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Stereoselective Total Synthesis of Antitumor Macrolide (+)-Rhizoxin D†

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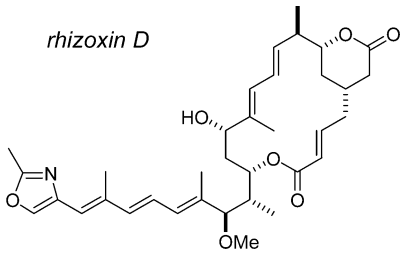
ABSTRACT



A convergent, stereoselective total synthesis of the macrolide antitumor agent rhizoxin D is described. (+)-DIPCl-promoted asymmetric aldol reaction, Evans–Tishchenko 1,3-diol synthesis, modified Julia coupling, and Horner–Wadsworth–Emmons reactions are featured.

Rhizoxin, **1**, (Scheme 1) and its congeners constitute a family of 16-membered macrolactones first isolated in 1984 from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and co-workers.[1] Rhizoxin is a tubulin-interactive antimitotic agent that exhibits pronounced antimicrobial and antifungal activity as well as potent in vitro cytotoxicity and in vivo antitumor activity.[2] Rhizoxin (**1**) has undergone extensive clinical trials as a potential drug candidate.[3] Rhizoxin D (**2**), a didesepoxy analogue of rhizoxin, was isolated in 1986 and is thought to be the biogenetic precursor of **1**.[4] Although rhizoxin D is equally potent as **1**, it has been less studied due to limited natural abundance.[5] Because of their significant biological activity, potential as chemotherapeutic agents, and unique structural features, the rhizoxins have attracted substantial interest as synthetic targets. One total synthesis of rhizoxin[6] and six syntheses of rhizoxin D,[7] along with several partial syntheses,[8] have been reported. In a culmination of our previous efforts,[9] we describe herein a total synthesis of rhizoxin D (**2**).

As outlined in Scheme 1, our convergent strategy breaks rhizoxin D into segments **3**−**5**. An asymmetric aldol reaction and an anti-stereoselective Evans−Tishchenko 1,3-diol syn-

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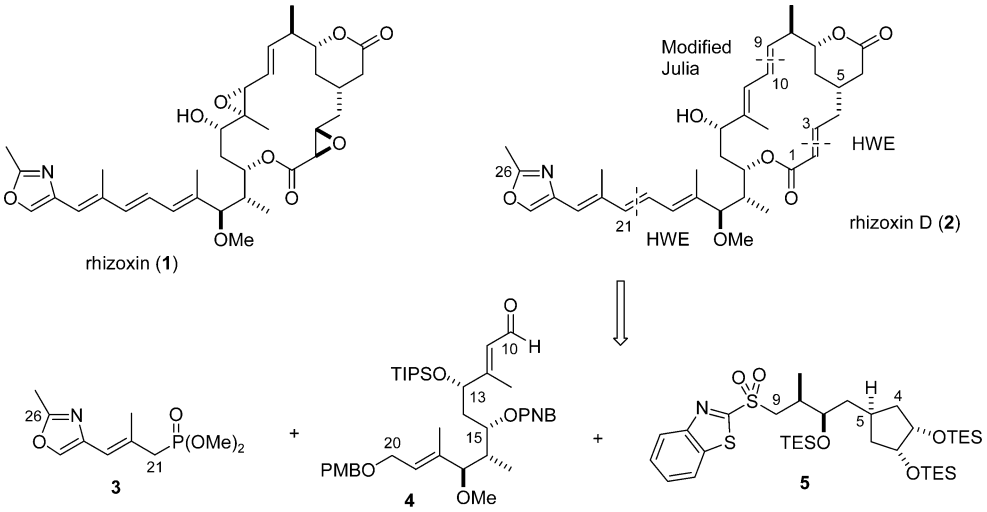
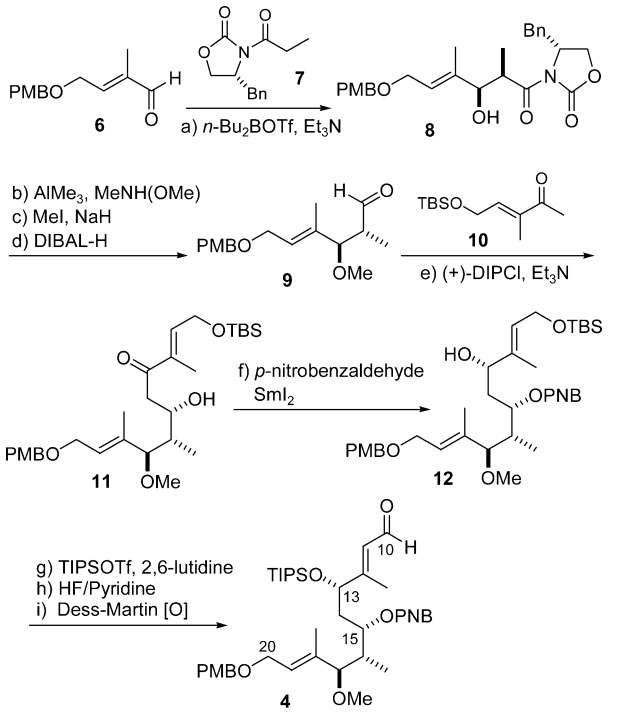
Scheme 1



thesis were envisioned as key steps to establish the C15 and C13 stereocenters in the central C10−C20 subunit. Modified Julia olefination (C9−C10) and intra- and intermolecular Horner−Wadsworth−Emmons (HWE) olefinations (C2−C3 and C20−C21, respectively) were planned for subunit coupling to establish the carbon skeleton of rhizoxin D.

