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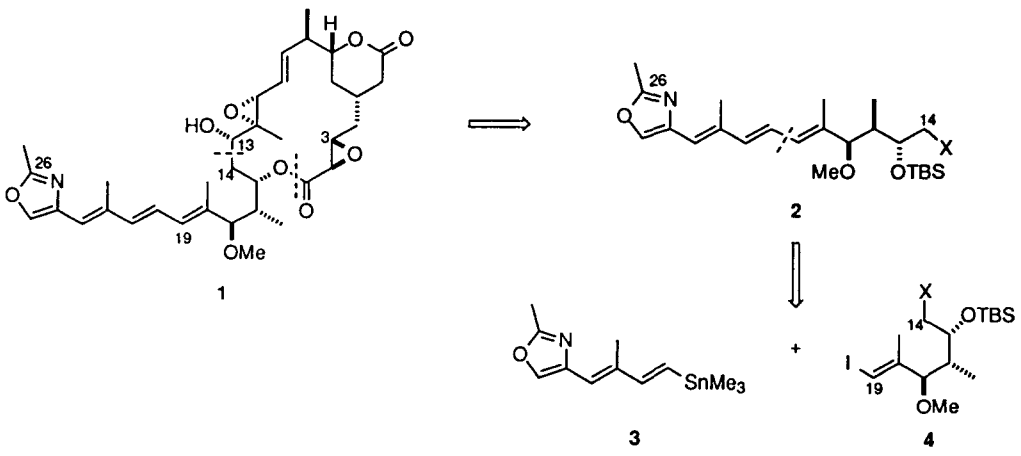
Studies on the Total Synthesis of the Macrolide Antitumor Agent Rhizoxin. 2. Synthesis of the C14-C26 Segment.

James D. White,* Mark A. Holoboski, and Neal J. Green

Department of Chemistry, Oregon State University, Corvallis, OR 97331-4003, U.S.A.

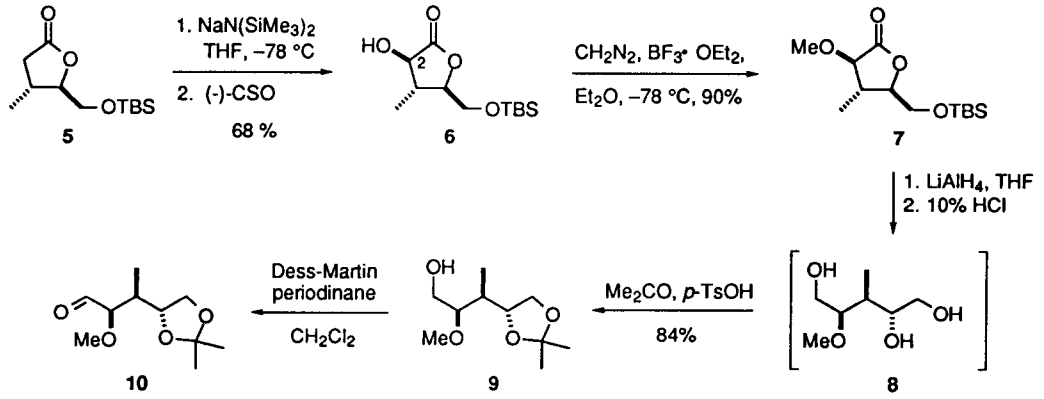
Abstract: An asymmetric synthesis of the C14-C26 segment of rhizoxin is described in which the three stereogenic centers are derived from a γ-lactone; stannylcupration-methylation of a terminal alkyne is used to generate an (*E*)-iodoalkene for Stille coupling with a dienylstannane that produces the conjugated (*E,E,E*)-triene unit of rhizoxin. © 1997 Elsevier Science Ltd.

The promising antitumor agent rhizoxin (**1**)[1] has been the subject of much synthetic interest.[2-4] In the preceding Letter we outlined a convergent approach to the synthesis of this 16-membered macrolide and we described a stereocontrolled route to a segment representing C3-C13 of **1**.[5] Herein, we report an efficient synthesis of the C14-C26 portion of rhizoxin, to which the previously prepared subunit will be attached. Construction of the trienyloxazole moiety **2** was envisioned through Stille coupling[6] of the vinyltin species **3** with vinyl iodide **4**, a strategy for which good precedent already exists.[3]

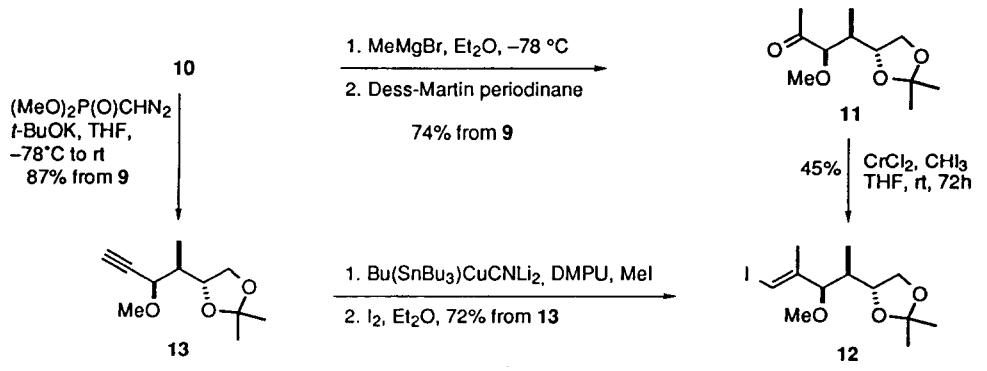


Synthesis of the C14-C19 subunit **4** began from the known γ-lactone **5**,[7] readily prepared from D-glutamic acid.[8] The functionality and stereochemistry present in **5** makes this template ideally suited to construction of the three contiguous asymmetric centers of **4** by stereocontrolled hydroxylation. Thus,

