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Total Synthesis of the Polyene Macrolide Roxaticin

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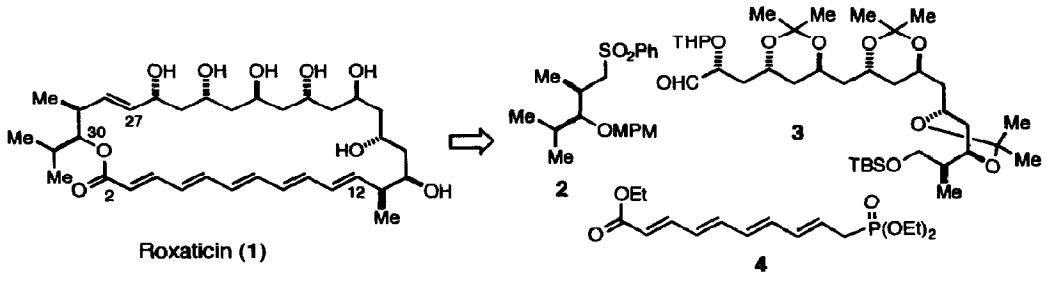
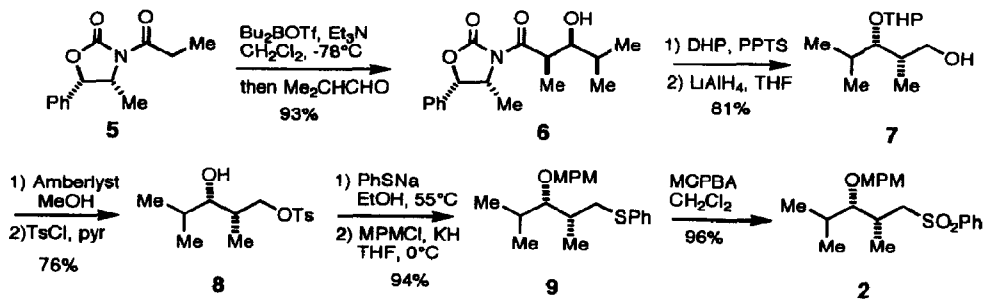
Abstract: Roxaticin has been synthesized in a convergent manner. The polyol and polyene fragments were coupled by Horner-Emmons reaction and the cyclization was achieved by macrolactonization.

Polyene macrolide antibiotics are an important class of clinically valuable natural products and used systemic fungal infections.[1] The unique structural and stereochemical features of polyene macrolides have aroused the interest of synthetic chemists and a variety of synthetic method has been developed.[2] Several members of this class have been synthesized in the past few years.[3]

Roxaticin (1) is an oxo pentaene macrolide[4] isolated from an unidentified streptomycete strain similar to *Streptomyces ruber* and showed antifungal activity.[5] The structure was determined by an X-ray crystal analysis of the roxaticin heptaacetate, which indicated the presence of an alternating polyol chain containing both *syn*- and *anti*-1,3-diol units.[5] We report here the convergent total synthesis of roxaticin in the natural form.[6]

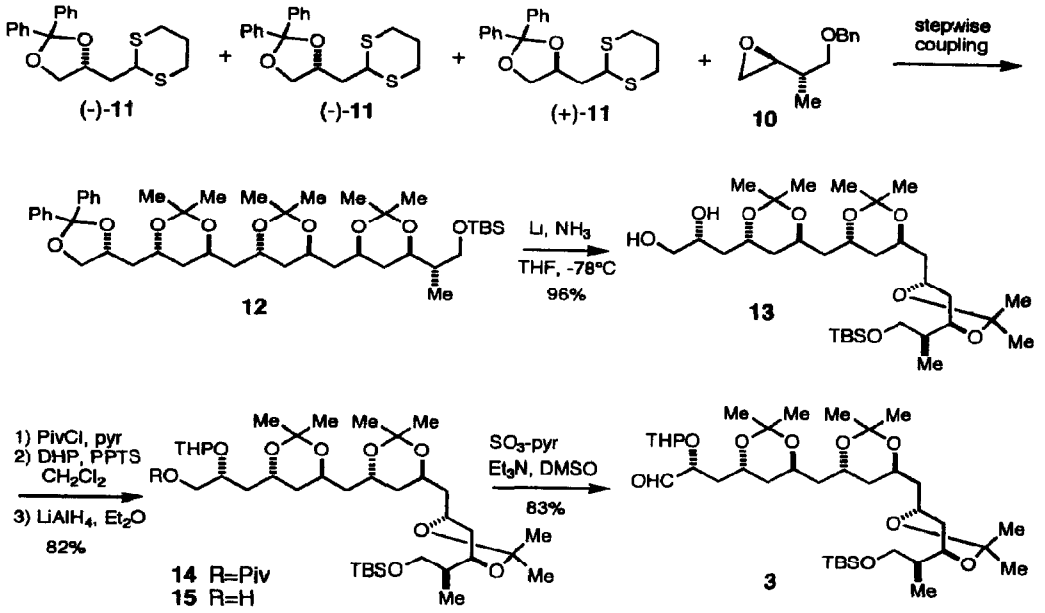


The C_{12}-C_{30} polyol chain of roxaticin can be prepared from two fragments **2** and **3** and the light-sensitive polyene portion must be introduced in the final stages of the synthesis. This approach would involve the formation of the macrocyclic ring by lactonization. The fragment **2** was prepared by the Evans' asymmetric aldol method[7] with isobutyraldehyde. The aldol **6**

