Filipin III: Configuration Assignment and Confirmation by Synthetic Correlation

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The stereochemical configuration of filipin III (**1**) was determined using the ^{13}C acetonide analysis. The relative configurations for the nine stereogenic centers in the top half of filipin were initially identified using just three acetonide derivatives (**2**, **3**, and **4**) arising from a two-step protection sequence. The structure was confirmed by synthesis and direct correlation of degradation products **8** (C26−C28) and **10** (C1−C16). Filipin tetraacetonide **2** and triacetonide **4** each contain an anti acetonide in a highly unusual chair conformation. Molecular modeling successfully reproduced the preference for a chair conformation over the normally more stable twist-boat conformation.

Although the flat structures of many polyene macrolide antibiotics are known, the complete stereochemical assignments have been made in only a handful of cases.[1] We have shown that syn and anti 1,3-diols can be easily distinguished by ^{13}C NMR analysis of the corresponding acetonides: the syn isomers have methyl resonances at ca. 19 and 30 ppm, whereas the anti isomers have methyl resonances at ca. 25 ppm.[2] We report herein the absolute and relative configuration of filipin III (**1**), Figure 1.[3] This stereochemical assignment was established using, in part, the ^{13}C acetonide analysis and was confirmed by synthesis of degradation fragments.

Filipin belongs to a class of natural products known as the polyene macrolide antibiotics. There are over 200 known representatives of this class, most of which are produced by soil actinomycetes belonging to the genus *Streptomyces*.[4,5] Although they exhibit antifungal activity, most polyene macrolide antibiotics, with the exception of amphotericin B and nystatin A_1, are too toxic for therapeutic applications. However, filipin has become a popular tool in cell membrane research as a probe for cholesterol.

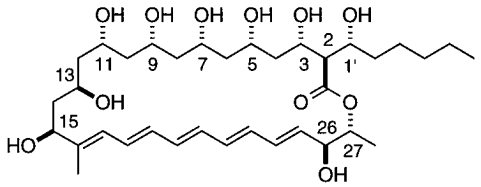

Figure 1. Structure and configuration of filipin III (**1**).

Filipin's interaction in cell membranes is an area of active research, and recently its use as a probe for cholesterol has been questioned.[6] Unlike amphotericin B and nystatin A_1 which form sterol-dependent ion channels, filipin is thought to be a simple membrane disrupter.[7] However, there is no generally accepted model that explains the action of filipin in cell membranes. The most popular model suggests that filipin binds 3-β-hydroxysterols in a 1:1 stoichiometry, forming large aggregates that lie parallel to and in the center of the lipid bilayer.[8] It is these aggregates that form the characteristic bulges observed in freeze-fractured or negatively stained membranes. Other models suggest that filipin and sterols aggregate at the membrane surface[9] or are localized in the upper layer of the membrane and cause deformations due to an increase in surface pressure.[10] The characteristic bulges could be caused by filipin−sterol aggregates or by filipin aggregates alone. Staining of free cholesterol with filipin is used clinically in the study and diagnosis of Type C Niemann−Pick disease.[11] The development of detailed models for the interaction of cholesterol with filipin or filipin aggregation has been hampered because, until now, the configuration of filipin III was unknown.

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1996.

(1) Configurational assignment by X-ray: (a) Amphotericin B, Mechlinski, H.; Schaffner, C. P.; Ganis, P.; Avitable, G. *Tetrahedron Lett.* **1970**, 3873. (b) Roxaticin, Maehr, H.; Yang, R.; Hong, L.-N.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816. Configuration by degradation, NMR analysis, and partial synthesis: (c) Mycoticin, Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001. (d) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, *28*, 6005. (e) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (f) Nystatin, Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4521. (g) Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517. (h) Nicolaou, K. C.; Ahn, K. H. *Tetrahedron Lett.* **1989**, *30*, 1217. Partial structure of lienomycin: (i) Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896. (j) Roflamycoin, Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1994**, *116*, 2623. (k) Pentamycin, Oishi, T. *Pure Appl. Chem.* **1989**, *61*, 427. (l) Nakata, T.; Hata, N.; Suenaga, T.; Oishi T. In *Abstract of Papers*, 30th Symposium on the Chemistry of Natural Products, Fukuoka, Oct 1988, p 540. Configuration by NMR analysis: (m) Pimaricin, Lancelin, J.-M.; Beau, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 4060. (n) Candidin, Pawlak, J.; Sowinski, P.; Borowski, E.; Gariboldi, P. *J. Antibiot.* **1993**, *46*, 1598.

(2) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(3) A prelimiary report of this work has appeared: Rychnovsky, S. D.; Richardson, T. I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1227−1230.

(4) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; p 351.

(5) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.

(6) (a) Milhaud, J.; Mazerski, J.; Dufourc, E. J. *Eur. Biophys. J.* **1989**, *17*, 151. (b) Castanho, M. A. R. B.; Prieto, M. J. E. *Eur. Biochem. J.* **1992**, *207*, 125.

(7) Bolard, J. *Biochim. Biophys. Acta.* **1986**, *864*, 257−304.

(8) De Kruijff, B.; Demel, R. A. *Biochim. Biophys. Acta.* **1974**, *339*, 57−70.

(9) Elias, P. M.; Friend, D. S.; Goerke, J. *J. Histochem. Cytochem.* **1979**, *27*, 1247−1260.

(10) Severs, N. J.; Robenek, H. *Biochim. Biophys. Acta.* **1983**, *737*, 373−408.

(11) Coxey, R. A.; Pentchev, P. G.; Campbell, G.; Blanchette-Mackie, E. J. *J. Lipid Res.* **1993**, *34*, 1165−1176.

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Table 1. Rate of Exchange between Acetone and 2,2-Dimethoxypropane Using 2.6 mM PPTS at 23 °C

time (h)	acetone (2.1 ppm)[a]	2,2-DMP (1.21 ppm)[a]
2	1	16
5	1	7
20	1.2	1
48	2.9	1
72	3.8	1

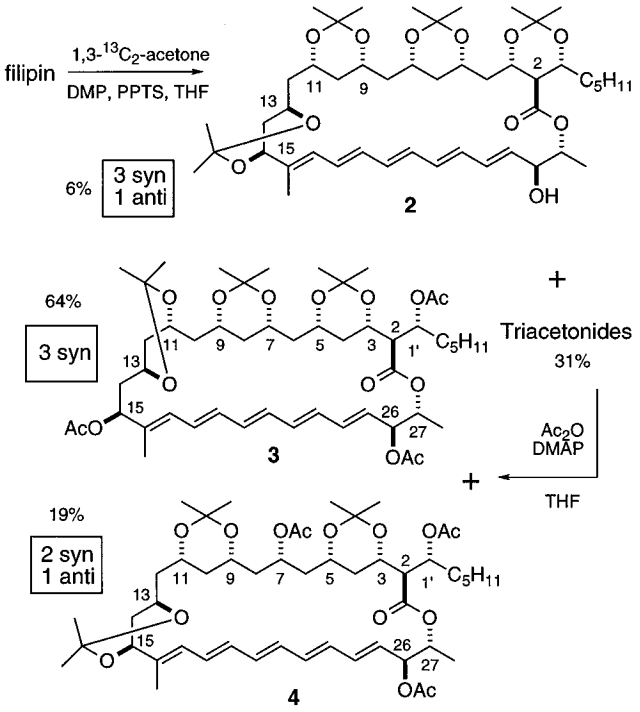
[a] The reaction between 2,2-DMP and d_6-acetone was monitored by ^{1}H NMR integration, and the integral ratios are listed.

Filipin was isolated in 1955 from *Streptomyces filipinensis* found in a sample of Philippine soil.[12] Much later it was shown to be a mixture of four components: filipins I (4%), II (25%), III (53%), and IV (18%).[13] The flat structure of filipin III, the major component of the filipin complex, was assigned in a series of degradation studies.[14] Filipin I, which has been difficult to characterize, is probably a mixture of several components each having two hydroxyl groups fewer than filipin III.[15] Filipin II is 1′-deoxyfilipin III.[16] Filipin IV is isomeric to filipin III and is probably epimeric at C1′ or C3.[17]

^{13}C-Enriched Acetone−DMP. The ^{13}C acetonide method is useful in the stereochemical analysis of polyols, but it is limited by the relative lack of sensitivity of ^{13}C NMR. When a natural product is precious, it is advantageous to use ^{13}C-enriched acetone to prepare the acetonide derivatives. This gives a many-fold boost in sensitivity and simplifies the assignment of the acetonide methyl peaks in the ^{13}C spectra. Normally a dehydrating agent such as 2,2-dimethoxypropane (DMP) is required to get good yields of acetonides from polyols. A mixture of acetone and DMP was found to exchange upon treatment with a mild acid like pyridinium *p*-toluenesulfonate (PPTS). Acetone-d_6 and DMP (2:1 volume ratio; 3.4:1 mol ratio) were mixed together with 2.6 mM PPTS. A ^{1}H NMR of the mixture was taken, and the ratio of integrated peaks at 2.1 ppm (acetone) and 1.21 ppm (DMP) was measured, Table 1. The results show that the isotopic label was completely scrambled between acetone and DMP after 72 h. This procedure was used to prepare an enriched mixture of [1,3-^{13}C]acetone and DMP for derivatizing filipin III. The ^{13}C-enriched solvent mixture was recovered by evaporation and trapping and could be reused.

Configuration of Filipin III. Initial attempts to prepare acetonide derivatives of filipin III using *p*-toluenesulfonic acid led to extensive decomposition. Treatment of filipin complex[18] (Sigma) with a mild acid catalyst, pyridinium *p*-toluenesulfonate (PPTS), in 2:1 acetone:DMP, followed by silica gel chromatography gave tetraacetonide **2** in 6% yield and a mixture of triacetonides in 31% yield (Scheme 1). The acetonide synthesis was carried out with 50% enriched [1,3-$^{13}C_2$]-acetone as described above to enhance sensitivity and simplify identification of the acetonide ^{13}C methyl signals. A highly purified sample of filipin III gave the same mixture of products when subjected to the reaction conditions, confirming that these derivatives arise from the major component of the complex. The mixture of triacetonides was acetylated and separated to give triacetonide **3** in 64% yield and triacetonide **4** in 19% yield. The structures of triacetonides **3** and **4**, including the positions of the acetates in each compound, were established using ^{1}H NMR and COSY data.

Scheme 1



Several resonances in the ^{1}H NMR spectrum of filipin and its acetonide derivatives **3** and **4** are easy to assign. The proton at C2 is distinct, being the only proton to resonate at ca. 2.5 ppm. In addition, the protons at C25−C28 are each easy to assign because they rarely overlap with other protons, and as a result the correlations between them can be identified in a COSY spectrum.

In the ^{1}H NMR spectrum of triacetonide **3** there are three acetate methyls and six acetonide methyls. There are four ester methine protons that resonate in the 5.3−5.7 ppm range. Two of these can be assigned to the protons at C26 and C27. Only one of these protons is correlated to the proton at C2. This proton must be due to an acetate at C1′ because if the acetate were at C3 it would be impossible to account for three acetates and three acetonides. The remaining proton is a doublet of doublets. This proton must be due to an acetate at C15 because it is the only proton in the polyol segment that could have such a simple splitting pattern. Therefore, in triacetonide **3**, the three acetates are at C1′, C15, and C26 and the three acetonides are at C3−C5, C7−C9, and C11−C13.

In the ^{1}H NMR spectrum of triacetonide **4** there are three acetate methyls and six acetonide methyls. There are four ester methine protons that resonate in the 5.3−5.7 ppm range. Two of these can be assigned to the protons at C26 and C27. Only one of these protons is correlated to the proton at C2. As in triacetonide **3**, this

(12) (a) Whitfield, G. B.; Brock, T. D.; Ammann, A.; Gottlieb, D.; Carter, H. E. *J. Am. Chem. Soc.* **1955**, *77*, 4799. (b) Ammann, A.; Gottlieb, D.; Carter, H. E. *Plant Dis. Rep.* **1955**, *39*, 219.

(13) Bergy, M. E.; Eble, T. E. *Biochemistry* **1968**, *7*, 653.

(14) (a) Berkoz, B.; Djerassi, C. *Proc. Chem. Soc.* **1959**, 316. (b) Djerassi, C.; Ishikawa, M.; Budzikiewicz, H.; Shoolery, J. N.; Johnson, L. F. *Tetrahedron Lett.* **1961**, 383. (c) Golding, B. T.; Rickards, R. W.; Barber, M. *Tetrahedron Lett.* **1964**, 2615. (d) Ceder, O.; Ryhage, R. *Acta Chem. Scand.* **1964**, *18*, 558.

(15) Pandey, R. C.; Rinehart, K. L. *J. Antibiot.* **1970**, *23*, 414.

(16) Edwards, D. M. F. *J. Antibiot.* **1989**, *42*, 322.

(17) Pandey, R. C.; Narasimhachari, N.; Rinehart, K. L.;. Millington, D. S. *J. Am. Chem. Soc.* **1972**, *94*, 4306.

(18) Filipin complex was obtained from Sigma (F-9765) as a crude mixture containing ~50% filipin III or from Upjohn (lot no. 2923-DEV-39) containing about ~8% filipin III. It can be purified by reversed-phase preparative HPLC.

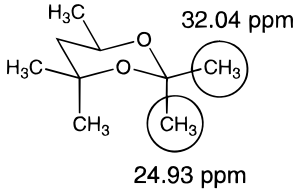


Figure 2. Chemical shift (^{13}C) of 2,2,4,4,6-pentamethyl-1,3-dioxane which adopts a chair conformation.

proton must be due to an acetate at C1′ because if the acetate were at C3 it would be impossible to account for three acetates and three acetonides. The remaining ester methine proton has a complex (dddd) splitting pattern. This proton cannot be due to an acetate at C15 or C3. It can only be assigned to C7 or C11. Fortunately, the protons in the ^{1}H NMR spectrum of this compound are well separated, and using COSY data we were able to assign this acetate to C7. Thus the triacetonide **4** has the three acetates at C1′, C7, and C26 and the three acetonides at C3−C5, C9−C11, and C13−C15.

