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Studies on the Total Synthesis of the Macrolide Antitumor Agent Rhizoxin. 1. Synthesis of the C3-C13 Segment.

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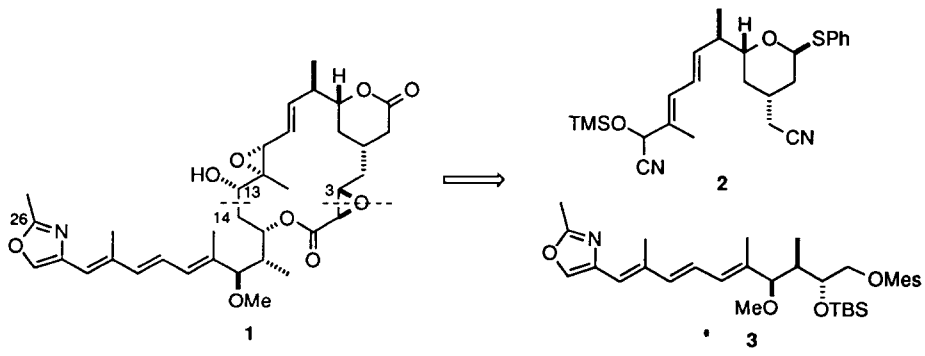
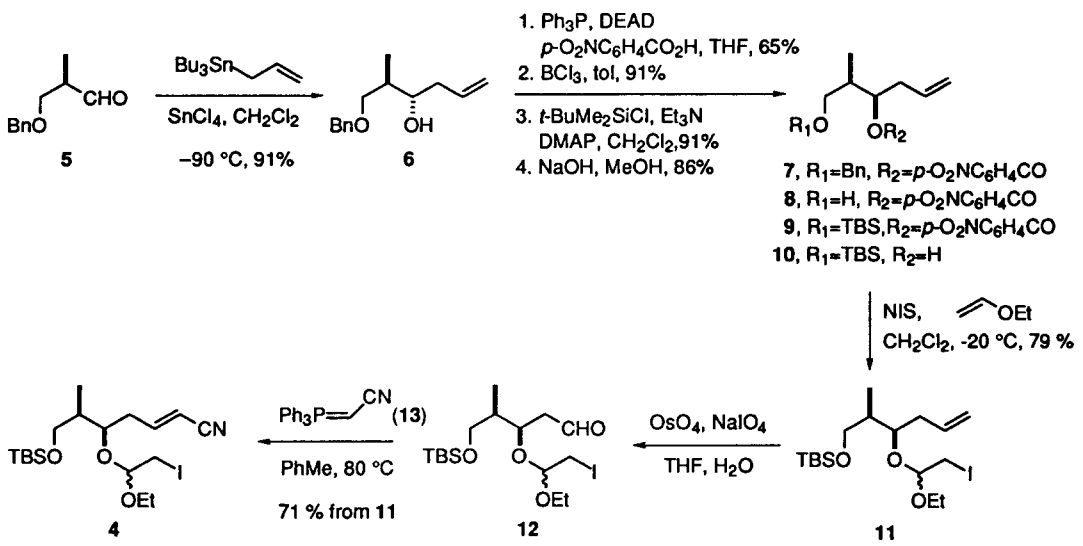
Abstract: An asymmetric synthesis of the C3-C13 segment of rhizoxin is described in which the relative stereochemistry of C7 and C8 is established through a chelation-controlled allylation followed by Mitsunobu inversion, and the pyran ring is constructed by a photochemically initiated 6-*exo* radical cyclization. © 1997 Elsevier Science Ltd.

Rhizoxin (**1**), a 16-membered macrolide isolated from *Rhizopus chinensis*,[1] exhibits antimicrobial and antifungal activity as well as potent *in vitro* cytotoxicity and *in vivo* antitumor activity.[2] Its impressive antitumor activity has enabled rhizoxin to progress to phase II clinical trials for the treatment of lung and breast cancers. The remarkable biological properties of rhizoxin along with its unique structure[3] have stimulated much interest in its synthesis, resulting in one total synthesis[4] and several related synthetic studies.[5]

Our approach to rhizoxin features a convergent strategy that combines the two major fragments **2** and **3**, each prepared from readily available and optically pure starting materials. Herein we describe the asymmetric synthesis of the protected cyanohydrin **2**, representing the C3-C13 segment of the macrolide, using a stereocontrolled 6-*exo* radical cyclization of iodoacetal **4** for construction of the pyran. In the accompanying Letter,[6] we report the synthesis of the C14-C26 subunit of rhizoxin.



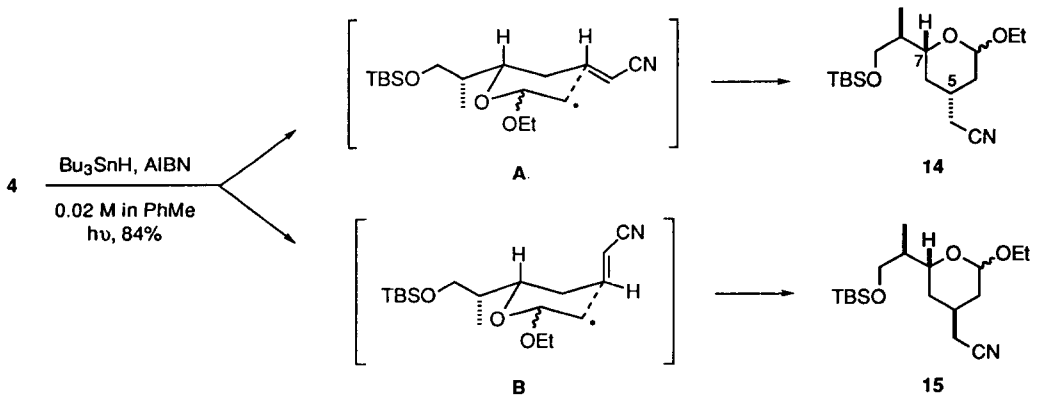
Synthesis of the radical cyclization precursor **4** commenced with chelation-controlled allylation[7] of aldehyde **5**[8] to furnish homoallylic alcohol **6** (*anti*:*syn* >20:1) (Scheme 1). Alcohol **6** was subjected to Mitsunobu inversion,[9] using *p*-nitrobenzoic acid as the nucleophile, to yield *syn* ester **7**. The benzyl ether was cleaved from **7** with boron trichloride,[10] and primary alcohol **8** was reprotected as its *t*-butyldimethyl-



