Total Synthesis of the Polyene Macrolide Roflamycoin

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Roflamycoin is an unusual member of the polyene macrolide antibiotics as it is the only oxopolyene macrolide that has been shown to form well-defined ion channels.[1] Most oxopolyene macrolides are simple membrane disrupters, and the other well-characterized ion-channel forming polyenes belong to the mycosamine-containing polyene macrolide antibiotics like nystatin and amphotericin B.[2] Roflamycoin was isolated from *Streptomyces roseoflavus* as an antifungal agent and initially named flavomycoin.[3] The flat structure was reported in 1981,[4] and the absolute configuration was determined in 1994 using the ^{13}C acetonide method.[5] Prior to the stereochemical elucidation, both Lipshutz[6] and Rychnovsky[7] had developed partial syntheses of roflamycoin stereoisomers, but no complete synthesis of roflamycoin or any stereoisomer has been described. Reported herein is the first total synthesis of natural roflamycoin.

Roflamycoin presents several challenges to synthetic chemists. In common with other oxopolyene macrolides like mycoticin[8] and roxaticin,[9] roflamycoin contains a stereochemically complex polyol chain and a polyene segment that is sensitive both to light and to many chemical reagents. Unlike these simpler oxopolyenes, roflamycoin contains a hemiacetal that is transformed to a spiroacetal *irreversibly* on treatment with mild acid (Figure 1).[5] All of the synthetic work in this area makes use of acid labile protecting groups to block the many hydroxyl groups in the target, so a late-stage acid-catalyzed deprotection would appear to be unavoidable.[10] A two-stage deprotection strategy was developed for the synthesis of roflamycoin in which the hydroxyl groups were to be deprotected in the penultimate step and the ketone would be liberated in the final step by neutral periodate cleavage of a 1,2-diol. Model studies were successful, and this deprotection strategy was incorporated into the synthetic plan for roflamycoin.

Convergent synthesis of the protected roflamycoin polyol **15** used cyanohydrin acetonide couplings[11] and optically pure C_2-symmetric electrophiles[12] previously developed in our group.

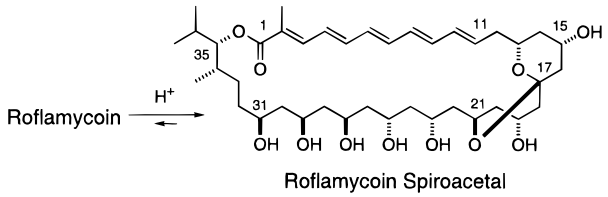
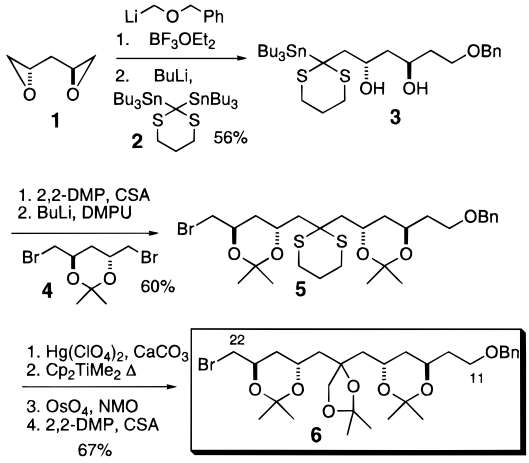
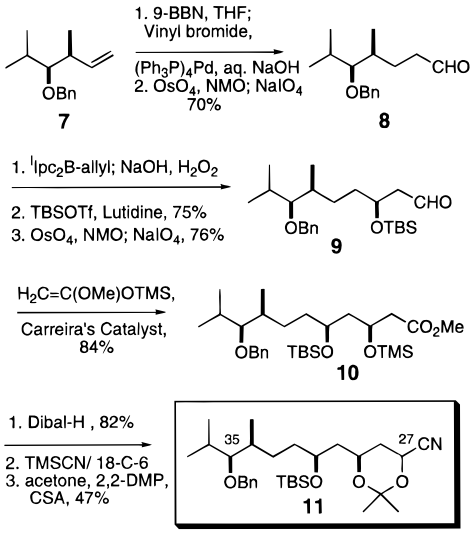


Figure 1. Roflamycoin spiroacetal formed irreversibly on treatment of natural roflamycoin with mild acid.

Scheme 1



Scheme 2



The major segments of roflamycoin, compounds **6** and **11**, were prepared as outlined in Schemes 1 and 2. The C11−C22 segment **6** was prepared by joining diepoxide **1** and dibromide **4** with a dithiane unit (Scheme 1). To diepoxide **1**, prepared by Noyori hydrogenation of 1,5-dichloro-2,4-pentandione,[12] was added (benzyloxy)methyllithium.[13] Monoaddition predominates when $BF_3{\cdot}OEt_2$ was used as a promoter.[12,14] The 2,2-bis-(tributyltin)dithiane (**2**)[15] was transmetallated with BuLi and added to the hydroxy oxirane to give 56% yield of the *anti*-diol **3**. Acetonide protection, transmetallation, and alkylation with excess dibromide **4** gave dithiane **5** in 60% overall yield. The stannylated dithiane was required to facilitate the second metallation reaction.[6b,15] Compound **5** has all of the carbons