The ^{13}C NMR spectrum of tetraacetonide **2** shows methyl signals at 31.0, 30.7, 30.5, 30.1, 24.8, 20.0, and 19.5 (×2) ppm. These signals correspond to three syn acetonides and one acetonide with methyl peaks at ca. 30 and 24.8 ppm. The ^{13}C NMR spectrum of triacetonide **3** shows methyl resonances at 30.8, 30.7, 30.0, 19.9, 19.8, and 19.4 ppm that correspond to three syn acetonides. The ^{13}C NMR spectrum of triacetonide **4** shows methyl resonances at 31.1, 30.5, 30.2, 24.7, 19.0, and 19.0 ppm. These signals correspond to two syn acetonides and one acetonide with methyl peaks at ca. 30 and 24.7 ppm. The overlapping acetonide rings in compounds **2**, **3**, and **4** cover all of the relative 1,3-diol relationships in the C1′ to C15 segment of filipin III.

A logical analysis of the three acetonide derivatives, **2**−**4** in Scheme 1, can be used to assign most of the stereochemical relationships in filipin III. Compound **3** showed only syn acetonides, so C3−C5, C7−C9, and C11−C13 were assigned syn. Compound **4** showed one anti acetonide, but C3−C5 was previously assigned as syn, so the anti ring must be either C9−C11 or C13−C15. Compound **2** showed only one anti ring and also incorporates both C9−C11 and C13−C15 acetonides. It has been established that one of these must be anti. With the anti ring accounted for, both C5−C7 and C1′−C3 must be syn. Combined with a straightforward analysis of the C2 configuration (see below), the ^{13}C acetonide analysis has reduced the number of possible diastereomers for the C1−C15 section of filipin III from 256 to 2.

Both compounds **2** and **4** show a very unusual set of methyl peaks for one of the acetonide rings. Over 200 acetonide rings were analyzed in a previous paper, and none of them showed a pair of methyl peaks at the unusual positions of ca. 25 and 30 ppm.[2c] One compound that does show similar ^{13}C chemical shifts for the acetonide methyl groups is 2,2,4,4,6-pentamethyl-1,3-dioxane, Figure 2. It is known to adopt a chair conformation because the quaternary center at C4 disfavors the twist-boat conformation.[19] The C2 axial and equatorial ^{13}C methyl groups appear at 24.93 and 32.04, respectively.[19] These are very close to the observed values of ca. 30 and 24.8 or ca. 30 and 24.7 ppm in compounds **2** and **4**, respectively. Apparently the macrocyclic ring

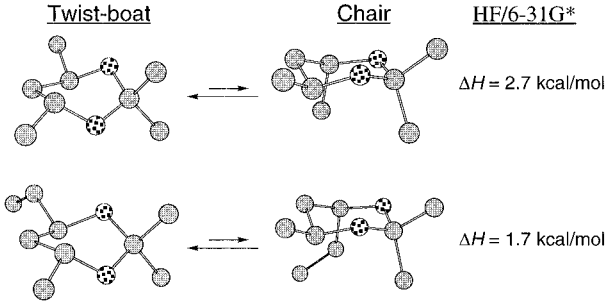
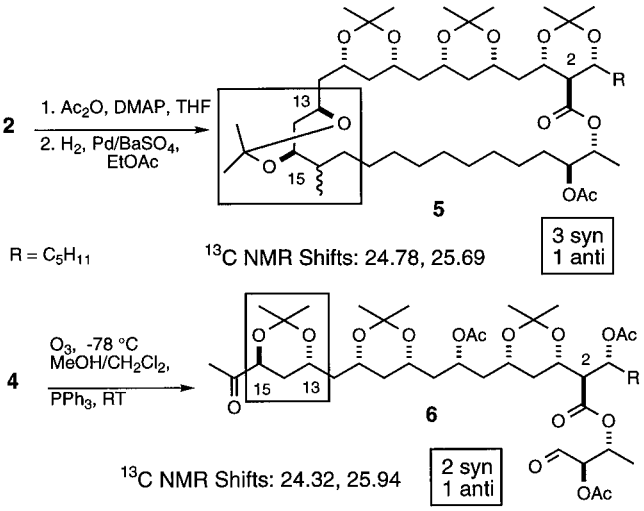


Figure 3. Chair and twist-boat conformation of methyl and vinyl acetonides at RHF/6-31G*//RHF/6-31G*.

Scheme 2



biases the anti 1,3-diol acetonide to adopt a chair conformation rather than the more stable twist-boat conformation. The chair conformation, although still energetically unfavorable, is more accessible for an alkene-substituted acetonide than for an alkyl-substituted acetonide, Figure 3.[20] Thus the most likely position of the anti acetonide is at C13−C15, which has an alkene at C16−C17 that can occupy an axial position on the acetonide ring.

To confirm the tentative conclusion that the anti diol in filipin III was at C13−C15, compounds **2** and **4** were degraded as shown in Scheme 2. Acetylation, followed by hydrogenation of **2**, gave the saturated macrocycle **5**, which showed methyl signals at 30.75, 30.69, 30.14, 25.69, 24.78, 19.95 (×2), and 19.45 ppm. The methyl peaks at 25.69 and 24.78 ppm fall in the expected range for a saturated anti acetonide. Triacetonide **4** was ozonized and reduced with triphenylphosphine to give triacetonide **6**, which showed methyl signals at 30.50, 30.30, 25.94, 24.32, 19.57, and 19.29 ppm. The methyl peaks at 25.94 and 24.32 ppm clearly represent an anti 1,3-diol acetonide. More significantly, the 1.62 ppm difference between the two peaks is larger than one would expect for a saturated anti 1,3-diol acetonide but is in line with an acyl-substituted anti acetonide.[2c] Thus the anti acetonide ring in both **2** and **4** is located at C13−C15, and the relative configurations for all the alcohol stereogenic centers in the C1′−C15 section are as shown in Figure 4.

The acetonide at C1′−C3 adopts a chair conformation in tetraacetonide **2**. The C2 proton in the ^{1}H NMR

(19) Pihlaja, K.; Kivimaki, M.; Myllyniemi, A.-M.; Nurmi, T. *J. Org. Chem.* **1982**, *47*, 4688.

(20) Rychnovsky, S. D.; Yang. G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251−5255.

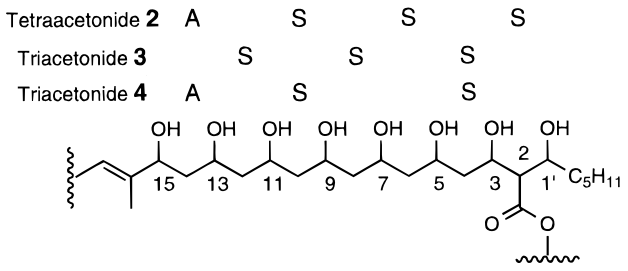
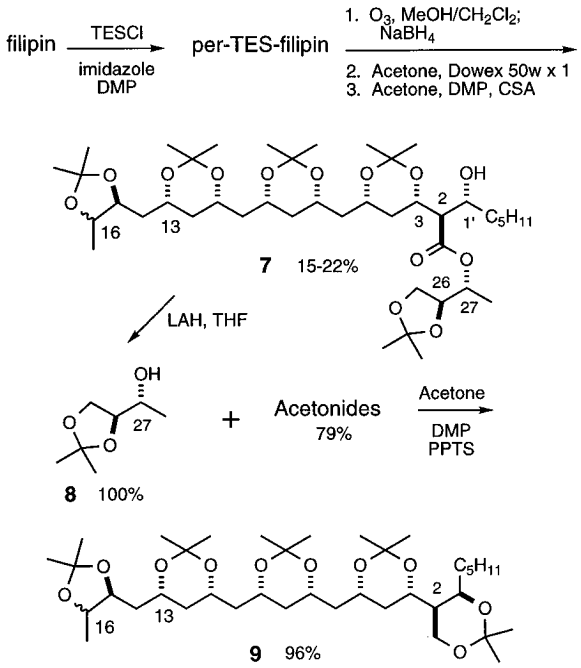


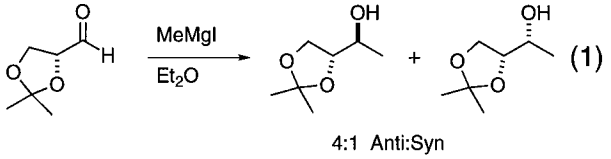
Figure 4. Overview of the configurational assignment of filipin III.

Scheme 3



spectrum of tetraacetonide **2** is a triplet with a diaxial coupling constant of 10.1 Hz. Therefore, the C2 ester is anti with respect to the hydroxyls at C1′ and C3.

The configuration of filipin III at the C26 and C27 stereogenic centers was determined by another degradation sequence (Scheme 3). Per-TES-filipin prepared from filipin complex (Upjohn or Sigma) was ozonized and then reduced with $NaBH_4$. The triethylsilyl (TES) protecting groups were exchanged for acetonides to give 15−22% of pentaacetonide **7** as a mixture of diastereomers at C16. The position of the lone hydroxyl was identified by COSY analysis of acetylated **7**. LAH reduction of **7** gave a quantitative yield of *anti*-1,2-di-*O*-isopropylidene-1,2,3-butanetriol (**8**) that was identified by direct comparison (^{1}H NMR, GC) with an authentic sample of the enantiomer prepared according to eq 1.[21] The absolute configuration of **8** was identified as (2*S*,3*R*) by comparison of the (*R*)- and (*S*)-Mosher's esters of **8** with those prepared from an authentic sample of (2*R*,3*S*)-1,2-di-*O*-isopropylidene-1,2,3-butanetriol.[21] The advanced Moshers analysis is reported in Figure 5.[22] Reduction of **7** gave a mixture of acetonides that was treated with acetone and acid to give pentaacetonide **9** in 76% yield. The ^{13}C NMR spectrum of **9** showed four syn 1,3-diol acetonides and a mixture of syn and anti 1,2-diol acetonides, which lends independent support for the relative configurations proposed in Figure 4.



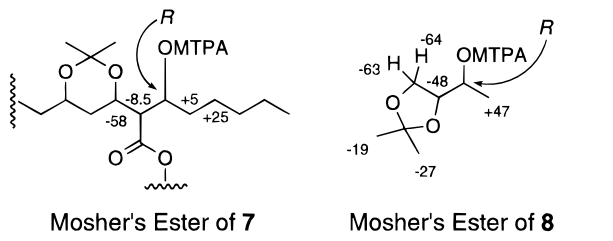


Figure 5. $\Delta\delta_H = (\delta_S - \delta_R)$ for the Mosher esters of **7** and **8** (in Hz) at 500 MHz.

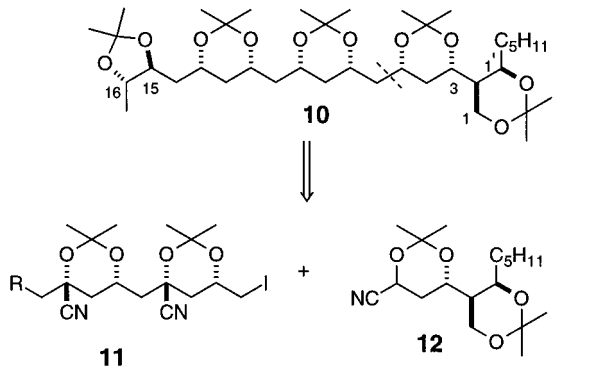


Figure 6. Retro-synthetic analysis of degradation fragment **10**.

The last question to be resolved is the absolute stereochemistry of the C1′−C15 fragment. An advanced Mosher ester analysis[22] of the C1′ alcohol of pentaacetonide **7** gives the $\Delta\delta_H$ ($= \delta_S - \delta_R$) values listed in Figure 5. These values indicate an (*R*) configuration at C1′, and complete the stereochemical assignment of filipin III. Thus the configurations of the stereogenic centers in filipin III are 1′*R*, 2*R*, 3*S*, 5*S*, 7*S*, 9*R*, 11*R*, 13*R*, 15*S*, 26*S*, and 27*R*.

Synthesis and Correlation of Degradation Fragment 10. Pentacetonide **10**, one of the degradation fragments from the stereochemical assignment of filipin III, was identified as an excellent synthetic target because it contains nine of the stereogenic centers present in the natural product. Pentaacetonide **9** is a mixture of epimers at the C16 center, and the C15/C16 anti isomer **10** was selected as the synthetic target. Correlation of the degradation product **10** with a sample prepared by total synthesis would confirm the relative and absolute assignment of filipin III's C1−C15 polyol segment.

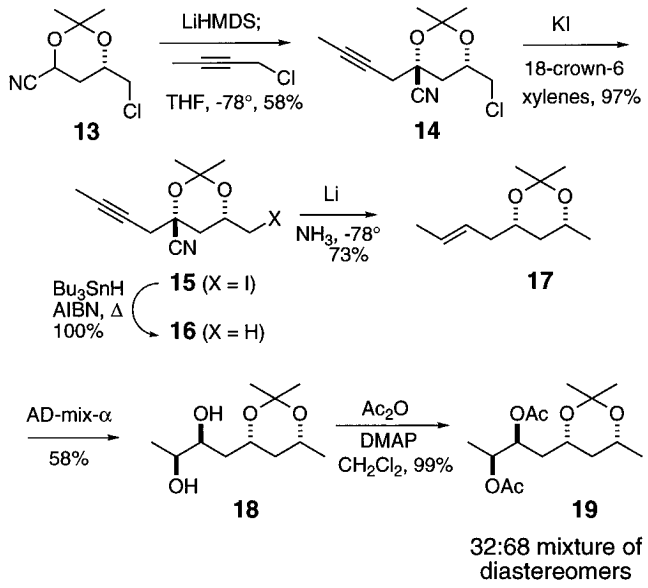
A retrosynthetic analysis of pentaacetonide **10** is shown in Figure 6. The proposed synthetic strategy relies on the alkylation and stereoselective reductive decyanation of cyanohydrin acetonides, a methodology designed to facilitate the *convergent* synthesis of alternating polyol chains.[23] Using this strategy, pentaacetonide **10** was

(21) Mulzer, J.; Angermann, A.; Münch, W.; Schlichthörl, G.; Hentzschel, A. *Liebigs Ann. Chem.* **1987**, 7.