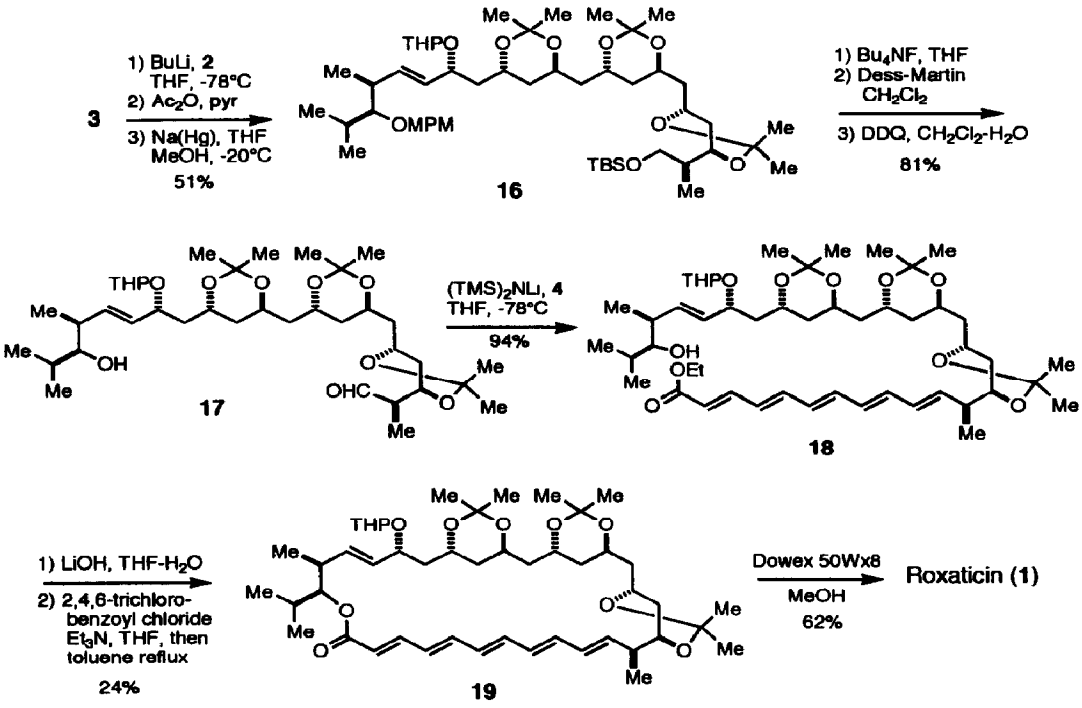


was converted to tosylate **8** in four steps (62%), reaction of which with sodium benzenethiolate followed by protection and oxidation gave sulfone **2** in 90% overall yield.

The C_{12}-C_{27} fragment **3** was prepared in enantiomerically pure form using a four-carbon chain extension strategy.[8] Four-carbon unit derivatives **10**, (+)-**11**, and (-)-**11** were coupled using lithiodithiane alkylation and 1,3-asymmetric reduction, which allowed for the stereoselective construction of 1,3-polyol chain **12**.[9] Treatment of **12** with lithium in ammonia resulted in the cleavage of the diphenylmethylene ketal. Selective protection of the resultant diol **13** with pivaloyl chloride followed by dihydropyran gave **14** as an inseparable 1:1 mixture of diastereomers of THP ether and the reduction with $LiAlH_4$ yielded **15** in 82% overall yield.



At this stage the mixture was separated by flash chromatography and the less polar isomer was used in the following sequences to simplify the spectral analysis of synthetic intermediates. Oxidation of the alcohol **15** with SO_3-pyridine produced the desired fragment **3** in 83% yield. The Julia coupling reaction[10] of **3** with the anion generated from **2** with n-BuLi proceeded to produce a mixture of ß-hydroxysulfones which was acetylated, and the product was subjected to reductive elimination with sodium amalgam. The coupled product **16** was obtained in 51% overall yield with excellent selectivity. In a model study, a pentaene ester was found to be intolerable under DDQ oxidation conditions;[11] giving a complex mixture of products, and therefore, **16** was converted to hydroxy aldehyde **17** in 81% overall yield by desilylation with n-Bu_4NF followed by Dess-Martin oxidation[12] and DDQ oxidation.



According to our synthetic plan, the polyol fragment **17** was coupled with the lithium salt of tetraene phosphonate **4**, prepared by an improved method of Hanessian's protocol,[13] to give polyene ester **18** in 94% yield. Macrolactonization of the seco acid obtained by hydrolysis of **18** was achieved using the Yamaguchi method[14] modified by Yonemitsu[15] to obtain lactone **19** in 24% yield. Final deprotection with acid-resin in methanol followed by purification by preparative reverse-phase TLC afforded synthetic roxaticin (**1**), $[\alpha]_D$ +7.14° (c=0.28, dioxane), [lit.[5] $[\alpha]_D$ +8.63° (c=0.15, dioxane)]. The ^1H NMR spectrum and TLC mobility were identical with those reported for natural roxaticin.[16]

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16. The ^{13}C NMR data are not reported in the references 5 and 6. ^{13}C NMR (100MHz, DMSO-d_6) of synthetic roxaticin, δ: 166.1, 144.6, 141.1, 139.2, 137.6, 135.7, 133.1, 131.0, 130.5, 129.4, 129.1, 128.7, 120.2, 79.3, 71.0, 69.8, 67.7, 64.9, 64.2, 62.9, 62.4, 47.3, 46.6 (two carbons), 44.4, 44.3, 42.6, 40.9, 35.7, 28.8, 19.6, 18.7, 13.7, 10.8.

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