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Stereoselective Syntheses of the Rhizoxin C(1)-C(9) and C(12)-C(26) Subunits

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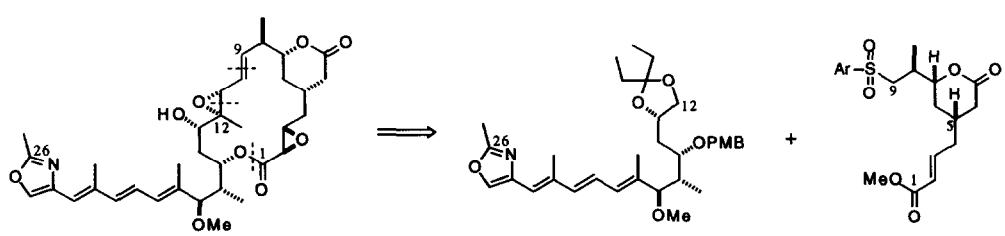
Abstract: Stereoselective syntheses of the C(1)-C(9) and C(12)-C(26) subunits of the macrolide antitumor agent rhizoxin are described. Chelation-controlled Ireland-Claisen rearrangement, stereoselective Horner-Wadsworth-Emmons reactions and a thermodynamically-controlled diastereotopic group differentiation are featured.

Rhizoxin (NSC-332598) and its congeners constitute a family of 16-membered macrolactones first isolated from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and coworkers in 1984.[1] Rhizoxin is a tubulin-interactive antimitotic agent which exhibits pronounced antimicrobial and antifungal activity as well as potent *in vitro* cytotoxicity and *in vivo* antitumor activity.[2] Phase I and II clinical trials have been completed with rhizoxin in ovarian cancer, colorectal and renal cancer, breast cancer and melanoma, head and neck cancer, and non-small-cell lung cancer,[3] and phase III clinical evaluations are currently underway. One striking observation is that rhizoxin is more potent but less toxic than vincristine. Rhizoxin's unique structural features, its pronounced biological activity and its potential as a cancer chemotherapeutic agent have stimulated us and others to undertake the total synthesis of this novel class of compounds.[4,5]

Our convergent strategy breaks the target molecule into two major segments, **2** and **3**, both derivable from readily available enantiopure starting materials. These subunits comprise most of the stereogenic centers and all but three carbons present in rhizoxin and its congeners. Herein we describe the stereoselective synthesis of C(12)-C(26) subunit **2** and C(1)-C(9) subunit **3**, featuring a chelation-controlled Ireland-Claisen rearrangement, a highly stereoselective Horner-Wadsworth-Emmons reaction for incorporation of the oxazole side-chain, and a diastereotopic group desymmetrization procedure for establishing the C(5) stereocenter.



rhizoxin (**1**) **2** **3**

Synthesis of the C(12)-C(26) subunit **2** began with protected D-glyceraldehyde **4**.[6] Addition of *trans*-propenyllithium in the presence of $ZnBr_2$ gave the *anti*-alcohol **5** with 8:1 diastereoselectivity.[7] Acylation