(22) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(23) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559−1563.

Scheme 4



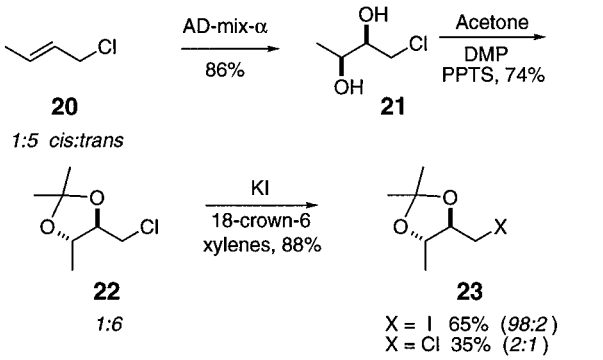
conveniently divided into two fragments, left-hand fragment **11** and right-hand fragment **12**.

Synthesis of Left-Hand Fragment 11. A model study was employed to test the possibility of installing the 1,2-diol late in the synthesis, Scheme 4. We envisioned that the nascent diol would be introduced as an alkyne and carried through the construction of the alternating polyol. The alkyne would be reduced to an (*E*)-alkene concurrently with the final reductive decyanation. Sharpless asymmetric dihydroxylation (AD) of the (*E*)-alkene would then be used to install the required 1,2-diol at C15−C16 with reagent-controlled stereoselectivity.

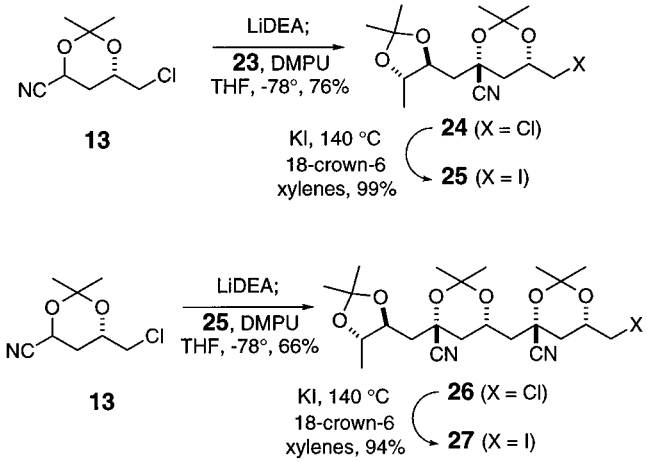
Chloro cyanohydrin acetonide **13** was prepared from ethyl 4-chloroacetoacetate (54% overall yield, 91% ee).[23] It was alkylated with 1-chloro-2-butyne in 58% yield to give nitrile **14**. The chlorine of **14** was then exchanged for iodine using KI and 18-crown-6 in refluxing xylenes for 3 days.[23] This gave a near quantitative recovery of material, but ^{1}H NMR showed only 79% conversion to the iodide. The iodide was then reduced with tributyltin hydride and AIBN in refluxing toluene. This gave a quantitative yield of nitrile **16** contaminated with 20% of the chlorine-containing nitrile **14**. The nitrile and the alkyne of **16** were reduced with Li in liquid ammonia to give alkene acetonide **17** as a single isomer in 73% yield. Sharpless asymmetric dihydroxylation of **17** gave a 58% yield of diol **18**. However, the ^{13}C and ^{1}H NMR spectra of **18** showed it to be a mixture of diastereomers. The diol was acetylated to give a 99% yield of diacetate **19**. GC analysis of this product revealed a 68:32 mixture of diastereomers that was not resolvable by silica gel chromatography. The poor selectivity in the dihydroxylation is not without precedent; as Sharpless noted in a recent review, the selectivity is often compromised if the "large" substituent of the target olefin is oxygenated.[24]

The model study demonstrated that the asymmetric dihydroxylation would not be selective in an advanced intermediate. The diol was instead introduced at the beginning of the synthesis using the previously reported asymmetric dihydroxylation of crotyl chloride as shown in Scheme 5.[25] Unfortunately crotyl chloride (**20**) is only available as a 5:1 mixture of *E* and *Z* isomers. Sharpless asymmetric dihydroxylation of **20** gave an 86% yield of chloro diol **21** which was converted to acetonide **22** under standard conditions. GC analysis of **22** showed a 6:1 mixture of trans and cis isomers. The trans isomer showed 81% ee by GC analysis using a chiral column. The chlorine of **22** was then exchanged for iodine by treatment with KI and 18-crown-6 in refluxing xylenes for 4 days. The trans isomer was selectively converted into the iodide: the mixture was composed of 65% of the iodide that was a 97:3 mixture favoring the trans isomer, while the recovered chloride made up 35% of the mixture and was as a 2:1 mixture favoring the trans isomer. The 1,2-diol synthon **23** was available in three steps as a 97:3 mixture of diastereomers with 81% ee.

Scheme 5



Scheme 6



The synthesis of the left-hand fragment was completed as shown in Scheme 6. Chloro cyanohydrin **13** (2 equiv) was deprotonated with lithium diethylamide and alkylated with iodide **23**. Diacetonide **24** was isolated in 76% yield (based on the iodide) as an 80:20 mixture of diastereomers[26] which was used without further purification. Chloride **24** was converted to iodide **25**, and alkylation of (2 equiv) chloro cyanohydrin anion **13** with **25** gave triacetonide **26** in 94% yield based on **25**. Triacetonide **26** was recrystallized to give a white crystalline solid, mp = 126−127 °C, in 70% yield with a diastereomeric purity of >97%.[27] The structure of **26** was

(24) Kolb, H. C.; VanKieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(25) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469.

(26) The ratio was determined by ^{1}H NMR integration of the major C16 methyl doublet at 1.29 ppm versus the minor C16 methyl doublet at 1.26 ppm.

(27) Diastereomeric purity determined by ^{1}H NMR analysis.

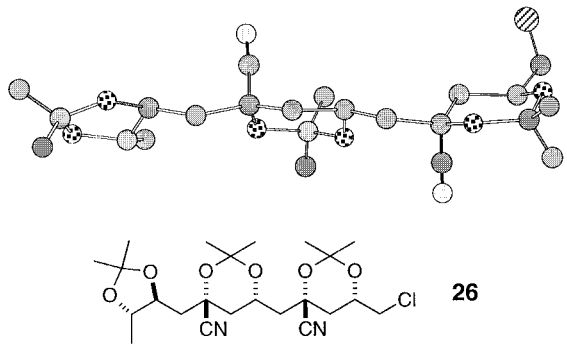
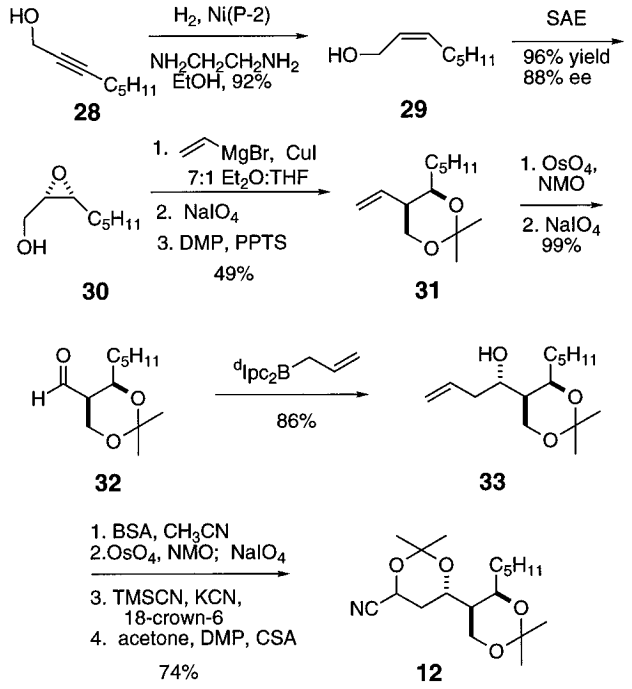


Figure 7. Crystal structure of **26** showing the relative and absolute configuration.

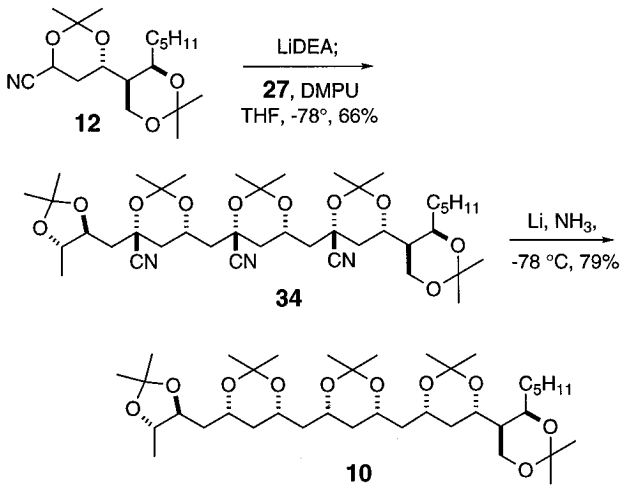
Scheme 7



confirmed by X-ray crystallography and is illustrated in Figure 7.[28] Chloride **26** was converted into iodide **27** to complete the synthesis of the left-hand fragment.

Synthesis of Right-Hand Fragment 12. Synthesis of the right-hand fragment is illustrated in Scheme 7. The asymmetry of right-hand fragment **12** was generated using a Sharpless asymmetric epoxidation of (*Z*)-2-octen-1-ol (**29**). Oxirane **30** was isolated in 96% yield and 88% ee.[29] Oxirane **30** was opened with vinylmagnesium bromide in the presence of CuI to give the expected alkenediol.[30] When this reaction was carried out on a small scale, a 77% yield of a 1:4 mixture of 1,2- and 1,3-diols was obtained. The diols were separated by MPLC on silica gel and characterized individually. When this reaction was carried out on a larger scale, the 1,2-diol was cleaved with $NaIO_4$, and the 1,3-diol was easily purified and isolated in 50% yield. The 1,3-diol was converted to acetonide **31** in 98% yield, and treatment of

Scheme 8



31 with OsO_4/NMO followed by $NaIO_4$ gave aldehyde **32** in 99% yield. Addition of $^dIpc_2BAllyl$ to **32** provided homoallylic alcohol **33** which was isolated as a single diastereomer in 86% yield. The minor diastereomer was separated and isolated in 5% yield. Synthesis of the right-hand fragment was completed by protection of homoallylic alcohol **33** as the TMS ether followed by oxidative cleavage of the alkene to the aldehyde, cyanohydrin formation, and ketalization to provide cyanohydrin acetonide **12** in 74% yield from alcohol **33**.

Final Coupling and Completion of the Synthetic Correlation. The final steps in the synthesis of pentaacetonide **10** are shown in Scheme 8. Cyanohydrin acetonide **12** (3 equiv) was deprotonated and alkylated with iodide **27** to give pentaacetonide trinitrile **34** in 66% yield based on the iodide. Stereoselective reductive decyanation of **34** provided pentaacetonide **10** in 79% yield. The ^1H NMR spectrum of synthetic pentaacetonide **10** was identical to that of one of the isomers of the degradation product **9**. The rotation of synthetic **10**, $[\alpha]^{26}_D = -19.2°$ (c = 1.05, $CHCl_3$), compares favorably with the rotation of the degradation product **9**, $[\alpha]^{26}_D = -20.5°$ (c = 1.43, $CHCl_3$). Although the degradation product is a 1:1 mixture of **10** and the C16 epimer, the very similar rotations clearly support the proposal that the synthetic **10** and degradation product **9** have the same absolute configuration.

Molecular Modeling of the Chair versus Twist-Boat Conformation of the C13−C15 Acetonide. The anti acetonide rings in both tetraacetonide **2** and triacetonide **4** adopt chair conformations on the basis of the NMR analysis described above. Are these conformational preferences reproduced by molecular modeling? Can molecular modeling predict which acetonides will adopt such unusual conformations?

Previous studies with MM2* have shown that it does not reproduce chair versus twist-boat preferences well.[20] Since that time the MM2* force field in MacroModel has been reoptimized to give better acetal structures and energies.[31] The chair versus twist-boat preferences calculated with the new MM2* force field in MacroModel 5.0 are shown in Table 2, and are compared with MM2* using Macromodel 3.5 and experimental results.[20] These results show that the new force field is less biased toward

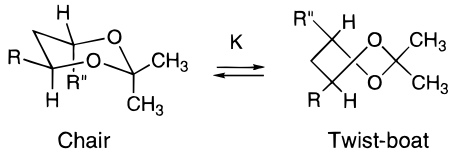
(28) We thank Victor G. Young for determining the crystal structure of **26**. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 lEZ, U.K.

(29) Enantiomeric purity by analysis using a chiral GC column. See Experimental Section for details.

(30) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131−4132.

(31) 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.

