NH_3 solution via cannula. After being stirred for 1 h, the reaction was quenched with 740 mg of solid NH_4Cl and warmed to room temperature, and the ammonia was allowed to evaporate. The remaining residue was dissolved in 20 mL of H_2O and 20 mL of CH_2Cl_2. The layers were separated, and the aqueous portion was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25% ethyl acetate/hexanes) gave the product (65.5 mg, 81%) as a colorless syrup: $[\alpha]^{27}_D$ = +20.5° (*c* 0.85, $CHCl_3$); IR (neat) 2989, 2941, 2870, 1379, 1266, 1225, 1199, 1168, 110, 1025, 968, 941, 872, 807 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz) δ 4.29 (m, 1 H), 4.22−4.02 (m, 7 H), 4.02−3.95 (m, 2 H), 3.69−3.63 (m, 2 H), 3.01 (dd, *J* = 4.2, 7.8 Hz, 1 H), 2.26 (ddd, *J* = 5.4, 9.2, 13.9 Hz, 1 H), 2.06 (quintet, *J* = 6.9 Hz, 1 H), 1.84 (m, 1 H), 1.64−1.11 (m, 22 H), 1.603 (s, 3 H), 1.585 (s, 3 H), 1.544 (s, 6 H), 1.487 (s, 3 H), 1.462 (s, 3 H), 1.436 (s, 3 H), 1.417 (s, 3 H), 1.368 (s, 3 H), 1.365 (s, 3 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.93 (m, 1 H), 0.76 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (C_6D_6, 75 MHz, DEPT) *C* 100.3, 98.6, 98.5 (2), 98.3; *C*H 79.9, 67.6, 66.7, 66.1, 65.6, 65.5, 65.4, 65.0, 64.9, 63.3, 62.5, 31.5, 28.4; *C*H$_2$ 60.0, 43.9 (2), 43.1, 43.0, 39.2, 38.7, 38.5, 37.8 (2), 32.2, 28.6, 27.6; *C*H$_3$ 30.7 (2), 30.7, 30.4, 25.0, 25.0, 20.7, 20.1, 20.0, 19.9, 19.5, 18.0, 15.8; HRMS (FAB) 767.5298 (M − CH_3). Anal. Calcd for $C_{44}H_{78}O_{11}$: C, 67.49; H, 10.04. Found: C, 67.32; H, 9.89.

Acknowledgment. Support has been provided by the National Institutes of Health (GM43854). Additional support was provided by Eli Lilly & Co., American Cyanamid, Hoffmann-La Roche, and Pfizer Inc. G.G. thanks the National Science Foundation and the University of Minnesota for Fellowship support. We would like to thank Mr. Guang Yang for technical assistance.

JA942542K