Total Synthesis

DOI: 10.1002/anie.201300576

Total Synthesis of the Tubulin Inhibitor WF-1360F Based on Macrocycle Formation through Ring-Closing Alkyne Metathesis **

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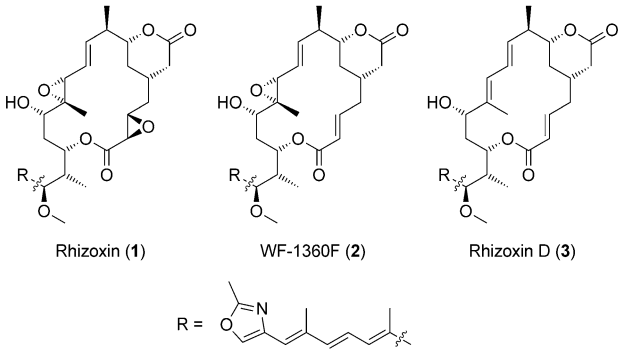
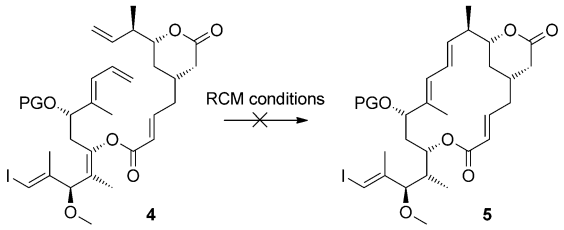
Rhizoxin (**1**) is a 16-membered macrolide that was first isolated in 1984 from the plant pathogenic fungus *Rhizopus chinensis* by Okuda and co-workers and shown to be the causative phytotoxin of the rice seedling blight.[1,2] In 2005, Hertweck and co-workers demonstrated that rhizoxin (**1**) is not a fungal metabolite but is produced by a bacterial endosymbiont of the genus *Burkholderia*.[3] Rhizoxin (**1**) is a potent inhibitor of eukaryotic tubulin polymerization[4] and it exhibits pronounced in vitro and in vivo antitumor activity;[5] the compound has been advanced to Phase II clinical trials but has not shown any relevant clinical efficacy.[6] In addition to **1**, a number of rhizoxin congeners have been isolated from fermentation broths of *Rhizopus chinensis*[4,5a,7] and *Burkholderia rhizoxina*.[8] These include the desepoxy variants WF-1360F (**2**) and rhizoxin D (**3**);[4] the growth inhibitory activity of WF-1360F (**2**) has been reported to be similar to that of **1**[5a] or even significantly higher.[8]



The total synthesis of rhizoxins has been explored in significant detail, with the majority of the work being directed at rhizoxin D (**3**) as the final target structure.[9] Only a single synthesis of rhizoxin (**1**) has been completed so far[10] and no synthesis of **2** has been reported. We have been interested in developing a new synthesis of **2** and **3** as part of a program directed at the biological evaluation of side-chain-modified rhizoxins. In this context we have explored the possibility of macrocycle formation by ring-closing metathesis (RCM),[11] a strategy that had not been employed in any previous rhizoxin synthesis; the immediate cyclization product was to be vinyl iodide **5**, which would serve as the common precursor for **2** and **3** and different side-chain-modified analogues (Scheme 1). However, in spite of extensive efforts, **5** could not be obtained from either diene **4** or a diverse number of alternative RCM substrates (Scheme 1).[12]



Scheme 1. PG = protecting group.

A modification of the synthetic strategy was thus required, leading us to consider ring-closing alkyne metathesis (RCAM)[13] as an alternative approach to macrocycle formation, as this would allow us to capitalize on the chemistry developed in the course of the synthesis of **4** to the largest extent possible. Based on Fürstner's excellent work on catalyst development,[14] RCAM has evolved into a valuable tool for the total synthesis of macrocycles.[15] In this report we now describe the first total synthesis of the natural product WF-1360F (**2**) based on macrocyclization by RCAM followed by a highly selective radical reduction/isomerization sequence to install the macrocyclic (*E*,*E*)-diene unit.