Table 2. Calculated ΔH for the Chair to Twist-Boat Equilibrium of *trans*-1,3-Dioxanes (kcal/mol). The MM2* Force Field in Macromodel 3.5 and 5.0 Are Compared



R =	C≡N	C≡CH	CHO	CO_2Me	$HC=CH_2$	Me
Macromodel 3.5	0.42	2.4	2.48	1.68	1.59	-1.74
Macromodel 5.0	0.88	0.89	0.95	0.10	0.11	-2.99
Expt. ΔG	0.85	0.26	-0.22	-0.77	-1.2	-1.8

chair conformations than the old force field, but it still predicts that the aldehyde, ester, and vinyl groups will slightly favor the chair conformation. The experimental results show that each one favors a twist-boat conformation. The predicted equilibrium for the methyl case appears to be worse than before, but this is deceptive as the methyl equilibrium has a large experimental uncertainty. The calculated methyl equilibrium is in good agreement with the 6-31G* value of −2.79 kcal/mol.[20] The vinyl group is the most relevant example for tetraacetonide **2**, where MM2* shows about a 1 kcal/mol bias in favor of the chair conformation. The new MM2* force field is much better than the old in its handling of acetals and in these simple cases reproduces the experimental values to within about 1 kcal/mol.

Filipin tetraacetonide **2** has many internal degrees of freedom, and therefore an exhaustive conformational search would be prohibitive. To model **2**, each acetonide ring was minimized separately and was not varied in the Monte Carlo conformational search. The polyene is most stable in the all-trans conformation, and internal torsions in the polyene region were ignored, as were torsions in the ester and the *n*-pentane side chain. The C13−C15 acetonide was built in as a chair or a 2,5 twist boat and not varied. Separate Monte Carlo conformational searches for both the chair and twist-boat starting geometries were setup in Macromodel 5.0 using MM2* with 11 variable torsional angles and were run for 5000 steps. The minima were resubmitted to another 5000-step conformational search that included some variable torsions in the side chain. All of the combined structures were reoptimized using the chloroform solvent set. The lowest energy minima for both the chair and twist-boat geometries were each found multiple times and are shown in Figure 8. The chair conformation shows 9 minima within 1.0 kcal/mol, while the twist-boat conformation shows 14 minima within 1.0 kcal/mol, showing that both minima are members of families of related structures. The lowest energy chair conformation is favored over the lowest energy twist-boat conformation by 3.6 kcal/mol. The MM2* bias for chair conformations is about 1 kcal/mol, but the other 2.6 kcal/mol can be attributed to a real preference for the chair conformation in the filipin ring system.

The C13−C15 anti acetonide ring in tetraacetonide **2** acts as a hinge. Figure 8 shows that the chair conformation is well placed to "turn the corner" on the macrocyclic ring, whereas the twist-boat conformation points the two ends of the chain in opposite directions and does nothing to facilitate closure of the macrocyclic ring. In an acyclic compound such as **6** the twist-boat is favored, but in a cyclic compound such as **2** the *overall* strain is reduced by adopting a chair conformation. Anti acetonides that adopt a chair conformation are very unusual, but the current example shows that they do occur. Molecular modeling with the improved MM2* force field should be a valuable tool to predict where other anti acetonide chairs might be found.

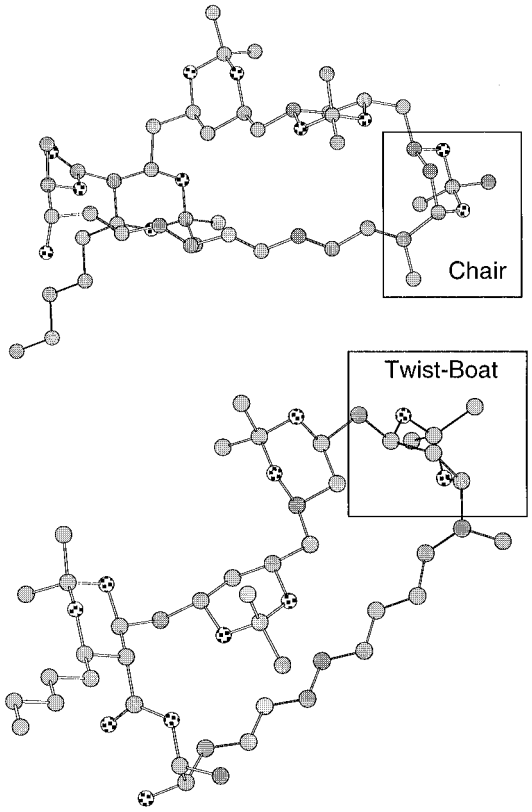


Figure 8. Minima of filipin tetraacetonide with C13−C15 chair (top) and C13−C15 twist-boat (bottom) conformations. Macromodel energies (kcal/mol) using MM2* with chloroform solvation are −102.24 for the chair and −98.64 for the twist-boat. Hydrogens have been omitted for clarity.

Conclusion

The relative and absolute configuration of filipin III was determined using the ^{13}C acetonide method in conjunction with the Mosher method. The assignment was confirmed by synthesis and spectroscopic correlation of degradation fragments **8** (C26−C28) and **10** (C1−C16).

It must be emphasized that the relative configurations for the nine stereogenic centers in the top half of filipin were initially identified using just three acetonide derivatives, **2**, **3**, and **4**, arising from a two-step protection sequence. Subsequent experiments confirmed the analysis. The stereochemical assignment of filipin III will facilitate rational modeling of filipin−cholesterol interactions.

Tetraacetonide **2** contains an unusual anti acetonide that adopts a chair conformation. Our published literature survey found no examples of anti acetonides with two sp^3 substituents that adopted a chair conformation.[2c] Molecular modeling correctly predicts that the chair conformation would be favored over the twist-boat conformation.

Experimental Section[32]

Degradation Studies on Filipin III. Filipin III (1). Filipin complex (Sigma no. F 9765) (11 mg) was taken up in a minimum amount of DMF and diluted with 65% MeOH/35% H_2O to make a 20 mg/mL solution. This solution was injected (20−40 μL each time) onto a reversed-phase HPLC column and eluted with 65% MeOH/35% H_2O at 2.25 mL/min. The major peak eluting at 18 min was collected to give 5.4 mg (8.2 μmol, 49%) of a slightly yellow solid: ^{1}H NMR (500 MHz, CD_3OD) δ 6.39 (dd, J = 13.9, 11.2, 1 H), 6.33 (dd, J = 8.9, 14.8 Hz, 1 H), 6.33−6.18 (m, 5 H), 5.94 (d, J = 11.2 Hz, 1 H), 5.89 (dd, J = 5.11, 14.8 Hz, 1 H), 4.72 (q, J = 6.3 Hz, 1 H, obscured by MeOH), 4.08 (ddd, J = 3.8, 7.4, 7.1 Hz, 1 H), 4.03 (dd, J = 4.5, 10.8 Hz, 1 H), 3.97 (dd, J = 6.3, 5.1 Hz, 1 H), 3.94−3.85 (m, 4 H), 3.75 (ddd, J = 2.1, 8.4, 8.8 Hz, 1 H), 3.12 (ddd, J = 3.4, 10.6, 10.5 Hz, 1 H), 2.45 (dd, J = 7.4, 8.8 Hz, 1 H), 1.79 (ddd, J = 3.4, 9.4, 10.8 Hz, 1 H), 1.67 (s, 3 H), 1.66−1.58 (m, 3 H), 1.32−1.44 (m, 8 H), 1.16−1.30 (m, 8 H), 1.19 (d, J = 6.3, 3 H), 0.816 (t, J = 7.1 Hz, 3 H); HRMS (FAB) calcd for $C_{35}H_{59}O_{11}$ 655.4058, found 655.4020 (M + H).

1′,3,5,7,9,11,13,15,16-*O*-Nonakis(triethylsilyl)filipin. Crude filipin complex (Upjohn U-5956 no. 2923-DEV-39) (2.0 g) and imidazole (5.2 g) were placed in a flask and flushed with argon. TESCl (9.3 mL) was dissolved in 50 mL of DMF, degassed with argon, and then transferred via cannula into the reaction flask. The reaction was stirred under argon in the dark for 9 h. The reaction was quenched with 50 mL of saturated NH_4Cl, and then the solution was extracted (3 × 50 mL) with Et_2O. The organic solution was washed with saturated $NaHCO_3$ (2×), water (2×), and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give a bright orange oil. The least polar material which fluoresced under long UV light was purified by silica gel flash chromatography (5 × 11 cm) eluting with 2% Et_2O/pentane to yield a yellow oil. The major product in this mixture was further purified on a silica gel MPLC column (4 × 30 cm) eluting with 2% Et_2O/pentane to give 470 mg (280 μmol, 9%) of per-TES-filipin as a yellow oil.

1′,3:5,7:9,11:13,15-Tetrakis-*O*-(1-methylethylidene)filipin III (2). Acetone (0.2 mL), [1,3-$^{13}C_2$]acetone (0.2 mL), and DMP (0.2 mL) were combined in 2.0 mL of THF and degassed with argon. PPTS (4.0 mg) was added and the solution allowed to stir 64 h. Filipin Complex (Sigma) (35 mg, 54 μmol) was added. The reaction was allowed to stir in the dark under argon for 6 h. The reaction was quenched with 4 mg of solid $NaHCO_3$. The solvent was evaporated under vacuum and recovered in a liquid nitrogen cooled trap. The solids were taken up in 30 mL of EtOAc. The organic solution was washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give 43 mg of a yellow oil. The mixture containing two major products was separated by silica gel flash chromatography (3.5 × 6.5 cm) eluting with 30% EtOAc/hexanes to give 2.8 mg (3.4 μmol, 6.4%) of tetraacetonide **2** (R_f = 0.44, 50% EtOAc/hexanes) as a yellow glass. The EtOAc concentration was raised to 65% in 5% increments eluting 100 mL each time to isolate 11 mg of a mixture of triacetonides (R_f = 0.12, 50% EtOAc/hexanes). The more polar material (24 mg) was then eluted with 100% EtOAc. The more polar material was taken up in the recovered solvent. PPTS (3 mg) was added and the solution allowed to stir overnight. The reaction was quenched with 5 μL of Et_3N and the solvent evaporated under reduced pressure to give a yellow solid. More of the triacetonide mixture (2 mg) was isolated by silica gel chromatography (2 × 6 cm) eluting with 30−50% EtOAc/hexanes (5% increments, 50 mL each time). Total yield for the triacetonide mixture was 13.0 mg (16.8 μmol, 31%).

Tetraacetonide **2**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.78−6.67 (m, 2 H), 6.57−6.51 (m, 2 H), 6.48−6.42 (m, 2 H), 6.37−6.25 (m, 2 H), 5.87 (dd, J = 5.0, 15.3 Hz, 1 H), 4.89 (dq, J = 6.0, 6.4 Hz, 1 H), 4.48 (ddd, J = 2.6, 10.0, 10.0 Hz, 1 H), 4.42−4.36 (m, 2 H), 4.28−4.22 (m, 2 H), 4.06−4.01 (m, 2 H), 3.90−3.84 (m, 1 H), 3.75 (ddd, J = 4.1, 6.0, 7.4 Hz, 1 H), 2.49 (t, J = 10.1 Hz, 1 H), 2.26 (d, J = 13.8 Hz, 1 H), 2.12−1.20 (m, 19 H), 1.85 (s, 3 H), 1.543 (s, 3 H), 1.538 (s, 3 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.46 (s, 3 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 1.212 (s, 3 H), 1.206 (d, J = 6.4 Hz, 3 H), 0.869 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 31.0, 30.5, 30.5, 30.1, 24.8, 20.0, 19.5 (2); HRMS (FAB) calcd for $C_{47}H_{74}O_{11}$ 814.5233, found 814.5239 (M).

26-*O*-Acetyl-1′,3:5,7:9,11:13,15-tetrakis-*O*-(1-methylethylidene)-16,17,18,19,20,21,22,23,24,25-decahydrofilipin III (5). Tetraacetonide **2** (2.0 mg, 2.4 μmol) was dissolved in 0.5 mL of THF and degassed with argon. Ac_2O (30 μL, 0.32 mmol) and DMAP (10 mg, 82 μmol) were added. The reaction was allowed to stir under argon in the dark for 1.25 h. The reaction was quenched with 50 μL of MeOH, and then the solution was diluted with 20 mL of EtOAc. The organic solution was washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give an oil. The product was purified by silica gel flash chromatography (1 × 8 cm) eluting with 30% EtOAc/hexanes to yield 1.0 mg of an oil. The product was further purified by preparative reversed-phase HPLC eluting with 95% MeOH/5% H_2O at 2.5 mL/min. The major peak at 22.5 min was collected to yield 0.3 mg of an oil. The oil was taken up in 1 mL of EtOAc. Pd($BaSO_4$) was added, and the solution was stirred under H_2 for 2.25 h. The catalyst was filtered and the solvent evaporated under reduced pressure to yield 0.3 mg (0.35 μmol, 14%) of a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 5.19−5.25 (m, 2 H), 4.49 (ddd, J = 3.1, 7.7, 10.5 Hz, 1 H), 4.34−4.23 (m, 2 H), 4.22−4.09 (m, 2 H), 3.99 (m, 1 H), 3.89 (dd, J = 7.2, 14.1 Hz, 1 H), 3.82 (m, 1 H), 2.59 (t, J = 10.3 Hz, 1 H), 2.24−2.08 (m, 2 H), 2.00 (m, 1 H), 1.90−1.16 (m, 36 H), 1.82 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.55 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.38 (s, 3 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.911 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 30.8, 30.7, 30.1, 25.7, 24.8, 19.9 (2), 19.4; HRMS (FAB) calcd for $^{12}C_{46}{}^{13}C_2H_{83}O_{12}$ 853.5954, found 853.6042 (M − CH_3).

1′,15,26-Tri-*O*-acetyl-3,5:7,9:11,13-tris-*O*-(1-methylethylidene)filipin III (3) and 1′,7,26-Tri-*O*-acetyl-3,5:9,11:13,-15-tris-*O*-(1-methylethylidene)filipin III (4). The triacetonide mixture (13 mg, 16.8 μmol) from the preparation of tetraacetonide **2** was taken up in 1 mL of THF and degassed with argon. Ac_2O (160 μL, 1.7 mmol) and DMAP (60 mg, 0.49 mmol) were added. The reaction was allowed to stir under argon in the dark for 1.25 h. The reaction was quenched with 50 μL of MeOH, and then the solution was diluted with 40 mL of EtOAc. The organic solution was washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give a yellow oil. The mixture containing two products was separated by silica gel flash chromatography (2 × 5 cm) eluting with 25% (200 mL) and then 30% (200 mL) EtOAc/hexanes to give 9.5 mg (10.5 μmol, 64%) of triacetonide **3** (R_f = 0.50, 50% EtOAc/hexanes) and 2.9 mg (3.2 μmol, 19%) of triacetonide **4** (R_f = 0.38, 50% EtOAc/hexanes).

