Total Synthesis of (+)-Mycotrienol and (+)-Mycotrienin I

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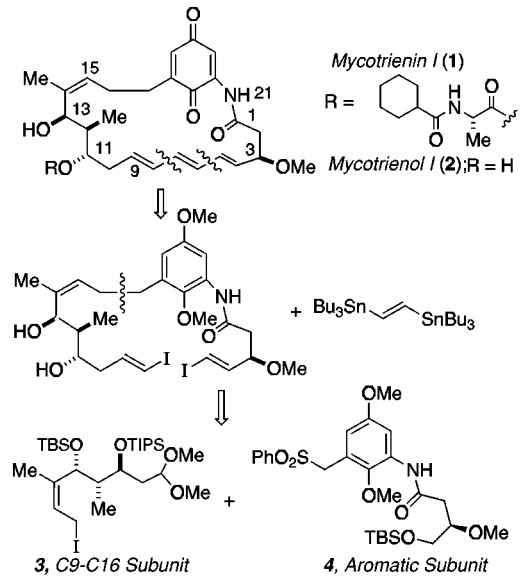
In 1985, Umezawa and co-workers reported the isolation of five novel ansamycin antibiotics, trienomycins A−E, from the culture broth of *Streptomyces sp.* No. 83-16.[1] These molecules exhibited strong cytotoxicity in vitro against HeLa S_3 cells.[2] Their relative and absolute stereochemistry has been determined by Smith through careful degradative and spectroscopic methods.[3] The (+)-mycotrienins I and II, which have previously been isolated from the fermentation broth of *Streptomyces rishiriensis T-23*, have displayed potent antifungal activity.[4] Stereochemical correlation studies have extended the absolute stereochemical assignments of the trienomycins to the (+)-mycotrienins I and II, and therefore to the mycotrienols (Scheme 1).[5] To date, Smith and co-workers have reported the only total synthesis of members of this class of compounds, specifically the synthesis of trienomycins A and F.[6]

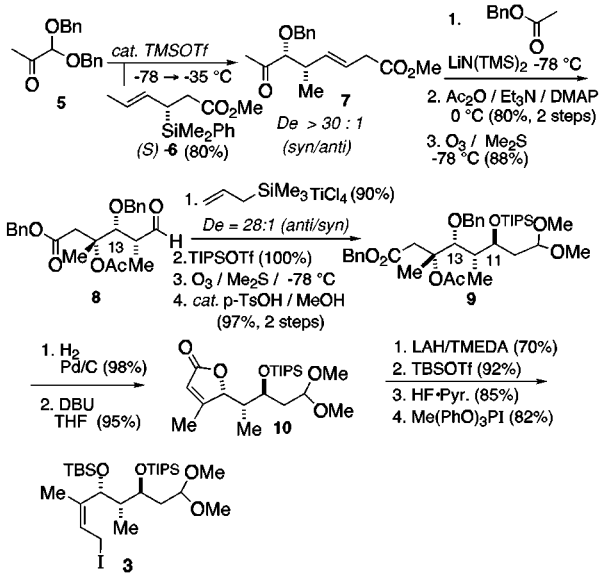
Our retrosynthetic plan for the synthesis of members of this class of antitumor antibiotics, illustrated in Scheme 1, allows for a high degree of convergency and is highlighted by a tandem inter/intramolecular Stille coupling to effect macrocyclization. Analysis of the mycotrienol skeleton reveals two distinct subunits: (i) the C9−C16 polypropionate subunit **3** whose stereochemical issues are readily accessible through chiral allylsilane bond construction methodology;[7] (ii) the aromatic subunit **4** whose single stereocenter at C3 can also be addressed using a chiral (*E*)-crotylsilane reagent.

The construction of the C9−C16 subunit was initiated by an asymmetric crotylation between the α-keto-dibenzylacetal **5** and silane reagent (*S*)-**6** to establish the C12−C13 centers (Scheme 2). This first addition proceeds through an antiperiplanar transition state where the observed stereochemistry is consistent with an *anti*-S_E' mode of addition. Homologation of the homoallylic ether **7** by treatment with the ester enolate of benzyl acetate gave a β-tertiary alcohol which was immediately converted to the tertiary acetate under DMAP-catalyzed acetylation conditions. Oxidative cleavage of the (*E*)-olefin by ozonolysis furnished aldehyde **8**. This was followed by a chelation controlled asymmetric allylsilane addition reaction to install the C11 hydroxyl stereocenter (diastereoselection = 28:1 *anti*/*syn*). The 1,3-anti relationship is believed to arise from nucleophilic addition to a titanium chelate between the C13 benzyloxy group and the aldehyde carbonyl.[8] Elaboration of the C14−C15 (*Z*)-double bond was initiated by cleavage of the terminal olefin to give the β-(silyloxy) aldehyde which was masked as the dimethyl acetal **9**. Cleavage of the benzyl groups via hydrogenation and simultaneous cyclization of the derived hydroxy acid gives the lactone, which upon elimination of the tertiary β-acetoxy group with DBU gave the α,β-unsaturated lactone **10**. Subsequently, the