Retrosynthetically, the initial disconnections of WF-1360F (**2**) and rhizoxin D (**3**) led to diyne **6** (Scheme 2), which was to be elaborated into the natural products by RCAM/triple-bond reduction, followed by Stille coupling, to complete the side chain, deprotection of the C13 hydroxy group, and directed epoxidation (for **2**). Diyne **6** would be obtained by Horner–Wadsworth–Emmons (HWE) reaction between phosphonate **7** and aldehyde **8**. The former would be accessed from methyl ketone **9** and unsaturated aldehyde **10** by means of a Paterson aldol reaction,[16] followed by stereoselective

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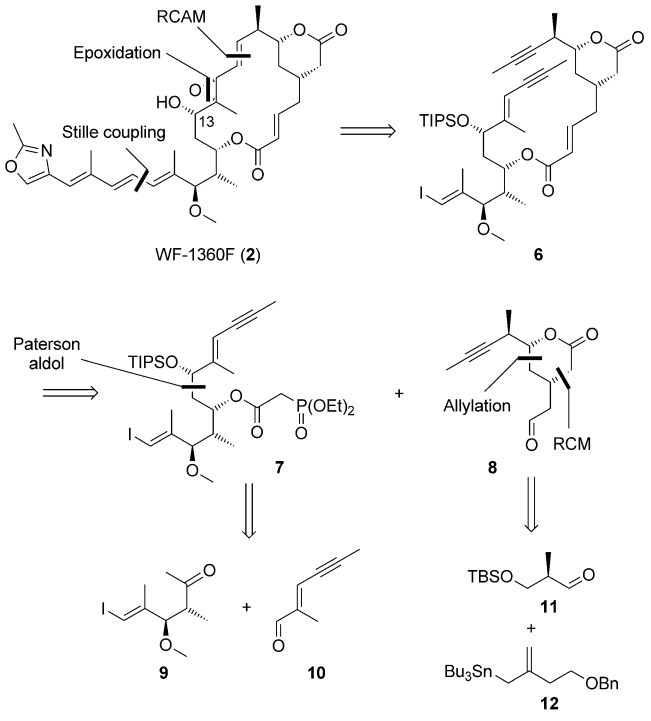
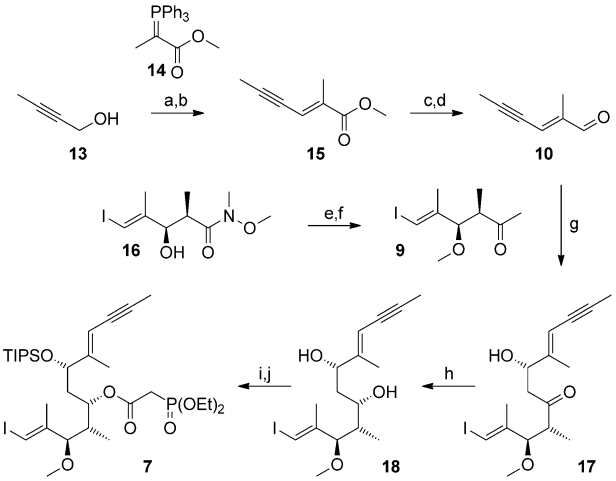
[**] This work was supported by the Swiss National Science Foundation (SNF) (Project 200021_126511). We are very grateful to Prof. Dr. Alois Fürstner, MPI für Kohlenforschung, Mülheim (Germany), for the generous donation of samples of his catalysts.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300576.



Scheme 2. Target structure and retrosynthesis. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