Triacetonide **3**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.51 (dd, J = 10.4, 13.6 Hz, 1 H), 6.45−6.30 (m, 4 H), 6.27−6.21 (m, 2 H), 6.13 (dd, J = 10.6, 15.1 Hz, 1 H), 5.81 (dd, J = 5.8, 15.6 Hz, 1 H), 5.69 (ddd, 3.0, 6.3, 10.0 Hz, 1 H), 5.62 (dd, J = 4.6, 10.6 Hz, 1 H), 5.37 (dd, J = 6.0, 9.3 Hz, 1 H), 5.31 (dq, J = 6.0, 6.1

(32) **General Experimental.** Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM reagent silica gel 60 (230−400 mesh). HPLC purifications were carried out on a C-18 reversed-phase column (Spherisorb S5 ODS2, 250 × 10 mm) eluting with water/methanol mixtures. Tetrahydrofuran and ether were distilled from benzophenone ketyl. Methylene chloride was distilled from calcium hydride. Dimethylformamide was distilled from barium hydroxide. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of nitrogen or argon using oven-dried glassware and standard syringe/septa techniques. NMR data for ^{13}C DEPT experiments are reported as quaternary (*C*), tertiary (*C*H), secondary (*C*H_2), and primary (*C*H_3) carbon atoms. For overlapping signals the number of carbon atoms is given in parentheses. GC analysis was carried out using an HP 5890 GC with an Alltech SE-54 column. Unless otherwise noted, the GC temperature program was 50 °C for 5 min, then 50−250 °C at 5 °C/min. A Chiraldex G TA capillary column (0.32 mm × 30 m) was used to separate enantiomers.

Hz, 1 H), 4.29 (ddd, J = 2.1, 8.6, 10.8 Hz, 1 H), 4.12−4.07 (m, 1 H), 4.06−3.99 (m, 1 H), 3.90−3.81 (m, 2 H), 3.77−3.70 (m, 1 H), 3.11 (dd, J = 6.1, 8.0 Hz, 1 H), 2.25 (ddd, J = 3.4, 10.1, 13.5 Hz, 1 H), 2.10−1.16 (m, 19 H), 1.78 (s, 3 H), 1.73 (s, 3 H), 1.66, (s, 6 H), 1.55 (s, 3 H), 1.54 (s, 3 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.30 (s, 3 H), 1.22 (s, 3 H), 1.15 (d, J = 6.1 Hz, 3 H), 0.861 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 30.8, 30.7, 30.0, 19.9, 19.8, 19.4; HRMS (FAB) calcd for $C_{50}H_{76}O_{14}$ 900.5237, found 900.5226 (M).

Triacetonide **4**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.91 (dd, J = 11.5, 14.3 Hz, 1 H), 6.74 (dd, J = 11.1, 14.5 Hz, 1 H), 6.66−6.55 (m, 2 H), 6.50−6.34 (m, 3 H), 6.28 (dd, J = 11.3, 14.1 Hz, 1 H), 6.09 (dd, J = 4.9, 14.6 Hz, 1 H), 5.70 (ddd, J = 2.8, 7.4, 10.1 Hz, 1 H), 5.49 (dd, J = 5.0, 9.6 Hz, 1 H), 5.33 (dq, J = 5.0, 6.3 Hz, 1 H), 5.30 (m, 1 H), 4.52 (m, 1 H), 4.39 (d, J = 5.6 Hz, 1 H), 4.28 (ddd, J = 2.4, 7.3, 11.4 Hz, 1 H), 3.91−3.84 (m, 2 H), 3.74 (m, 1 H), 3.16 (dd, J = 7.4, 7.4 Hz, 1 H), 2.63 (d, J = 14.1 Hz, 1 H), 2.04−1.21 (m, 19 H), 1.87 (s, 3 H), 1.85 (s, 3 H), 1.77 (s, 3 H), 1.67 (s, 3 H), 1.56 (s, 3 H), 1.52 (s, 3 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.28 (s, 3 H), 1.19 (d, J = 6.3 Hz, 3 H), 0.840 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 31.1, 30.5, 30.2, 24.7, 19.0, 19.0; HRMS (FAB) calcd for $C_{50}H_{76}O_{14}$ 900.5237, found 900.5150 (M).

[2(1*R*),3*S*,5*R*,7*S*,9*S*,11*R*,13*S*,15*S*]-2-(1-(Acetyloxy)hexyl)-7-*O*-acetyl-3,5:9,11:13,15-tris-*O*-(1-methylethylidene)-3,5,7,9,11,13,15-heptahydroxy-16-oxoheptadecanoic Acid, (2*R*,3*R*)-2-(Acetyloxy)-1-methyl-3-oxopropyl Ester (6). Triacetonide **4** (1.5 mg, 1.7 μmol) was dissolved in 1 mL of CH_2Cl_2. MeOH (100 μL) was added and the solution cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted, and then nitrogen was bubbled through until the solution was clear. PPh_3 (4 mg, 15 μmol) was added and the reaction mixture allowed to warm to room temperature. After overnight stirring, the reaction mixture was concentrated under reduced pressure to give a colorless oil. The product was purified by silica gel flash chromatography (1 × 5 cm) eluting with 60% EtOAc/hexanes to yield 0.6 mg (0.7 μmol, 41%) of a colorless oil; ^{1}H NMR (500 MHz, C_6D_6) δ 9.18 (s, 1 H), 5.66 (ddd, J = 2.8, 5.8, 9.2 Hz, 1 H), 5.45 (m, 1 H), 5.38 (dq, J = 3.4, 6.7 Hz, 1 H), 5.06 (d, J = 3.4 Hz, 1 H), 4.34 (dd, J = 10.5, 11.1 Hz, 1 H), 4.12−3.89 (m, 5 H), 3.17 (dd, J = 7.6, 7.6 Hz, 1 H), 2.04−1.10 (m, 23 H), 1.78 (s, 3 H), 1.77 (s, 3 H), 1.72 (s, 3 H), 1.49 (s, 3 H), 1.42 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 6 H), 1.29 (s, 3 H), 1.12 (d, J = 6.6 Hz, 3 H), 0.855 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 30.5, 30.3, 25.9, 24.3, 19.6, 19.3.

[2(1*R*),3*S*,5*R*,7*S*,9*R*,11*S*,13*S*,15*S*,16*S*]- and [2(1*R*),3*S*,-5*R*,7*S*,9*R*,11*S*,13*S*,15*S*,16*R*]-2-(1-Hydroxyhexyl)-3,5:7,9:11,13:15,16-tetrakis-*O*-(1-methylethylidene)-3,5,7,9,11,13,-15,16-octahydroxyheptadecanoic Acid, [1*S*,1(4*R*)]-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl Ester (7). Per-TES-filipin (470 mg, 280 μmol) was dissolved in 20 mL of a 2:1 mixture of CH_2Cl_2/MeOH and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted, and then nitrogen was bubbled through until it was clear. $NaBH_4$ (200 mg, 5.3 mmol) was added and the reaction mixture allowed to warm to room temperature. After the mixture was stirred for 2 h, the reaction was quenched with 10 mL of saturated $NaHCO_3$. The aqueous phase was extracted (3 × 10 mL) with CH_2Cl_2. The combined organic portions were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure to give 430 mg of a colorless oil. The colorless oil was taken up in 20 mL of acetone and treated with Dowex 50w × 1 ion exchange resin (H^+ form). After being stirred for 2.5 h, the reaction mixture was filtered and concentrated under reduced pressure to give a yellow oil. The oil was taken up in 60 mL of Et_2O, washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give a colorless oil. The desired product was separated from the mixture by silica gel flash chromatography (4 × 8 cm) eluting with 30% EtOAc/hexanes to give 15 mg of a colorless oil. The more polar material was eluted with 100% EtOAc. The more polar material was taken up in 10 mL of acetone and 5 mL of DMP. PPTS (5 mg) was added. The solution was flushed with nitrogen and allowed to stir for 9.75 h. The reaction was quenched with 10 μL of Et_3N and then the solvent evaporated under reduced pressure to give a colorless oil. The desired product was separated by silica gel chromatography. The combined yield for the desired product was 32.3 mg (41.1 μmol, 15%); ^{1}H NMR (500 MHz, C_6D_6) δ 5.07 (dq, J = 6.2, 6.2 Hz, 1 H), 4.52 (ddd, J = 2.1, 8.8, 11.1 Hz, 1 H), 4.36 (ddd, J = 3.5, 6.0, 9.5 Hz, 1 H), 4.30 (ddd, J = 2.9, 7.9, 10.8 Hz, 1 H), 4.12−4.00 (m, 4 H), 3.88 (m, 1 H), 3.81 (ddd, J = 1.3, 6.2, 8.2 Hz, 1 H), 3.75 (m, 1 H), 3.63 (m, 1 H), 3.49 (m, 1 H), 2.83 (dd, J = 8.6, 8.6 Hz, 1 H), 2.10−1.99 (m, 2 H), 1.71−1.15 (m, 19 H), 1.54 (s, 3 H), 1.52 (s, 3 H), 1.50 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.343 (s, 3 H), 1.337 (s, 3 H), 1.26 (s, 3 H), 1.18 (d, J = 5.6 Hz, 3 H), 1.14 (d, J = 6.0 Hz, 3 H), 0.879 (t, J = 6.2 Hz, 3 H); HRMS (FAB) calcd for $C_{42}H_{75}O_{13}$ 787.5209, found 787.5198 (M + H).

(*S*)-MTPA Ester of Pentaacetonide 7. Pentaacetonide **7** (2.8 mg, 3.6 μmol) was dissolved in 2 mL of CH_2Cl_2. DMAP (4.0 mg, 33 μmol) and (*R*)-MTPA-Cl (3 μL, 16 μmol) were added. The reaction was allowed to stir under N_2 for 1 h. The reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was extracted (2 × 10 mL) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure to give a colorless oil. The product was purified by silica gel flash chromatography (1 × 5 cm) eluting with 30% EtOAc/hexanes to yield 3.6 mg (3.6 μmol, 100%) of a yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.48−7.52 (m, 2 H), 7.37−7.40 (m, 3 H), 5.45 (ddd, J = 5.5, 5.6, 8.3 Hz, 1 H), 4.80 (dq, J = 6.1, 6.2 Hz, 1 H), 4.23 (m, 1 H), 4.06−3.89 (m, 7 H), 3.84 (ddd J = 3.0, 6.9, 10.5 Hz, 1 H), 3.71−3.65 (m, 2 H), 3.53 (s, 3 H), 2.91 (dd, J = 7.0, 8.0 Hz, 1 H), 1.82−1.76 (m, 2 H), 1.68−1.60 (m, 2 H), 1.48−1.10 (m, 19 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 6 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.20 (d, J = 6.4 Hz, 3 H), 0.846 (t, J = 7.1 Hz, 3 H); HRMS (FAB) calcd for $C_{52}H_{82}O_{15}F_3$ 1003.5607, found 1003.5541 (M + H).

(*R*)-MTPA Ester of Pentaacetonide 7. The (*R*)-MTPA ester of pentaacetonide **7** was prepared from pentaacetonide **7** following the same procedure used to prepare the (*S*)-MTPA ester described above. **7**: yield 3.5 mg, 3.5 μmol, 97%; ^{1}H NMR (500 MHz, C_6D_6) δ 7.54−7.50 (m, 2 H), 7.36−7.41 (m, 3 H), 5.47 (dd, J = 6.3, 12.4 Hz, 1 H), 4.85 (dq, J = 6.3, 6.3 Hz, 1 H), 4.23 (m, 1 H), 4.04−3.89 (m, 8 H), 3.71 (ddd, J = 4.2, 8.7, 11.6 Hz, 1 H), 3.67 (m, 1 H), 3.47 (s, 3 H), 2.93 (dd, J = 7.3, 7.3 Hz, 1 H), 1.81−1.74 (m, 2 H), 1.65−1.60 (m, 2 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 6 H), 1.31 (s, 3 H), 1.30 (s, 3 H), 1.20 (d, J = 6.4 Hz, 1 H), 0.821 (t, J = 6.8 Hz, 1 H); HRMS (FAB) calcd for $C_{52}H_{82}O_{15}F_3$ 1003.5607, found 1003.5659 (M + H).

(2*S*,3*R*)-1,2-Di-*O*-isopropylidene-1,2,3-butanetriol (8). Pentaacetonide **7** (22 mg, 28 μmol) was placed in a flask and flushed with argon. In another flask LAH (32 mg, 840 μmol) was dissolved in 5 mL of THF and then transferred via cannula to the reaction flask. After the mixture was stirred for 1.75 h, the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ (200 mg). The solids were filtered and washed with THF. The organic solution was concentrated under reduced pressure to give a colorless oil. The desired product was separated from the mixture by silica gel flash chromatography (2 × 5 cm) eluting with 70% Et_2O/pentane to give acetonide alcohol **8** (4.1 mg, 28 μmol, 100%) as a colorless oil. A mixture of acetonide isomers (14.2 mg, 22 μmol, 79%) representing the large polyol was also collected.

Acetonide alcohol **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03−3.87 (m, 4 H), 1.93 (d (broad), J = 2.6 Hz, 1 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.14 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.1, 79.4, 66.7, 64.4, 26.4, 25.2, 18.2; HRMS (CI) calcd for $C_7H_{15}O_3$ 147.1021, found 147.1017 (M + H).