Scheme 1



Scheme 2



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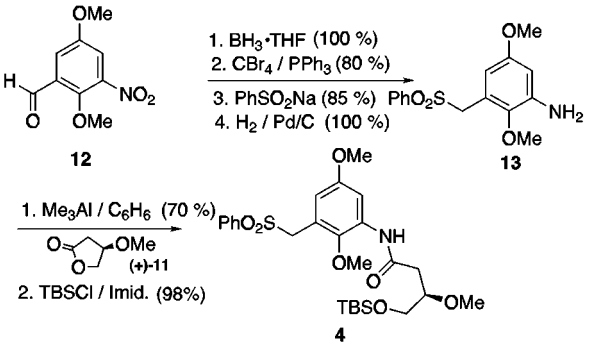
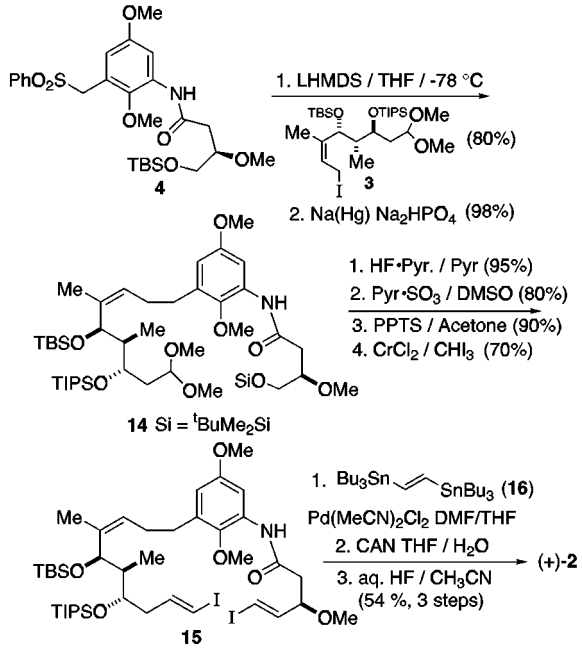
Scheme 3



Scheme 4

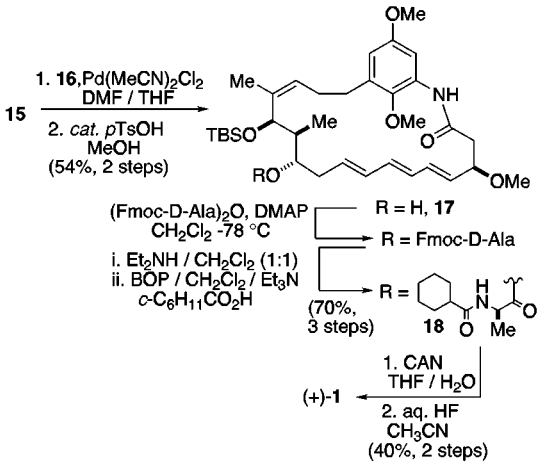


lactone was reductively opened using LAH to give the (*Z*)-olefinic diol. Protection of the primary and secondary hydroxyl groups as their TBS ethers and then selective conversion to the allylic iodide completes the construction of **2**.

The aromatic core was constructed from 2,5-dimethoxy-3-nitrobenzaldehyde **12**[9] (Scheme 3). This aromatic substitution pattern was chosen for its synthon equivalency and ease of conversion to the amidobenzoquinone system of mycotrienol. Borane reduction of the aldehyde, conversion to the benzylic bromide, displacement with sodium benzenesulfinate, and reduction of the nitro group furnished benzylic sulfone **13**. Completion of subunit **4** was achieved by Weinreb-type amidation[10] of the derived aniline with lactone **11**[11] and protection of the primary hydroxyl as its TBS ether.

Coupling of the subunits was accomplished by deprotonation of sulfone **4** with LHMDS to generate a stable lithium dianion, which was efficiently alkylated at the benzylic position by the allylic iodide **3** (Scheme 4);

Scheme 5



reductive desulfonylation gives adduct **14**. At this stage, we initiated construction of the key bis-(*E*,*E*)-vinyl iodide for macrocyclization. Selective deprotection of the primary TBS ether was followed by a Parikh−Doering oxidation[12] of the derived primary alcohol to give the *N*-acylhemiaminal. Hydrolysis of the dimethyl acetal and homologation using the Takai protocol[13] furnished the bis-(*E*,*E*)-vinyl iodide **15** as the key cyclization substrate. This set the stage for the crucial Stille-type "stitching" macrocyclization[14] of **15** with the missing two-carbon enedistannane **16**[15] (C6−C7) to give the (*E*,*E*,*E*)-triene. Subsequent oxidation of the aromatic core with CAN and removal of the silicon protecting groups with aqueous HF furnished synthetic mycotrienol (**2**). Alternatively, selective deprotection of the TIPS group of the (*E*,*E*,*E*)-triene, installation of the amino acid side chain according to literature precedent,[16] and desilylation gave (+)-mycotrienin I (**1**) (Scheme 5). Both **1** and **2** were identical in all respects with the corresponding natural products (^1H and ^{13}C NMR, IR, HRMS, optical rotation, and TLC in two solvent systems).[4]

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Supporting Information Available: General experimental data as well as spectral data for all products (92 pages).

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(9) For the preparation of **12** as well as its conversion to the quinone core see: Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587−10588.

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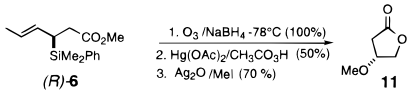
(11) Ozonolysis of silane (*R*)-**6** and *in situ* reduction of the derived silyl aldehyde afforded the β-silyl-lactone which was subjected to silyl to hydroxyl interconversion (Fleming, I. *Chemtracts Org. Chem.* **9**, 1−64) and methylation (Lardon, A.; Reichstein, T. *Helv. Chim. Acta* **1949**, *32*, 2003) to afford lactone **11** (see Supporting Information for experimental details).



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