Total Synthesis of Filipin III

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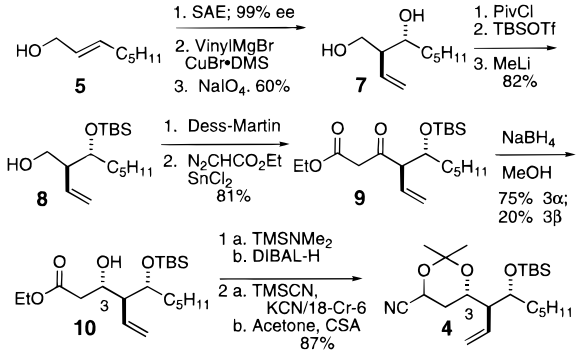
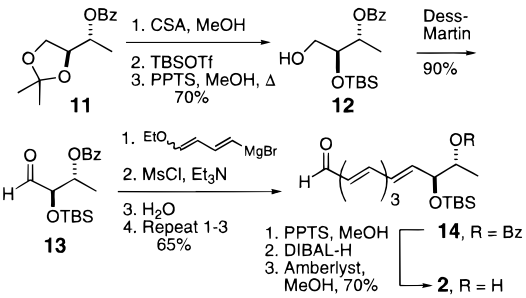
Filipin, a polyene macrolide antibiotic, was isolated from cell culture filtrates of *Streptomyces filipinensis*[1] and subsequently shown to be a mixture of four components: filipin I (4%), II (25%), III (53%), and IV (18%).[2] The structure of filipin III, the major component of the filipin complex, was assigned in a series of degradation studies.[3] Recently, we completed the structure determination of filipin III (**1**) by reporting its relative and absolute stereochemistry.[4] Filipin is structurally and functionally distinct from both the oxopolyene macrolides[5] and the more common mycosamine-containing polyene macrolides like amphotericin B.[6] Filipin is a membrane disrupter that selectively binds cholesterol.[7] It has found widespread use as a histochemical stain for cholesterol and has even been used to quantitate cholesterol in cell membranes.[8] Described herein is the first total synthesis of filipin III (**1**).[9]

The polyol segment of filipin was to be assembled using cyanohydrin acetonide **4**, which contained the pentane side chain and the C1 carboxylic acid masked as an alkene. The synthesis of cyanohydrin **4** (Scheme 1) began with the allylic alcohol **5**, which was obtained in 98% yield by Red-Al reduction of 2-octyn-1-ol. Sharpless asymmetric epoxidation of **5** provided the expected epoxide in near quantitative yield and 99% ee. Copper catalyzed nucleophilic opening of the epoxide with vinyl magnesium bromide gave a 2:1 mixture of regioisomers.[11] The minor, undesired 1,2-diol was oxidatively cleaved with periodate to facilitate purification of the desired 1,3-diol **7**. A three step protection−deprotection sequence provided mono-TBS protected diol **8**. Oxidation of **8** to the aldehyde with Dess−Martin reagent[12] followed by reaction with ethyl diazoacetate catalyzed by $SnCl_2$ using Roskamp's procedure[13] provided β-keto ester **9** in 81% yield. The C3 α-alcohol was most conveniently prepared by sodium borohydride reduction of the ketone, which gave 75% of the desired alcohol **10** and 20% of the β-isomer. Protection of the free alcohol of **10** with TMS followed by reduction of the ester to an aldehyde and cyanohydrin acetonide formation completed the synthesis of cyanohydrin acetonide **4**.

Scheme 1



Scheme 2



The polyene segment **2** was prepared as outlined in Scheme 2. Protected butane triol **11** was obtained conveniently on a large scale from L-ascorbic acid.[14] The acetonide was cleaved with CSA and MeOH, and then both alcohols were protected as TBS ethers. Selective hydrolysis of the primary TBS with PPTS in MeOH gave **12**, and oxidation with Dess−Martin reagent produced aldehyde **13**. Aldehyde **13** was treated with the Grignard reagent derived from 1-(tributylstannyl)-4-ethoxybutadiene (Wollenberg's reagent)[15] followed by mesylation and solvolysis[16] of the secondary alcohol to give the expected dienal. Repeating this sequence provided tetraenal **14** in 65% overall yield. Synthesis of the polyene was completed by removing the benzoate protecting group of **14** using a three step procedure: protection of the aldehyde as the dimethyl acetal, cleavage of the benzoate with DIBAL-H, and then regeneration of the aldehyde with Amberlyst acid resin in MeOH. Tetraenal **2** degraded quickly on standing under ambient light and was best prepared and used immediately.

The polyol segment of filipin III was assembled as outlined in Scheme 3. Cyanohydrin acetonide **15**, the key 1,3-diol synthon in our iterative polyol strategy, was prepared in ca. 94% ee as previously described.[16] Alkylation of cyanohydrin acetonide **15** with alkyl iodide **16**[17] provided **17** in good yield. Alkyl iodide **18** was formed in excellent yield from **17** under forcing Finkelstein conditions.[16] Alkylation of a second equiv of **15** with alkyl iodide **18** gave **19**, and subsequent conversion to the iodide **20** proceeded uneventfully. Deprotonation of cyanohydrin acetonide **4** and alkylation with iodide **20** gave the coupled product **21** in 70−80% yield.[18] Reductive decyanation with concurrent deprotection of the benzyl group gave

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(18) The addition of DMPU to this coupling reaction resulted in lower yield due to accelerated degradation of the anion **4**. The anion was stable in THF without DMPU at −30 °C, and prolonged alkylation times (16 h) at this temperature resulted in consistently high yields.