(*S*)-MTPA and (*R*)-MTPA Esters of (2*S*,3*R*)-1,2-Di-*O*-isopropylidene-1,2,3-butanetriol (8). Acetonide alcohol **8** (1.5 mg, 10 μmol) was dissolved in 2 mL of CH_2Cl_2. DMAP (10 mg, 82 μmol) and (*R*)-MTPA-Cl (8 μL, 43 μmol) were added. The reaction mixture was allowed to stir under N_2 for 45 min,

diluted with 10 mL of CH_2Cl_2, and washed with saturated $NaHCO_3$. The aqueous layer was extracted (2 × 10 mL) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure to give a colorless oil. The product was purified by silica gel flash chromatography (1 × 5 cm) eluting with 30% EtOAc/hexanes to yield 3.2 mg (8.8 μmol, 88%) of a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.52 (m, 2 H), 7.37−7.40 (m, 3 H), 5.07 (dq, J = 6.4, 6.4 Hz, 1 H), 4.01 (ddd, J = 6.4, 6.3, 6.1 Hz, 1 H), 3.87 (dd, J = 6.3, 8.6 Hz, 1 H), 3.61 (dd, J = 6.1, 8.6 Hz, 1 H), 3.56 (s, 3 H), 1.39 (d, J = 6.4 Hz, 3 H), 1.31 (s, 3 H), 1.29 (s, 3 H); HRMS (CI) calcd for $C_{17}H_{22}O_5F_3$ 363.1420, found 363.1415 (M + H).

The (*R*)-MTPA ester of acetonide alcohol **8** was prepared from acetonide alcohol **8** following the same procedure used to prepare the (*S*)-MTPA ester described above. **8**: yield 3.4 mg, 9.4 μmol, 94%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.52 (m, 2 H), 7.37−7.40 (m, 3 H), 5.14 (dq, J = 6.2, 6.3 Hz, 1 H), 4.10 (ddd, J = 6.4, 6.4, 6.2 Hz, 1 H), 3.99 (dd, J = 6.4, 8.4 Hz, 1 H), 3.73 (dd, J = 6.4, 8.4 Hz, 1 H), 3.51 (s, 3 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.29 (d, J = 6.3 Hz, 3 H); HRMS (CI) calcd for $C_{17}H_{22}O_5F_3$ 363.1420, found 363.1432 (M + H).

[1(4*R*,5*R*),1*S*,3*R*,5*S*,7*R*,9*S*,11*R*,13*S*,14*S*]- and [1(4*R*,5*R*),-1*S*,3*R*,5*S*,7*R*,9*S*,11*R*,13*S*,14*R*]-1-(2,2-Dimethyl-4-pentyl-1,3-dioxan-5-yl)-1,3:5,7:9,11:13,14-tetrakis-*O*-(1-methylethylidene)pentadecan-1,3,5,7,9,11,13,14-octol (9). The mixture of acetonide isomers from the preparation of acetonide alcohol **8** was dissolved in 5 mL of acetone and 2.5 mL of DMP. PPTS (5 mg) was added, and the reaction was stirred for 11 h. The reaction was quenched with 5 μmol Et_3N, and then the solution was concentrated under reduced pressure to give a colorless oil. The product was purified by silica gel flash chromatography (3 × 5 cm) eluting with 30% EtOAc/hexanes to give pentaacetonide **9** (14.3 mg, 20.9 μmol, 96%) as an inseparable 1:1 mixture of C16 epimers. The product was a colorless oil: $[\alpha]^{26}_D$ −20.5° (c = 1.43, $CHCl_3$); ^{13}C NMR (125 MHz, C_6D_6, isotopically enriched acetonide methyls) δ 29.0, 27.8, 27.6, 26.1 (1,2 diol acetonides) 30.8, 30.7, 30.7, 30.2, 20.0, 19.9, 19.8, 19.0 (1,3-diol acetonides); HRMS (FAB) calcd for $C_{38}H_{69}O_{10}$ 685.4893, found 685.4929 (M + H).

[13*S*,14*S*] isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28−4.19 (m, 1 H), 4.06−3.95 (m, 7 H), 3.81 (dd, J = 3.2, 12.1 Hz, 1H), 3.68−3.66 (m, 2 H), 1.84−1.76 (m, 2 H), 1.72−1.10 (m, 19 H), 1.423 (s, 3H), 1.41 (s, 6H), 1.40 (s, 3 H), 1.36 (s, 3 H) 1.35 (s, 6 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.31 (s, 3 H), 1.23 (d, J = 5.4 Hz, 3 H), 0.866 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.7, 98.5, 98.4, 98.3 (2), 79.0, 77.1, 71.7, 66.7 (2), 65.7, 65.2 (2), 65.0, 61.0, 42.7 (2), 41.1, 39.6, 37.5, 36.5, 34.8, 33.1, 31.9, 30.3, 30.2 (2), 29.7, 27.3 (2), 25.3, 22.6, 20.0, 19.8 (2), 18.9, 17.2, 14.1.

[13*S*,14*R*] isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28−4.19 (m, 1 H), 4.06−3.95 (m, 7 H), 3.78 (dd, J = 3.2, 12.1 Hz, 1 H), 3.64−3.56 (m, 2 H), 1.84−1.76 (m, 2 H), 1.72−1.10 (m, 19 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.36 (s, 6 H), 1.35 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H), 1.30 (s, 3 H), 1.11 (d, J = 6.1 Hz, 3 H), 0.866 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.2, 98.8, 98.5, 98.4, 98.3, 77.1, 74.4, 73.8, 70.3, 68.7, 66.3, 65.2 (2), 65.0, 59.0, 45.1, 42.7, 42.5, 41.1, 37.5, 36.9, 34.7, 31.7, 30.2 (2), 30.1, 29.7, 28.6, 25.9, 24.8, 22.6, 21.2, 20.0, 19.8 (2), 18.9, 17.1, 15.8.

Synthesis of Correlation Fragment 10. (2*R*,3*S*)-1-Chlorobutane-2,3-diol (21). AD-mix-α (17.0 g, 12 mmol), $NaHCO_3$ (3.05 g, 36 mmol), methanesulfonamide (1.15 g, 12 mmol), 60 mL of water, and 60 mL of *tert*-butyl alcohol were placed in a 500 mL flask equipped with an overhead stirrer. The solution was stirred at room temperature until all the solids dissolved. The solution was cooled to 0 °C, and then crotyl chloride (1.09 g, 12 mmol) was added. The solution was stirred for 3 days. The reaction was quenched with 18 g of Na_2SO_3, and the solution was stirred for 1 h at room temperature. The aqueous layer was extracted (3 × 90 mL) with EtOAc. The combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (4 × 6 cm) eluting with 90% Et_2O/pentane to yield 1.29 g (10.3 mmol, 86%) of a colorless oil: IR (neat) 3372, 2976, 2934, 2911, 1321, 1137, 1060, 991 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (dt, J = 11.1, 6.4 Hz, 2 H), 6.67−3.52 (m, 3 H), 3.20 (broad s, 2 H), 1.26 (d, J = 6.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 75.3, 68.0; *C*H_2, 46.6; *C*H_3, 19.4; HRMS (CI) calcd for $C_4H_{13}ClNO_2$ 142.0636, found 142.0640 (M + NH_4). Anal. Calcd for $C_4H_9ClO_2$: C, 38.57; H, 7.28. Found: C, 38.32; H, 7.19.

(4*R*,5*S*)-4-(Chloromethyl)-2,2,5-trimethyl-1,3-dioxolane (22). Chloro diol **21** (1.25 g, 10 mmol) was dissolved in 60 mL of acetone and 30 mL of DMP. PPTS (260 mg, 1 mmol) was added. The reaction mixture was tightly capped under N_2 and stirred for 22 h. The reaction was quenched with 250 μL Et_3N, and then the mixture was concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (4 × 8 cm) eluting with 5% Et_2O/pentane to yield 1.22 g (7.46 mmol, 74%) of product as an 86:14 mixture of anti (t_R = 17.11 min) to syn (t_R = 18.18 min) isomers by GC analysis: IR (neat) 2987, 2936, 2883, 1380, 1246, 1221, 1173, 1090, 1048 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (dt, J = 7.6, 6.0 Hz, 1 H), 3.75 (m, 1 H), 3.60 (dd, J = 4.8, 11.4 Hz, 1 H), 3.54 (dd, J = 5.8, 11.4 Hz, 1 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.33 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 109.0; *C*H, 81.5, 75.4; *C*H_2, 43.8; *C*H_3, 27.4, 26.8, 18.4; HRMS (CI) calcd for $C_7H_{14}ClO_2$ 165.0683, found 165.0679 (M + H). Anal. Calcd for $C_7H_{13}ClO_2$: C, 51.07; H, 7.96. Found: C, 50.97; H, 7.83.

Analysis of the product by GC on a chiral column (Chiraldex G TA) showed the major isomer was 81% ee and the minor isomer was 47% ee.

(4*R*,5*S*)-4-(Iodomethyl)-2,2,5-trimethyl-1,3-dioxolane (23). Acetonide **22** (1.10 g, 6.72 mmol) was placed in a 100 mL flask with 40 mL of xylenes. KI (27.9 g, 168 mmol) and 18-crown-6 (2.66 g, 10.0 mmol) were added. The reaction was heated to reflux and stirred for 4 days under N_2. The reaction was quenched with 20 mL of saturated Na_2SO_3, and then the solution was diluted with water until all the solids dissolved. The aqueous layer was extracted (3 × 25 mL) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (6 × 6 cm) eluting with 5% Et_2O/pentane to yield 1.51g of a colorless oil that was a 35:65 mixture of starting material as a 2:1 mixture of anti (t_R = 17.13 min) to syn (t_R = 18.19 min) and product as a 97:3 mixture of anti (t_R = 23.66 min) to syn (t_R = 24.76 min) by GC analysis. The product was a colorless oil: IR (neat) 2985, 2934, 2880, 1379, 1243, 1222, 1175, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (dt, J = 13.5, 6.1 Hz, 1 H), 3.55 (m, 1 H), 3.24−3.22 (m, 2 H), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.33 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 108.7; *C*H, 81.1, 77.4; *C*H_2, 4.9; *C*H_3, 27.6, 27.2, 18.6; HRMS (CI) calcd for $C_7H_{14}IO_2$ 257.0039, found 257.0048 (M + H).

(2*S*,3*S*,5*S*,7*S*)-2,3:5,7-Bis-*O*-(1-methylethylidene)-8-chloro-5-cyanooctane-2,3,5,7-tetrol (24). A solution of chloro cyanohydrin acetonide **13** (760 mg, 4.0 mmol) in 2 mL of THF was cooled to −78 °C and then added via cannula to 4.7 mmol of $LiNEt_2$ in 5 mL of THF under Ar at −78 °C. The reaction was stirred for 1 h. A solution of compound **23** (512 mg, 1.49 mmol) in 2 mL of THF was cooled to −78 °C and then transferred to the reaction flask via cannula. The solution was stirred for 1 h and then warmed to −27 °C with a MeOH/ice bath. The reaction was allowed to warm slowly to 15 °C over 15 h. The reaction was quenched with 6 mL of saturated NH_4Cl. Water was added until all the solids dissolved. The solution was diluted with 25 mL of CH_2Cl_2. The aqueous layer was extracted (3 × 25 mL) with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (3 × 8 cm) eluting with 10% EtOAc/hexanes to yield 361.4 mg (1.14 mmol, 76%) of a colorless oil which crystallized upon standing: mp = 46−48 °C; IR (neat) 2987, 2936, 2886, 1382, 1251, 1206, 1177, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (ddt, J = 1.8, 11.7, 5.3 Hz, 1 H), 3.82 (dt, J = 3.2, 8.2 Hz, 1 H), 3.74 (m, 1 H), 3.55 (dd, J = 5.5, 11.4 Hz, 1 H), 3.50 (dd, J = 5.2, 11.4 Hz, 1 H), 2.18 (dd, J = 2.1, 13.9 Hz, 1 H), 2.02 (dd, J = 3.2, 14.2 Hz, 1

H), 1.95 (dd, J = 8.1, 14.2 Hz, 1 H), 1.72 (s, 3 H), 1.62 (dd, J = 11.7, 13.9 Hz, 1 H), 1.39 (s, 3 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.28 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 120.9, 108.7, 101.6, 69.1; *C*H, 77.8, 77.0, 66.7; *C*H_2, 46.3, 45.2, 37.6; *C*H_3, 30.7, 27.3, 27.1, 21.6, 17.0; HRMS (CI) calcd for $C_{15}H_{25}ClNO_4$ 318.1473, found 318.1484 (M + H). Anal. Calcd for $C_{15}H_{24}ClNO_4$: C, 56.69; H, 7.61. Found: C, 56.50; H, 7.75.