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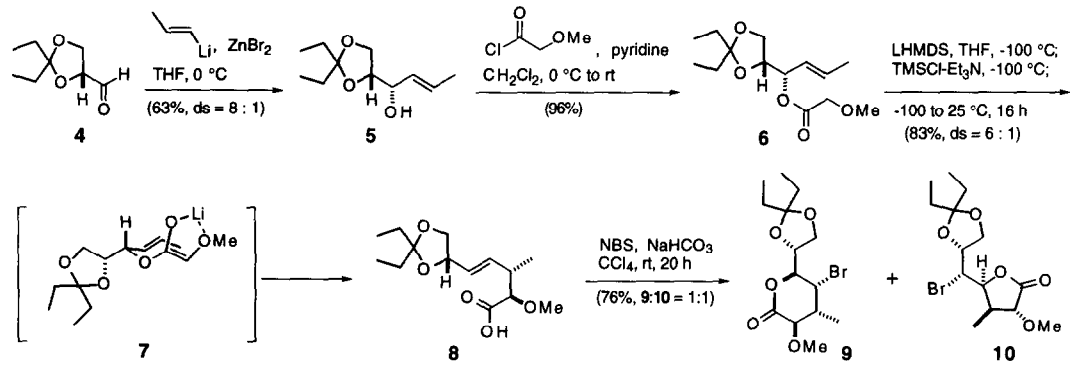
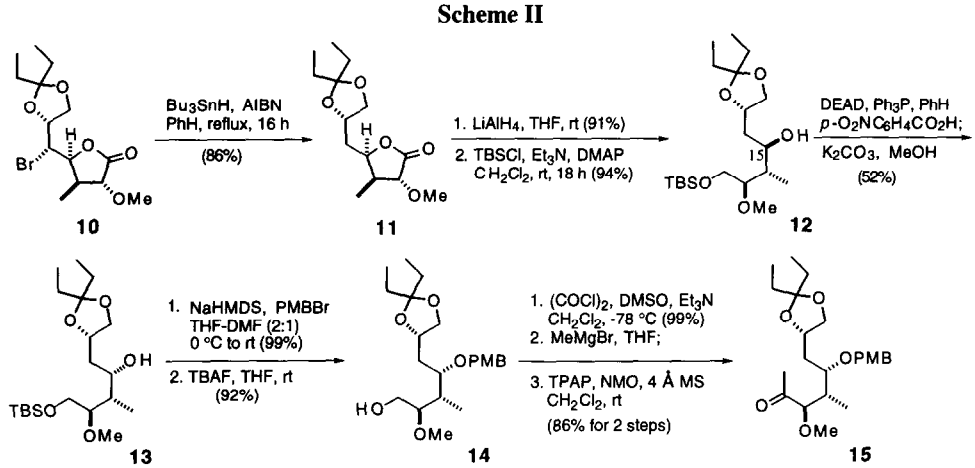
with methoxy acetyl chloride provided allylic glycolate ester **6**. The crucial chelation-controlled Ireland-Claisen rearrrangement[8] proceeded smoothly *via* the silyl ketene acetal derived from enolate **7**, affording acid **8** in 83% yield with a 6:1 diastereomeric ratio.[8b] Subsequent bromolactonization with NBS under kinetic conditions gave both δ- and γ-lactones (**9** and **10**) in about a 1:1 ratio.[9a] These were separated by flash chromatography, and recycling of **9** *via* **8** was accomplished in 87% yield by reductive fragmentation with zinc dust in NH_4OAc-buffered THF.

Scheme I



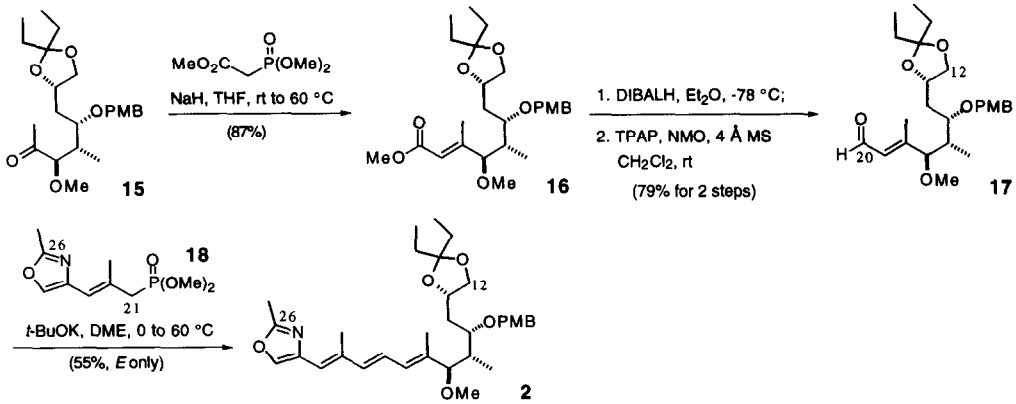
Radical reduction of desired bromolactone **10** gave lactone **11**, which was then reduced with lithium aluminum hydride. The primary hydroxyl group of the resulting diol was selectively protected as TBS ether **12**.[9b] The C(15) stereogenic center of alcohol **12** was inverted *via* the Mitsunobu reaction,[10] and the resulting alcohol **13** was protected as its *p*-methoxybenzyl ether. Subsequent silyl group removal afforded primary alcohol **14**, which was transformed to methyl ketone **15** using a standard sequence.