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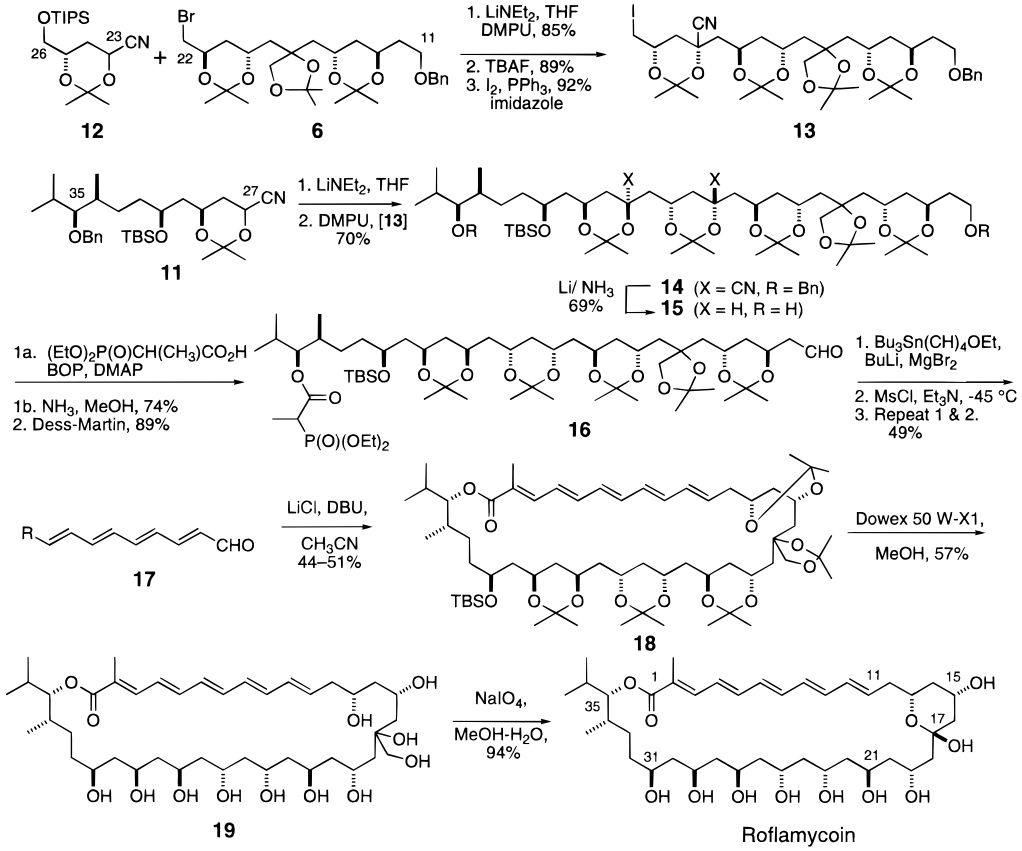
Scheme 3



of the C11−C22 fragment, but the dithiane was not an appropriate protecting group for the C17 ketone. Dithiane **5** was converted to the protected 1,2-diol **6** by deprotection, olefination,[16] dihydroxylation, and protection. Segment **6** was generated as a 2:1 mixture of stereoisomers, both of which would be viable precursors to roflamycoin. To facilitate NMR analysis, the mixture was separated and the major isomer was used in subsequent steps.

The C27−C37 segment was prepared as outlined in Scheme 2. Benzyl ether **7** was prepared by enantioselective crotylborane addition to isobutyraldehyde followed by benzylation.[17] A Suzuki homologation[18] and oxidation gave aldehyde **8** that was coupled with Brown's Ipc_2B-allyl reagent.[19] Protection and oxidation gave aldehyde **9**. The final relevant stereogenic center in **11** could be introduced by another allylborane addition, but it was more efficient to use Carreira's enantioselective aldol reaction[20] because it led directly to the β-silyloxy ester **10**. DIBAL-H reduction, cyanohydrin formation, and acetonide protection gave the C27−C37 segment **11** as a mixture of cyanohydrin stereoisomers that was used without separation.

Roflamycoin was assembled as illustrated in Scheme 3. Alkylation of bromide **6** with 2.5 equiv of the anion of nitrile **12** gave the alkylated nitrile in 85% yield. Compound **12**[11] can be used in the iterative construction of polyol chains by alkylation followed by conversion of the TIPS-protected alcohol to an alkyl iodide.[21] Deprotection of the TIPS alcohol and alkyl iodide formation[22] gave **13** in excellent yield. Alkylation of the anion of the C27−C35 segment **11** with iodide **13** gave **14** in 70% yield based on **13**. Reductive decyanation gave the protected roflamycoin polyol **15** as a single stereoisomer in 69% yield. Both nitriles were replaced by axial hydrogen atoms, and the benzyl groups were removed in this single step. Diol **15** was next converted into the macrocyclic pentaene **18**. Acylation of both alcohols with diethyl phosphonopropionic acid, followed by selective hydrolysis of the primary ester and Dess−Martin oxidation gave aldehyde **16**. Aldehyde **16** was converted to a tetraenal by addition of the Grignard reagent derived from Wollenberg's 1-(tributylstannyl)-4-ethoxybutadiene,[23] followed by mesylation and solvolysis of the resulting secondary alcohol.[24] Repeating the Wollenberg homologation sequence[23] gave tetraenal **17**, and intramolecular phosphonate−Wittig cyclization gave the pentaene **18** in 44−51% yield as a single alkene isomer.[25] The key deprotection steps proceeded uneventfully. Acid-catalyzed deprotection gave the polyol **19**, and periodate cleavage of the 1,2-diol gave roflamycoin. Synthetic and natural roflamycoin were found to be identical by TLC mobility and by ^{1}H NMR, FAB MS, UV, and reversed-phase HPLC analysis.

The longest linear sequence in the synthesis of roflamycoin is 24 steps starting from isobutyraldehyde. This highly convergent route to natural roflamycoin is well-suited to the preparation of stereoisomers and other analogues.[21]

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Supporting Information Available: Experimental details for the preparation of **6** and **11**, the combination of **6**, **11**, and **12** to make **15**, and the final conversion of **15** to roflamycoin (26 pages). See any current masthead page for ordering and Internet access instructions.

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