(2*S*,3*S*,5*S*,7*S*)-2,3:5,7-Bis-*O*-(1-methylethylidene)-5-cyano-8-iodooctane-2,3,5,7-tetrol (25). A 25 mL Schlenk flask was charged with diacetonide nitrile **24** (437 mg, 1.37 mmol), 18-crown-6 (500 mg, 1.89 mmol), and 10 mL of xylenes. The solution was degassed with Ar for 15 min followed by addition of KI (5.7 g, 34 mmol). The reaction was heated to reflux and stirred for 2 days. The reaction was quenched with 20 mL of saturated Na_2SO_3, and then the solution was diluted with water until all the solids dissolved. The aqueous layer was extracted (3 × 25 mL) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10% EtOAc/hexane to yield 555 mg (1.36 mmol, 99%) of a colorless oil: $[\alpha]^{26}_D$ = 22.3 (c = 0.96, $CHCl_3$); IR (neat) 3032, 2985, 2970, 2933, 2886, 1430, 1380, 1298, 1265, 1236, 1179, 1136, 1100, 1074, 1047, 1036, 1012, 984, 948, 936 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (dddd, J = 2.0, 5.1, 6.3, 11.5 Hz, 1 H), 3.79 (ddd, J = 3.3, 8.1, 8.1 Hz, 1 H), 3.72 (dq, J = 8.1, 6.0 Hz, 1 H), 3.18 (dd, J = 5.1, 10.4 Hz, 1 H), 3.13 (dd, J = 6.3, 10.4 Hz, 1 H), 2.22 (dd, J = 2.0, 13.8 Hz, 1 H), 1.99 (dd, J = 3.3, 14.2 Hz, 1 H), 1.93 (dd, J = 8.1, 14.2 Hz, 1 H), 1.68 (s, 3 H), 1.49 (dd, J = 11.5, 13.8 Hz, 1 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.26 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 120.9, 108.7, 101.9, 69.1; *C*H, 77.8, 76.9, 66.4; *C*H_2, 45.1, 40.1, 7.6; *C*H_3, 30.7, 27.3, 27.1, 21.6, 17.1; HRMS (CI) calcd for $C_{15}H_{28}IN_2O_2$ 427.1094, found 427.1099 (M + NH_4). Anal. Calcd for $C_{15}H_{24}INO_4$: C, 44.02; H, 5.91. Found: C, 44.22; H, 5.84.

(2*S*,3*S*,5*S*,7*R*,9*S*,11*S*)-5,9-Dicyano-12-chloro-2,3:5,7:9,11-tris-*O*-(1-methylethylidene)dodecane-2,3,5,7,9,11-hexol (26). A solution of chloro cyanohydrin acetonide **13** (130 mg, 0.68 mmol) in 300 μL of THF was added via syringe to 0.81 mmol of $LiNEt_2$ in 1 mL of THF under Ar at −63 °C. The reaction mixture was stirred for 1 h, then cooled to −78 °C, and stirred for another hour. DMPU (400 μL, 3.31 mmol) and a solution of iodide **25** (140 mg, 0.34 mmol) in 250 μL of THF were added to the reaction flask via syringe. The solution was stirred for 15 min and then warmed to −25 °C with a MeOH/ice bath. The reaction mixture was allowed to warm slowly to 15 °C over 16 h. The reaction was quenched with 5 mL of saturated NH_4Cl. Water was added until all the solids dissolved. The aqueous layer was extracted (3 × 20 mL) with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (4 × 10 cm) eluting with 10% EtOAc/hexanes to yield 151 mg (0.32 mmol, 94%) of a colorless oil which crystallized upon standing. Recrystallization from hexanes gave 105.8 mg (0.22 mmol, 66%) of a white crystalline solid: mp = 123−124° C; $[\alpha]^{26}_D$ = 39.9° (c = 1.30, $CHCl_3$); IR (KBr) 2986, 2939, 2988, 2879, 1384 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (dddd, J = 2.0, 3.5, 7.3, 11.7 Hz, 1 H), 4.35 (dddd, J = 2.1, 4.9, 5.1, 11.8 Hz, 1 H), 3.80 (dt, J = 2.9, 8.3 Hz, 1 H), 3.73 (dq, J = 8.2, 5.9 Hz, 1 H), 3.57 (dd, J = 4.9, 11.5 Hz, 1 H), 3.52 (dd, J = 5.1, 11.5 Hz, 1 H), 2.11−2.03 (m, 4 H), 2.00 (dd, J = 2.9, 14.1 Hz, 1 H), 1.92 (dd, J = 8.4, 14.1 Hz, 1 H), 1.86 (dd, J = 2.1, 13.6 Hz, 1 H), 1.72 (s, 3 H), 1.71 (s, 3 H), 1.62 (dd, J = 11.8, 14.0 Hz, 1 H), 1.43 (s, 3 H), 1.364 (s, 3 H), 1.357 (s, 3 H), 1.34 (s, 3 H), 1.28 (d, J = 5.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 121.6, 121.0, 108.7, 101.7, 101.2, 69.5, 67.6; *C*H, 77.8, 76.9, 66.4, 61.8; *C*H_2, 46.5, 46.1, 54.1, 39.9, 35.2; *C*H_3, 30.8, 30.6, 27.2, 27.1, 21.5, 21.4, 17.0; HRMS (CI) calcd for $C_{23}H_{39}ClN_3O_6$ 488.2527, found 488.2536 (M + NH_4). Anal. Calcd for $C_{23}H_{35}ClN_2O_6$: C, 58.65; H, 7.49. Found: C, 58.47; H, 7.40.

(2*S*,3*S*,5*S*,7*R*,9*S*,11*S*)-5,9-Dicyano-12-iodo-2,3:5,7:9,11-tris-*O*-(1-methylethylidene)dodecane-2,3,5,7,9,11-hexol (27). A 25 mL Schlenk flask was charged with triacetonide dinitrile **26** (250 mg, 0.531 mmol), 18-crown-6 (168 mg, 0.636 mmol), and 5 mL of xylenes. The solution was degassed with Ar for 15 min followed by addition of KI (5.7 g, 34 mmol). The reaction was heated to reflux and stirred for 2 days. The reaction mixture was quenched with 25 mL of saturated Na_2SO_3. The aqueous layer was extracted (3 × 25 mL) with CH_2Cl_2. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10−20% EtOAc/hexane to yield 280 mg (0.498 mmol, 94%) of a colorless oil: $[\alpha]^{24}_D$ = 38.3 (c = 1.07, $CHCl_3$); IR (neat) 2983, 2934, 2875, 1379 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (dddd, J = 1.8, 4.1, 6.3, 11.6 Hz, 1 H), 4.02 (dddd, J = 2.3, 5.2, 5.2, 11.0 Hz, 1 H), 3.80 (dt, J = 3.1, 8.2 Hz, 1 H), 3.73 (dq, J = 8.2, 6.0 Hz, 1 H), 2.23 (dd, J = 5.2, 10.6 Hz, 1 H), 3.19 (dd, J = 5.2, 10.6 Hz, 1 H), 2.97−2.08 (m, 5 H), 1.92 (dd, J = 8.2, 14.1 Hz, 1 H), 1.89 (dd, J = 2.3, 13.6 Hz, 1 H), 1.74 (s, 3 H), 1.70 (s, 3 H), 1.61 (dd, J = 13.6, 11.6 Hz, 1 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.27 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 121.7, 120.9, 108.7, 101.9, 101.1, 65.5, 68.3; *C*H, 77.8, 76.9, 65.8, 61.7; *C*H_2, 46.0, 45.1, 39.9, 38.0, 8.6; *C*H_3, 30.8, 30.6, 27.3, 27.1, 21.7, 21.5, 17.0; HRMS (FAB) calcd for $C_{23}H_{36}IN_2O_6$ 563.1620, found 563.1625 (M + H). Anal. Calcd for $C_{23}H_{35}IN_2O_6$: C, 49.12; H, 6.27. Found: C, 49.12; H, 6.36.

(*Z*)-2-Octen-1-ol (29). A sample of $Ni(OAc)_2{\cdot}4H_2O$ (4.00 g, 16.0 mmol) was placed in a Parr hydrogenation bottle with 150 mL of absolute EtOH. The solution was purged with a stream of N_2. A solution of $NaBH_4$ (600 mg, 16.0 mmol) in 20 mL of EtOH was transferred to the hydrogenation bottle via cannula. The solution was stirred vigorously for 15 min. Ethylenediamine (2.0 mL, 32 mmol) was added via syringe. A sample of 2-octyn-1-ol (20.0 g, 160 mmol) was transferred to the hydrogenation bottle via cannula. The solution was shaken in a Parr hydrogenation apparatus under 50 psi of H_2 for 2 h. The catalyst was filtered off through charcoal. The purple solution was diluted with 300 mL of water and 200 mL of Et_2O. The layers were separated, and then the aqueous layer was extracted (3 × 100 mL) with Et_2O. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and then concentrated under reduced pressure to give 21 g of a slightly yellow oil. Distillation (40 °C at 0.4 Torr) gave 18.9 g (147 mmol, 92%) of a colorless oil: IR (neat) 3327, 3016, 2958, 2937, 2867, 1656, 1453, 1380, 1340, 1312, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60−5.45 (m, 2 H), 4.15 (t, J = 5.6 Hz, 2 H), 2.03 (q, J = 6.8 Hz, 2 H), 1.82 (d, J = 5.2 Hz, 1 H), 1.38−1.18 (m, 6 H), 0.857 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 133.3, 128.3; *C*H_2, 58.6, 31.4, 29.3, 27.4, 22.5; *C*H_3, 14.0; HRMS (EI) calcd for $C_8H_{16}O$ 128.1202, found 128.1199 (M). Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.93; H, 12.48.

(2*S*,3*R*)-3-Pentyloxirane-2-methanol (30). (*E*)-2-Octen-1-ol, $Ti(OiPr)_4$, and L-(+)-diethyl tartrate were freshly distilled. A 500 mL two-neck flask was flame dried and flushed with Ar. Activated 4 Å sieves (1.5 g) and 200 mL of CH_2Cl_2 were added. The solution was cooled to −20 °C. A solution of L-(+)-diethyl tartrate (1.54 g, 7.50 mmol) in 10 mL of CH_2Cl_2, a solution of $Ti(OiPr)_4$ (1.86 mL, 6.2 mmol) in 10 mL of CH_2Cl_2, and *tert*-butyl hydroperoxide (13.4 mL of a 5.8 M solution in decane) were each separately stirred with 4 Å sieves for 15 min and then transferred to the reaction flask via cannula. The reaction was stirred at −20 °C for 40 min. Then a solution of (*Z*)-2-octen-1-ol (4.0 g, 31.2 mmol) in 10 mL of CH_2Cl_2 was stirred with 4 Å sieves for 15 min and then transferred to the reaction flask via cannula. The reaction mixture was stirred at −15 °C for 45 h. The reaction mixture was then warmed to 0 °C, 35 mL of water was added, and the mixture was stirred for 1 h. A 30% NaOH aqueous solution saturated with NaCl (6 mL) was added. After 20 min of stirring, the solution had separated into two phases. The aqueous phase was extracted (2 × 100 mL) with CH_2Cl_2. The combined organic layers were washed with brine. The brine was back extracted (2 × 30 mL) with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography

(6 × 5 cm) eluting with 10−50% EtOAc/hexanes to yield 4.4 g (30 mmol, 98%) of the product. Analysis using a chiral GC column showed the material was 88% ee. The product was isolated as a white solid: mp = 27−28° C; $[\alpha]^{23}_D = -2.9$ (c = 1.072, $CHCl_3$); IR (neat) 3414, 2957, 2928, 2860, 1467, 1379, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (ddd, J = 4.0, 7.0, 11.6 Hz, 1 H), 3.57 (ddd, J = 4.6, 7.0, 11.9 Hz, 1 H), 3.80 (dt, J = 7.9, 4.3 Hz, 1 H), 2.99−2.93 (m, 2 H), 1.50−1.20 (m, 8 H), 0.810 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 57.3, 57.0; *C*H_2, 60.9, 31.6, 27.9, 26.3, 22.5; *C*H_3, 13.9; HRMS (CI) calcd for $C_8H_{20}NO_2$ 162.1495, found 162.1493 (M + NH_4). Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.59; H, 10.93.

(3*R*,4*R*)-3-(Hydroxymethyl)-1-nonen-4-ol. CuI (800 mg, 4.20 mmol) was suspended in 100 mL of Et_2O under Ar at −10 °C. Vinylmagnesium bromide (42 mL of 1.0 M solution in THF) was added via syringe. The solution was stirred for 10 min and then cooled to −25 °C. A solution of epoxide **30** (2.0 g, 13.9 mmol) in 5 mL of Et_2O was added via cannula. After the mixture was stirred under Ar at −25 °C for 9 h, the reaction was quenched with 40 mL of saturated NH_4Cl which had been brought to pH 8 with NH_4OH. The aqueous layer was extracted (3 × 50 mL) with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (7 × 6 cm) eluting with 50% EtOAc/hexanes. The mixture of diols was taken up in 100 mL of 1:1 THF/water. A solution of $NaIO_4$ (3.0 g, 14 mmol) in 20 mL of water was added. The reaction mixture was stirred 3 h and then diluted with 100 mL of brine. The aqueous phase was extracted (3 × 50 mL) with Et_2O. The combined organic layers were dried ($MgSO_4$) and then concentrated under reduced pressure. The crude product was purified by MPLC on SiO_2 (30 × 4 cm) eluting with 50% EtOAc/hexanes to give 1.19 g (6.92 mmol, 50%) of a colorless oil: $[\alpha]^{24}_D = 4.5°$ (c = 1.05, $CHCl_3$); IR (neat) 3371, 3076, 2956, 2931, 2873, 1640, 1467 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddd, J = 8.9, 10.4, 17.4 Hz, 1 H), 5.21 (dd, J = 1.8, 10.4 Hz, 1 H), 5.14 (ddd, J = 0.9, 1.8, 17.4 Hz, 1 H), 3.80−3.68 (m, 3 H), 2.75 (t, J = 4.9 Hz, 1 H), 2.58 (d, J = 4.6 Hz, 1 H), 2.28 (dddd, J = 3.4, 5.8, 8.9, 11.9 Hz, 1 H), 1.46−1.38 (m, 3 H), 1.31−1.22 (m, 5 H), 0.858 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H, 134.8, 72.7, 50.6; *C*H_2, 118.7, 64.6, 34.8, 31.8, 25.5, 22.6; *C*H_3, 14.0; HRMS (CI) calcd for $C_{10}H_{24}NO_2$ 190.1808, found 190.1800 (M + NH_4). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.48; H, 11.54.