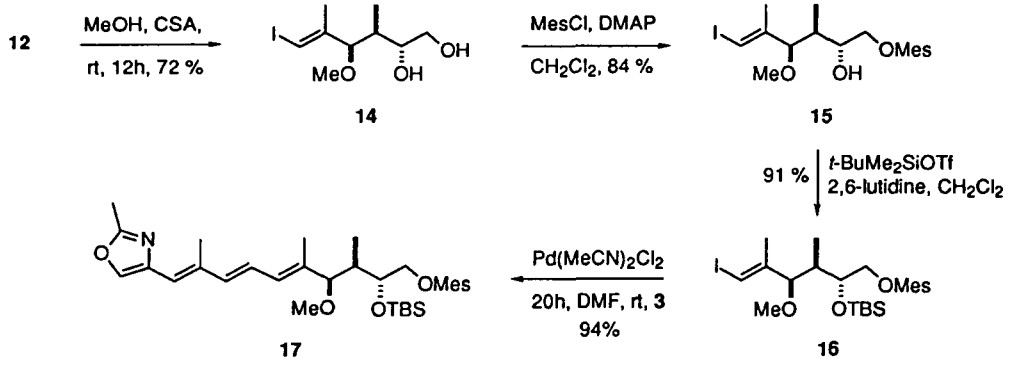
exposure of the *sodium* enolate of **5** to (1*R*)-(-)-(10-camphorsulfonyl)oxaziridine (CSO)[9] afforded (2*R*) alcohol **6** in 30:1 excess over the (2*S*) stereoisomer.[10] Methylation of this sterically hindered alcohol proved difficult but was accomplished by successive addition of diazomethane to **6** in the presence of boron trifluoride. The resultant lactone **7** was reduced to the water-soluble triol **8** which was converted without purification to its acetonide **9**. The latter underwent oxidation with Dess-Martin periodinane[11] to aldehyde **10**.



Our initial plan for elaboration of the trisubstituted alkene moiety of **4** required ketone **11**, which was readily prepared by a Grignard reaction of **10** with methylmagnesium bromide, followed by Dess-Martin oxidation of the resulting secondary alcohol. However, a Takai reaction[12] of **11** with iodoform in the presence of chromous chloride furnished a low yield of iodoalkenes as a 2:1 mixture of **12** and its (*Z*) isomer, respectively. Fortunately, an improved and completely stereoselective pathway to **12** was realized via the alkyne **13**, prepared from **10** by reaction with dimethyl diazomethylphosphonate.[13] Although zirconium-catalyzed carboalumination-iodination of **13** under Negishi's conditions[14] was unsuccessful, stannylcupration-methylation[15] of this alkyne along lines reported by Kocienski,[16] followed by iodination, furnished pure **12** in good yield.



Selective functionalization of the primary alcohol terminus of diol **14**, obtained after acidic methanolysis of **12**, could not be accomplished by tosylation. However, this selectivity was readily achieved by reaction of **14** with the more sterically demanding mesitylenesulfonyl (Mes) chloride, and the resultant alcohol **15** was protected as its silyl ether **16**. Stille coupling of **16** with the known stannane **3**,[3] prepared by reaction of the corresponding iodoalkene with $(Me_3Sn)_2$ in the presence of $Pd(PPh_3)_2Cl_2$ as catalyst, afforded the *(E,E,E)* triene **17**[17] in excellent yield. This material is now available in quantity for coupling with the C3-C13 portion of rhizoxin already in hand.



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10. By contrast, the potassium enolate of **5** with CSO gave a (2*R*:2*S*) ratio of 14:1. Poor stereoselectivity was observed in hydroxylation of **5** with MoOPH. Assignment of configuration to **6** was made from the coupling constant (10.2 Hz) between H2 and H3.
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17. Spectral data for compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (s, 1H), 6.96 (s, 2H), 6.59 (dd, J = 10.8, 15 Hz, 1H), 6.37 (d, J = 15.3 Hz, 1H), 6.30 (s, 1H), 6.03 (d, J = 10.6 Hz, 1H), 3.85-4.05 (m, 2H), 3.80 (m, 1H), 3.50 (m, 1H), 3.16 (s, 3H), 2.61 (s, 6H), 2.53 (s, 3H), 2.32 (s, 3H), 2.15 (s, 3H), 1.87 (m, 1H), 1.73 (s, 3H), 0.88 (m, 12H), 0.05 (s, 3H), 0.0 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.93, 143.09, 139.93, 138.88, 137.44, 137.01, 135.93, 135.71, 131.70, 130.85, 128.03, 124.09, 120.43, 86.66, 71.92, 70.64, 56.47, 41.09, 29.72, 25.82, 22.64, 21.05, 18.04, 14.43, 13.86, 13.27, 9.49, –4.34, –4.97.

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