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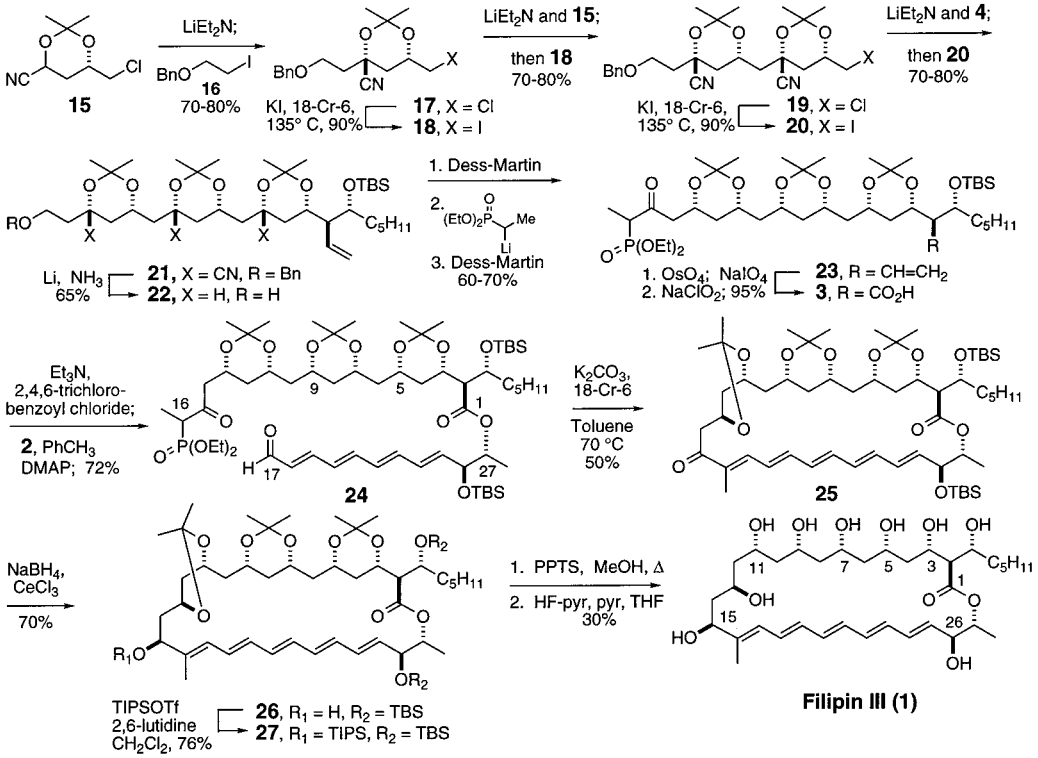
Scheme 3



polyol **22** as a single diastereomer.[19] Oxidation to the aldehyde, addition the lithium anion of ethyl diethylphosphonate, and oxidation of the resulting secondary alcohol provided β-keto phosphonate **23** as a 1:1 mixture of diastereomers. Stepwise oxidation of the olefin in **23** gave the carboxylic acid **3** in excellent yield and completed the synthesis of the polyol segment. This highly convergent and efficient strategy provided us with multigram quantities of the advanced intermediate **21**.

Union of the polyene segment **2** and the polyol segment **3** proved difficult due to steric congestion about the C1 carboxylic acid. After screening a variety of standard methods it was found that this coupling could be accomplished efficiently using Yamaguchi's esterification protocol.[20] The difficulty encountered in this apparently simple esterification reaction convinced us to focus on a Horner−Emmons cyclization route rather than the alternative macrolactonization. The formation of trisubstituted alkenes in macrocyclizations is uncommon.[21] We are aware of only one other ketophosphonate macrocyclization to form a trisubstituted alkene,[22] and base-induced elimination was not an issue in that case. Formation of the macrocycle from **24** was unsuccessful under the Masamune conditions (LiCl and DBU).[23] The macrocyclization did proceed in reasonable yield when the reaction was initiated with K_2CO_3 and 18-crown-6 in warm toluene.[24] As predicted, the C15 ketone of **25** was reduced to the C15-(*S*) alcohol **26** with 3:1 selectivity.[25] All that remained was the deprotection of macrocycle **26**.

Omura classifies filipin III as a methylpentaene macrolide, and the C16 methyl group confers increased acid lability when compared with other polyene macrolide antibiotics.[6] Both the acetonide and TBS protecting groups in **26** are acid labile, but direct deprotection under acidic conditions was unsuccessful due to competitive decomposition. The acid lability of **26** was presumably associated with solvolysis of the C15 or C26 allylic alcohols. Similar mixtures of degradation products were generated by exposing **26** or natural filipin III to acidic conditions. Alcohols protected as silyl ethers can have reduced propensity toward elimination. Thus, the TIPS protected derivative **27** was prepared and exposed to PPTS in warm methanol until most of the acetonides were cleaved as judged by TLC. These conditions also resulted in incomplete cleavage of the TBS groups. Final deprotection of the mixture by treatment with HF-pyridine provided synthetic filipin III. Synthetic and natural filipin III were identical by ^{1}H NMR and HPLC.

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Supporting Information Available: Complete spectral data for compounds **2**−**14**, **17**−**27**, and filipin III and modeling of **25** (10 pages). See any current masthead page for ordering and Internet access instructions.

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(25) The major product of the reduction was predicted based on the most accessible face of the macrocycle. The macrolide **25** was modeled using a Monte Carlo search in Macromodel, and the minimum energy conformation is illustrated in the Supporting Information. Ratio was determined by NMR analysis of the C15 acetate prepared by treating **26** with Ac_2O and DMAP in THF. The major, desired diastereomer was isolated by flash chromatography.