Synthesis of the C10−C20 subunit **4** began from α,β-unsaturated aldehyde **6**[7d] (Scheme 2). Evans aldol reaction with **7** gave the corresponding syn adduct **8** exclusively.[10] Conversion of imide **8** to the Weinreb amide,[11] followed by *O*-methylation and DIBAL-H reduction, provided aldehyde **9**. An aldol reaction between **9** and the enolate of methyl ketone **10**,[12] prepared with (+)-chlorodiisopinocamphenyl borane (DIP-Cl),[13] afforded β-keto alcohol **11** in 65% yield

Scheme 2[a]



[a] Conditions: (a) **7**, *n*-Bu_2BOTf, Et_3N, 0 °C, then add **6**, CH_2Cl_2, −78 °C to room temperature, 85%; (b) $AlMe_3$, MeNH(OMe), CH_2Cl_2, 0 °C to room temperature; (c) MeI, NaH, THF−DMF (3:1), 0 °C, 78% for two steps; (d) DIBAL-H, THF, −78 °C, 98%; (e) **10**, (+)-DIP−Cl, Et_3N, then add **9**, CH_2Cl_2, −78 °C, 65%; (f) *p*-nitrobenzaldehyde, SmI_2, THF, 0 °C, 86%; (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C; (h) HF/Pyridine, THF, 0 °C to room temperature, 83% for two steps; (i) Dess−Martin periodinane, CH_2Cl_2, rt, 81%.

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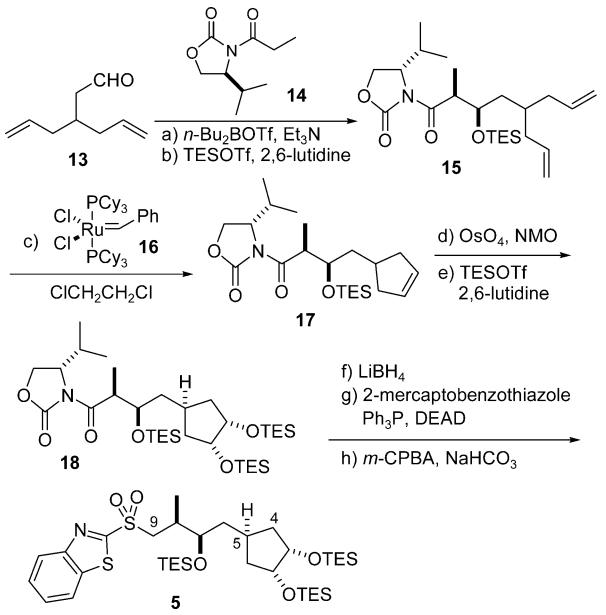
(12) Ketone **10** was prepared in two steps from the known (2*E*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-but-2-enal[7c] by methyl Grignard addition and Swern oxidation.

Scheme 3[a]



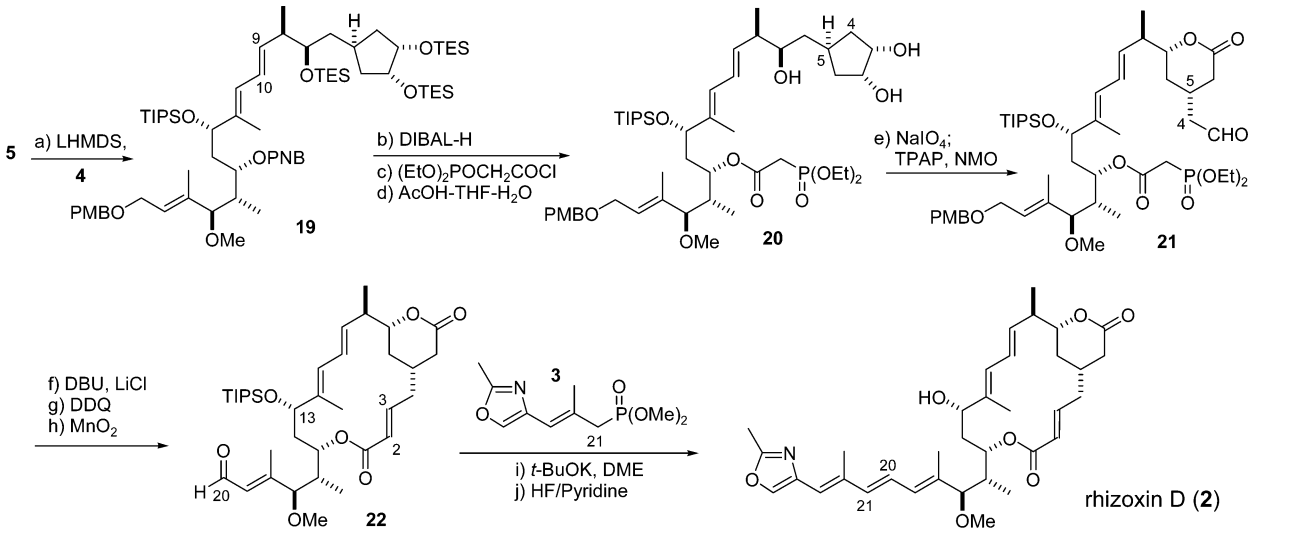
[a] Conditions: (a) *n*-Bu_2BOTf, Et_3N, **14**, CH_2Cl_2, −78 to 0 °C, 88%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 85%; (c) **16** (3.6 mol %), $ClCH_2CH_2Cl$, rt, 91%; (d) OsO_4 (6 mol %), NMO, acetone−H_2O (8:1), rt, 87%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 95%; (f) $LiBH_4$, MeOH, THF, 0 °C to room temperature, 58%; (g) 2-mercaptobenzothiazole, Ph_3P, DEAD, THF, 0 °C to room temperature, 98%; (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 97%.