Scheme II



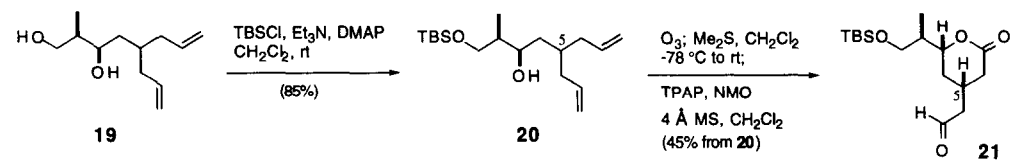
The desired *E*-trisubstituted olefin **16** was obtained by a Horner-Wadsworth-Emmons reaction.[11] A reduction-oxidation sequence then provided the C(12)-C(20) aldehyde **17**. Upon treatment of aldehyde **17** and phosphonate **18**[12] with *t*-BuOK in DME, a second Horner-Wadsworth-Emmons coupling reaction[13] completed the introduction of the *E,E,E*-triene to afford the desired C(12)-C(26) segment **2**.[14]

Scheme III



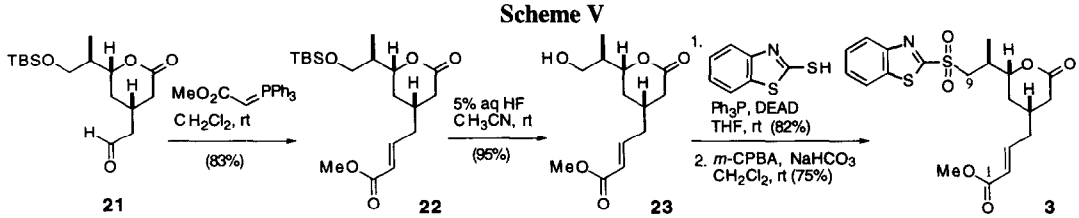
The synthesis of **3** began with the known diol **19**.[5d] The primary hydroxyl group was selectively protected as its TBS ether to afford the diene **20**. C(5) Diastereotopic group differentiation was accomplished by one-pot ozonolysis and TPAP oxidation to provide lactone aldehyde **21** in 45% overall yield.[15] This tactic for establishing the C(5) stereocenter is analogous to those employed by Keck[5d] and Williams,[4d] and relies upon thermodynamic diequatorial deployment of the side chains.

Scheme IV



The resultant lactonyl aldehyde **21** was subjected to Wittig chain extension to give ester **22**. Removal of the TBS group with aqueous HF afforded primary alcohol **23**, which was converted to the corresponding benzothiazole sulfide under Mitsunobu conditions.[16] Subsequent *m*-CPBA oxidation provided the C(1)-C(9) lactone subunit **3**.[17]

Scheme V



In summary, we have achieved the stereoselective syntheses of two major subunits of the antitumor macrolide rhizoxin. Extension of **2** to include the C(10)-C(11) carbons, fragment coupling with **3** *via* a modified Julia procedure,[16] and macrolactonization are being pursued actively in our laboratories to complete this synthetic route.