Scheme 1

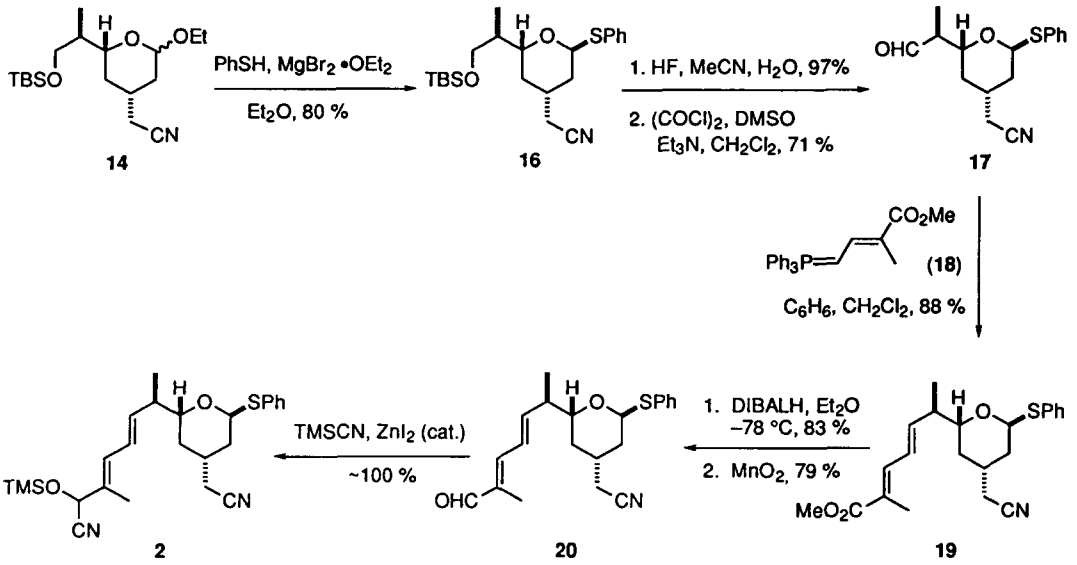
silyl ether **9**.[11] Hydrolysis of the *p*-nitrobenzoate ester of **9** afforded **10**, which was treated with N-iodosuccinimide and ethyl vinyl ether to give iodoacetal **11** as a 1:1 mixture of stereoisomers. Oxidative cleavage of the terminal olefin yielded aldehyde **12**, and a Wittig reaction with phosphorane **13** then furnished the α,β-unsaturated nitrile **4**.

Several reaction conditions were investigated for initiating the radical cyclization of **4**. Thus, when iodoacetal **4** was treated with tri-*n*-butyltin hydride and AIBN in hot toluene (80 °C), a pair of cyclic products **14** and **15** was obtained in 91% yield and a 1.5:1 ratio, respectively.[12] These pyrans were separated by flash chromatography, and **14** was shown by NMR studies on the derived δ-lactone to possess *cis* configuration of the alkyl chains.[13] The major product **14** presumably arises from the thermodynamically favored chair-like transition state **A** in which the alkene adopts an equatorial orientation, whereas the minor epimer **15** is formed via transition state **B** in which the olefin is axially oriented. It was reasoned that cyclization of **4** at a lower



reaction temperature would favor transition state **A** and therefore would lead to a higher proportion of the desired pyran **14**. In fact, when **4** was exposed to a sun lamp in the presence AIBN the ratio of cyclization products **14**:**15** increased to 4.2:1, respectively, although the yield decreased to 84%.

Before continuing the synthesis towards **2**, it was found convenient to convert the acid-labile ethyl acetal of **14** to a more robust mixed thioacetal. This was achieved by the action of thiophenol and magnesium bromide etherate (Scheme 2)[14] and gave **16** as a single anomer.[15] Removal of the *t*-butyldimethylsilyl ether from **16**, followed by oxidation of the primary alcohol under Swern conditions,[16] afforded aldehyde **17**. The dienyl chain was installed in a single operation by reaction of **17** with the stable phosphorane **18**,[17] which gave the (*E*,*E*)-dienyl ester **19** in high yield. Selective reduction of the ester of **19** in the presence of the nitrile was achieved with DIBALH in ether at –78 °C, and oxidation of the resultant allylic alcohol with manganese dioxide produced aldehyde **20**. The latter was converted to the TMS-protected cyanohydrin **2**[18] by exposure of **20** to TMSCN in the presence of a catalytic amount of zinc iodide.[19]



Scheme 2

In summary, we have achieved the synthesis of a major segment of rhizoxin (**1**) with excellent stereocontrol using a radical cyclization to construct the pyran moiety. This sequence provides an efficient route to the C3-C13 portion of the macrolide in a form appropriately functionalized for its coupling to a substance representing the C14-C26 segment.

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