with a 10:1 diastereomeric ratio. An intramolecular Evans−Tishchenko reaction with *p*-nitrobenzaldehyde afforded **12** with the C13 stereocenter installed and the C15 hydroxyl protected as the *p*-nitrobenzoate (PNB) ester.[14] Subsequent alcohol protection (TIPS), selective cleavage of the C10-siloxy group, and Dess−Martin oxidation[15] gave the desired C10−C20 segment **4**.

Synthesis of the C3−C9 subunit **5** started with the known aldehyde **13**[16] (Scheme 3). An Evans aldol condensation[10] of **13** with the boron enolate of **14** afforded the aldol product as a single diastereomer, which was protected as its TES ether **15**. Ring-closing metathesis of the diene using Grubbs' catalyst **16** gave cyclopentene **17** in 91% yield.[17] Dihydroxylation of **17** afforded the cis diol with a diastereomeric ratio of 8:1,[18] which upon silylation gave **18**. Reductive removal of the chiral auxiliary using $LiBH_4$ yielded the primary alcohol, which was converted to the corresponding benzothiazole sulfide under Mitsunobu conditions.[19] Subsequent *m*-CPBA oxidation provided the C3−C9 sulfone subunit **5**.

Coupling of enal **4** and sulfone **5**, utilizing the one-pot modified Julia protocol,[20] selectively gave **19** as the *E*-isomer in 80% yield (Scheme 4). The PNB ester was reductively removed, and the resulting alcohol was esterified with diethylphosphonoacetyl chloride. Subsequent removal of the three TES groups afforded the triol **20**. Differentiation of the C5 diastereotopic groups was achieved by one-pot oxidative cleavage of the vicinal diol and TPAP oxidation to provide lactone aldehyde **21** in 75% overall yield.[21] This tactic for establishing the C5 stereocenter is analogous to those employed by Keck[8d] and Williams,[7b] and relies upon thermodynamic diequatorial deployment of the side chains in the intermediate hemiacetal. An intramolecular Horner−Wadsworth−Emmons coupling reaction established the macrolactone C2−C3 bond in 80% yield.[22] Oxidative removal of PMB group,[23] followed by MnO_2 allylic oxidation,[24] afforded aldehyde **22**. Treatment of **22** and phosphonate **3**[9a,b] with *t*-BuOK in DME gave only (*E*,*E*,*E*)-triene via HWE

Scheme 4[a]



[a] Conditions: (a) LHMDS, THF, −78 °C, 0.5 h, then **4**, THF, −78 °C to room temperature, 80%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 99%; (c) diethylphosphonoacetyl chloride, pyridine, THF, 0 °C to room temperature, 90%; (d) AcOH−THF−H_2O (3:2:1), rt, 88%; (e) $NaIO_4$, THF−H_2O (1:1); TPAP, NMO, 4 Å MS, CH_2Cl_2, 75%; (f) DBU, LiCl, CH_3CN, rt, 5×10^{-4} M, 80%; (g) DDQ, CH_2Cl_2−H_2O (20:1), rt, 92%; (h) MnO_2, CH_2Cl_2, rt, 71%; (i) **3**, *t*-BuOK, DME, 0 °C, 39%; (j) HF/pyridine, THF, 0 °C to room temperature, 70%.

C20−C21 coupling.[25,26] Final deprotection of the C13 TIPS ether afforded rhizoxin D (**2**), $[\alpha]^{23}_{D}$ +271.56 (*c* 0.41, MeOH), with all data (^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with those reported for the natural product.[4a,7f,g] A stereoselective synthesis of rhizoxin D has thus been accomplished with the longest linear sequence requiring 19 steps.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds and ^{1}H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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