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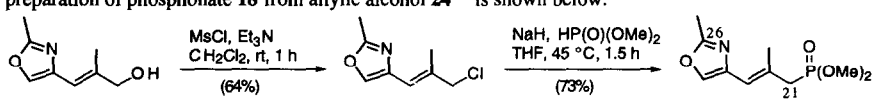

24 **25** **18**

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14. Data for **2**: R_f 0.31 (50% Et_2O in hexanes, PMA); $[a]^{22}_D$ +36.2 (*c* 0.90, CH_2Cl_2); **IR** (thin film) 2966, 2929, 1612, 1514, 1464, 1248, 1173, 1109, 1076, 1038, 920, 822 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) d 7.25 (m, 2H), 7.07 (s, 1H), 6.79 (m, 2H), 6.68 (dd, 1H, *J* = 15.1, 10.7 Hz), 6.45 (d, 1H, *J* = 15.4 Hz), 6.40 (s, 1H), 6.17 (d, 1H, *J* = 10.7 Hz), 4.42 (AB_q, 2H, J_{AB} = 11.0 Hz, Dv_{AB} = 48.4 Hz), 4.32 (m, 1H), 3.93 (dd, 1H, *J* = 8.1, 6.3 Hz), 3.65 (dt, 1H, *J* = 8.1, 4.0 Hz), 3.46 (t, 1H, *J* = 8.1 Hz), 3.35 (d, 1H, *J* = 7.7 Hz), 3.29 (s, 3H), 3.13 (s, 3H), 2.32 (s, 3H), 2.29 (m, 1H), 1.97 (s, 3H), 1.72 (d, 3H, *J* = 0.7 Hz), 1.70 (q, 2H, *J* = 7.7 Hz), 1.69 (m, 2H), 1.62 (q, 2H, *J* = 7.4 Hz), 1.22 (d, 3H, *J* = 7.0 Hz), 1.01 (t, 3H, *J* = 7.4 Hz), 0.94 (t, 3H, *J* = 7.4 Hz); **^{13}C NMR** (C_6D_6, 75 MHz) d 161.0, 159.8, 140.0, 138.4, 137.2, 13.6, 136.2, 131.6, 129.6, 124.4, 120.8, 114.2, 112.4, 89.1, 77.3, 74.4, 71.7, 71.2, 56.2, 54.7, 38.6, 35.1, 30.8, 30.5, 30.3, 14.5, 13.5, 12.5, 10.5, 8.8, 8.6; **HRMS** (EI) *m/e* calcd for $C_{33}H_{47}NO_6$ (M^+) 553.3403, found 553.3382.
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17. Data for **3**: R_f 0.23 (50% EtOAc in hexanes, PMA); $[a]^{22}_D$ -24.6 (*c* 1.12, CH_2Cl_2); **IR** (thin film) 2947, 2922, 1723, 1657, 1471, 1318, 1237, 1147, 1082, 765 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) d 8.19 (m, 1H), 8.00 (m, 1H), 7.61 (dq, 2H, *J* = 7.4, 1.5 Hz), 6.82 (dt, 1H, *J* = 15.8, 6.6 Hz), 5.86 (d, 1H, *J* = 15.8 Hz), 4.60 (dt, 1H, *J* = 11.8, 2.6 Hz), 3.81 (dd, 1H, *J* = 14.3, 6.3 Hz), 3.72 (s, 3H), 3.47 (dd, 1H, *J* = 14.3, 6.3 Hz), 2.70 (m, 1H), 2.62 (m, 1H), 2.17 (m, 1H), 1.88 (m, 1H), 1.33 (m, 1H), 1.16 (d, 3H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75 MHz) d 169.7, 166.1, 165.7, 152.3, 144.0, 136.4, 127.9, 127.5, 123.7, 122.1, 80.6, 57.1, 51.4, 38.2, 35.6, 32.3, 31.3, 30.6, 13.4; **HRMS** (EI) m/e calcd for $C_{20}H_{23}NO_6S_2$ (M^+) 437.0967, found 437.0978.