(3*R*,4*R*)-2,2-Dimethyl-3-ethenyl-4-pentyl-1,3-dioxane (31). (3*R*,4*R*)-3-(Hydroxymethyl)-1-nonen-4-ol (1.10 g, 6.39 mmol) was dissolved in 40 mL of acetone and 20 mL of DMP. PPTS (100 mg, 0.4 mmol) was added. The reaction was tightly capped under N_2 and stirred for 16 h. The reaction was quenched with 100 μL of Et_3N, and then the solution was concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (6 × 6 cm) eluting with 10% Et_2O/pentane to yield 1.19 g (5.55 mmol, 87%) of a colorless oil: $[\alpha]^{22}_D = 6.4°$ (c = 0.98, $CHCl_3$); IR (neat) 3073, 2992, 2956, 2936, 2860, 1641, 1461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.21 (dt, J = 17.4, 10.1 Hz, 1 H), 5.14−5.05 (m, 2 H), 4.12 (dd, J = 3.1, 11.3 Hz, 1 H), 3.89 (m, 1 H), 3.69 (dd, J = 1.5, 11.3 Hz, 1 H), 1.94 (m, 1 H), 1.44 (s, 3 H), 1.39 (s, 3 H), 1.41−1.19 (m, 8 H), 0.857 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 98.7; *C*H, 136.0, 71.1, 43.1; *C*H_2, 116.6, 65.9, 33.4, 31.7, 24.6, 22.6; *C*H_3, 29.6, 19.1, 14.0; HRMS (CI) calcd for $C_{13}H_{25}O_2$ 213.1856, found 213.1853 (M + H). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.31; H, 11.56.

(4*R*,5*R*)-2,2-Dimethyl-5-ethenyl-4-pentyl-1,3-dioxane (32). Acetonide **31** (300 mg, 1.4 mmol) was dissolved in 10 mL of acetone and 3 mL of water in a 50 mL round bottom flask followed by the addition of NMO (245 mg, 2.1 mmol) and a 2.5% solution of OsO_4 in *tert*-butyl alcohol (900 μL, 0.07 mmol). The reaction mixture was stirred for 6 h followed by the addition of a solution of $NaIO_4$ (900 mg, 4.2 mmol) in 7 mL of water. The mixture was stirred for 2 h during which time a white precipitate formed. The solution was extracted (3 × 25 mL) with Et_2O. The organic phase was washed with 0.5 M $Na_2S_2O_3$ (2×) and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (3 × 6 cm) eluting with 15% Et_2O/pentane to yield 300 mg (1.39, mmol, 99%) of a colorless oil: $[\alpha]^{23}_D = 13.6°$ (c = 0.94, $CHCl_3$); IR (neat) 2993, 2934, 2872, 2751, 1720, 1462, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.05 (d, J = 4.0 Hz, 1 H), 4.14−4.03 (m, 3 H), 1.99−1.97 (m, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.62−1.04 (m, 8 H), 0.830 (t, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 99.3; *C*H, 201.4, 70.2, 49.7; *C*H_2, 61.4, 33.2, 31.5, 24.9, 22.4; *C*H_3, 29.4, 19.8, 13.9. Anal. Calcd for $C_{12}H_{22}O_2$: C, 67.26; H, 10.35. Found: C, 67.21; H, 10.15.

(4a(*S*),5α)-2,2-Dimethyl-4-pentyl-α-(3-propenyl)-1,3-dioxane-5-methanol (33). A 100 mL round bottom flask was charged with aldehyde **32** (440 mg, 2.05 mmol) and 20 mL of Et_2O and cooled to −78 °C. A 1 M solution of ^{d}Ipc$_2$BAllyl in pentane (2.5 mL, 2.5 mmol) was added to the reaction flask via syringe. The reaction mixture was stirred for 21 h and then warmed to 0 °C. The reaction was quenched by the slow addition of 1 mL of 3 N NaOH and 2 mL of 30% H_2O_2, and then the solution was heated to reflux for 1 h. The aqueous layer was extracted (2 × 20 mL) with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$, water (2×), and brine and dried ($MgSO_4$). TLC showed incomplete oxidation. The solution was concentrated to an oil and then dissolved in 20 mL of THF followed by the slow addition of 1.5 mL of 3 N NaOH and 3 mL 30% H_2O_2. The solution was refluxed for 30 min and then extracted (3 × 25 mL) with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$, water (2×), and brine, dried ($MgSO_4$), and concentrated to a colorless oil. The crude product was purified by silica gel flash chromatography (5 × 6 cm) eluting with 10% EtOAc in 1:1 CH_2Cl_2:hexanes to yield 440 mg (1.72, mmol, 84%) of a colorless oil: $[\alpha]^{26}_D = 10.0°$ (c = 1.01, $CHCl_3$); IR (neat) 3437, 3074, 2290, 2932, 2868, 1640, 1462, 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, J = 5.5, 8.9, 10.1, 17.1 Hz, 1 H), 5.20−5.15 (m, 2 H), 4.07−3.94 (m, 4 H), 2.70 (ddddd, J = 1.7, 1.7, 2.9, 5.6, 14.5 Hz, 1 H), 2.37 (dt, J = 14.5, 9.6 Hz, 1 H), 1.98 (broad s, 1 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.62−1.24 (m, 9 H), 0.878 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 98.5; *C*H, 136.0, 71.3, 68.5, 10.8; *C*H_2, 118.4, 61.1, 40.2, 33.0, 31.8, 25.6, 22.6; *C*H_3, 29.7, 18.8, 14.1; HRMS (CI) calcd for $C_{15}H_{29}O_3$ 257.2118, found 257.2112 (M + H). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.16; H, 10.88.

[2*R*,4*S*,4(4*R*,5*R*)]- and [2*S*,4*S*,4(4*R*,5*R*)]-4-(2,2-Dimethyl-4-pentyl-1,3-dioxan-5-yl)-2,4-dihydroxy-2,4-*O*-(1-methylethylidene)butanenitrile (12). A 25 mL round bottom flask was charged with homoallylic alcohol **33** (400 mg, 1.56 mmol), 10 mL of CH_3CN, and bis(trimethylsilyl)acetamide (500 μL, 2.0 mmol). The reaction mixture was heated to reflux for 10 h. The solution was concentrated under reduced pressure to an oil which was flashed though a plug of silica gel eluting with 10% Et_2O/pentane to yield 490 mg of a colorless oil. The oil was dissolved in 10 mL of acetone and 3 mL of water in a 50 mL round bottom flask followed by the addition of NMO (260 mg, 2.22 mmol) and a 2.5% solution of OsO_4 in *tert*-butyl alcohol (1.10 mL, 0.09 mmol). The reaction mixture was stirred for 1 h followed by the addition of a solution of $NaIO_4$ (650 mg, 3.0 mmol) in 7 mL of water. The mixture was stirred for 30 min during which a white precipitate formed. The solution was extracted (3 × 25 mL) with Et_2O. The organic phase was washed with 0.5 M $Na_2S_2O_3$ (2×) and brine, dried ($MgSO_4$), and concentrated under reduced pressure to an oil which was flashed though a plug of silica gel eluting with 15% Et_2O/pentane to yield 413 mg of a colorless oil. The oil was placed in a 25 mL round bottom flask, flushed with argon, and cooled to 0 °C. TMSCN (230 μL, 1.90 mmol) and 1 mg of KCN/18-crown-6 complex were added. The ice bath was removed and the reaction mixture stirred for 1.5 h followed by the addition of a solution of 20 mg of CSA in 15 mL of 2:1 acetone/DMP. The reaction mixture was stirred for 16 h, and then the reaction was quenched with 20 μL of Et_3N. The solution was concentrated under reduced pressure to an oil which was flashed though a plug of silica gel eluting with 10% EtOAc/hexanes to yield 373 mg (1.15 mmol, 74%) of a colorless oil:

IR (neat) 2991, 2936, 2871, 2252, 1462, 1381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (dd, J = 2.7, 11.7 Hz, 1 H), 4.26 (ddd, J = 2.4, 5.8, 11.7 Hz, 1 H), 4.03−3.90 (m, 3 H), 2.19−2.03 (m, 2 H), 1.69 (s, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.33 (s, 3 H), 1.54−1.21 (m, 8 H), 0.873 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 118.0, 99.9, 98.7; *C*H, 71.3, 65.8, 59.6, 40.9; *C*H_2, 60.7, 33.1, 32.9, 31.7, 25.3, 22.6; *C*H_3, 30.1 (2), 19.2, 18.8, 14.1; HRMS (CI) calcd for $C_{18}H_{35}N_2O_4$ 343.2597, found 343.2596 (M + NH_4). Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60. Found: C, 66.59; H, 9.46.

[1(4*R*,5*R*),1*S*,3*S*,5*R*,7*R*,9*S*,11*S*,13*S*,14*S*]-1-(2,2-Dimethyl-4-pentyl-1,3-dioxan-5-yl)-3,7,11-tricyano-1,3:5,7:9,11:13,-14-tetrakis-*O*-(1-methylethylidene)pentadecan-1,3,5,7,9,-11,13,14-octol (34). A solution of cyanohydrin acetonide **12** (87 mg, 0.267 mmol) in 200 μL of THF was added via syringe to 0.324 mmol of $LiNEt_2$ in 200 μL of THF under Ar at −78 °C. The reaction mixture was stirred for 1 h, and then the solution was warmed to −63 °C and stirred for another hour. A solution of iodide **27** (50 mg, 0.089 mmol) in 200 μL of THF was added to the reaction flask via syringe. The solution was warmed to −25 °C with a MeOH/ice bath and allowed to warm slowly to 10 °C over 14 h. The reaction was quenched with 20 mL of saturated NH_4Cl. The aqueous layer was extracted (3 × 25 mL) with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (3 × 5 cm) eluting with 20% *tert*-butyl methyl ether/hexanes to yield 35 mg of recovered cyanohydrin acetonide **12** and 45 mg (0.059 mmol, 66%) of a colorless oil: $[\alpha]^{26}_D$ = 23.2° (*c* = 1.80, $CHCl_3$); IR (neat) 2991, 2933, 2872, 2253, 1459, 1433, 1381 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.59−4.45 (m, 3 H), 4.04−3.99 (m, 2 H), 3.93 (dd, J = 3.1, 12.3 Hz, 1 H), 3.81 (dt, J = 3.1, 8.2 Hz, 1 H), 3.73 (dq, J = 5.8, 8.2 Hz, 1 H), 2.44 (dd, J = 12.0, 14.0 Hz, 1 H), 2.10−1.90 (m, 8 H), 1.77 (dd, J = 1.8, 13.4 Hz, 1 H), 1.72 (s, 6 H), 1.70 (s, 3 H), 1.61 (dd, J = 11.8, 13.9 Hz, 1 H), 1.59−1.28 (m, 10 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 6 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 1.28 (d, J = 5.8 Hz, 3 H), 0.883 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 122.1, 121.7, 121.0, 108.7, 101.5, 101.1(2), 98.5, 69.5, 68.3, 68.1; *C*H, 77.8, 76.9, 70.4, 64.7, 61.9(2), 39.8; *C*H_2, 59.8, 46.4, 46.3, 45.2, 40.0, 39.8, 38.1, 36.2, 31.7, 25.3, 22.6; *C*H_3, 31.0, 30.8, 30.7, 29.9, 27.3, 27.1, 21.6, 21.4, 21.2, 18.6, 17.0, 14.0; HRMS (FAB) calcd for $C_{41}H_{66}N_3O_{10}$ 760.4751, found 760.4760 (M + H). Anal. Calcd for $C_{41}H_{65}N_3O_{10}$: C, 64.80; H, 8.62. Found: C, 65.00; H, 8.82.

[1(4*R*,5*R*),1*S*,3*R*,5*S*,7*R*,9*S*,11*R*,13*S*,14*S*]-1-(2,2-Dimethyl-4-pentyl-1,3-dioxan-5-yl)-1,3:5,7:9,11:13,14-tetrakis-*O*-(1-methylethylidene)pentadecan-1,3,5,7,9,11,13,14-octol (10). A 25 mL round bottom flask equipped with a cold finger was cooled to −78 °C and charged with 5 mL of NH_3 and Li (6 mg, 0.86 mmol). A solution of pentaacetonide trinitrile **34** (30 mg, 0.039) in 1 mL of THF was transferred to the reaction flask via cannula. The reaction mixture was stirred for 1 h, and then the reaction was quenched with 200 mg of NH_4Cl. The mixture was allowed to warm to room temperature and the NH_3 allowed to evaporate. Water was then added and the solution extracted (3 × 10 mL) with CH_2Cl_2. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (2 × 4 cm) eluting with 30% EtOAc/hexanes to yield 21 mg (0.031 mmol, 79%) of a colorless oil: $[\alpha]^{26}_D$ = −19.2° (*c* = 1.05, $CHCl_3$); IR (neat) 2989, 2938, 2868, 1460, 1436, 1379 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.26 (ddd, J = 2.0, 6.0, 11.8 Hz, 1 H), 4.06−3.95 (m, 7 H), 3.89 (dd, J = 3.0, 12.1 Hz, 1 H), 3.68−3.66 (m, 2 H), 1.84−1.77 (m, 2 H), 1.73−1.10 (m, 19 H), 1.43 (s, 3 H), 1.42 (s, 6 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 6 H), 1.35 (s, 3 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.24 (d, J = 5.1 Hz, 3 H), 0.878 (t, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*, 107.7, 98.5, 98.4, 98.3, 98.2; *C*H, 79.0, 77.1, 71.6, 66.7, 66.6, 65.7, 65.3, 65.2, 65.1, 41.1; *C*H_2, 61.0, 42.7(2), 39.6, 37.4, 36.5, 34.8, 33.1, 31.9, 25.3, 22.6; *C*H_3, 30.3, 30.25, 30.23, 29.7, 27.3(2), 20.0, 19.9, 19.8, 18.9, 17.2, 14.1; HRMS (FAB) calcd for $C_{38}H_{69}O_{10}Na$ 707.4698, found 707.4710 (M + Na). Anal. Calcd for $C_{38}H_{68}O_{10}$: C, 67.01; H, 9.81. Found: C, 66.64; H, 10.01.

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