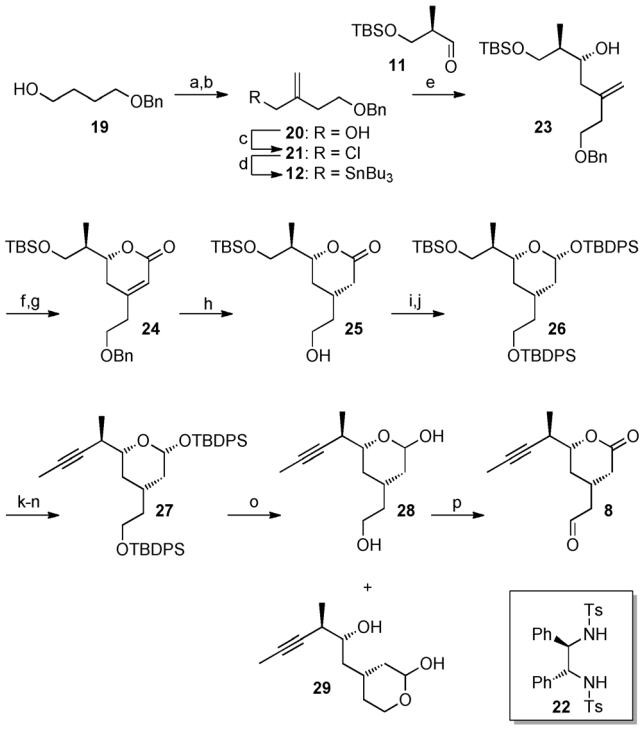


Scheme 3. a) MnO_2, CH_2Cl_2, RT; b) **14**, CH_2Cl_2, reflux, 45% (based on **14**); c) $LiAlH_4$, Et_2O, 0°C; d) MnO_2, CH_2Cl_2, RT, 82% (2 steps); e) NaH, MeI, THF/DMF 3:1, 0°C, 99%; f) MeMgCl, THF, −20°C→0°C, 93%; g) (+)-DIPCl, NEt_3, CH_2Cl_2, −78°C→−25°C; h) $(NMe_4)BH(OAc)_3$, AcOH, MeCN, −40°C→−20°C, 66% (2 steps); i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 97%; j) CME-carbodiimide-TsO, DMAP, $(EtO)_2P(O)CH_2COOH$, CH_2Cl_2, 0°C→RT, 82%. CME = *N*-cyclohexyl-*N*′-(2-morpholinoethyl), DIPCl = chlorodiisopinocampheylborane, DMAP = 4-dimethylaminopyridine, OTf = trifluoromethanesulfonate, TsO = *p*-toluenesulfonate.

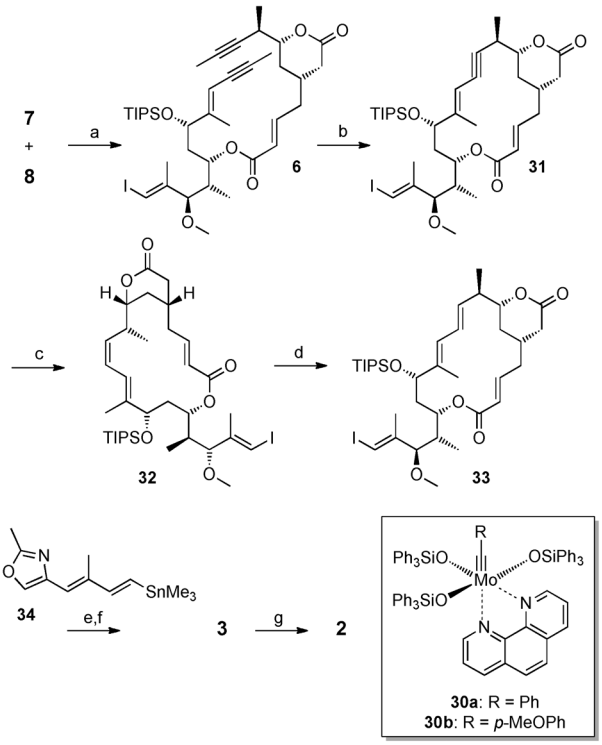
1,3-reduction of the resulting β-hydroxy ketone; aldehyde **8** was to be derived from aldehyde **11** and stannane **12** as early intermediates.

The synthesis of building block **7** commenced with the MnO_2-mediated oxidation of 2-butyn-1-ol (**13**) followed by Wittig olefination of the resulting aldehyde with phosphonium ylide **14**[17] to provide ester **15** in moderate yield (45%) (Scheme 3). Reduction of **15** with $LiAlH_4$ and oxidation of the resulting allylic alcohol with MnO_2 afforded the requisite aldehyde **10**. Reaction of **10** with the boron enolate derived from ketone **9**[18] (obtained from alcohol **16**[18] by methylation with MeI/NaH at 0°C followed by reaction with MeMgCl in 92% overall yield) under optimized conditions afforded β-hydroxy ketone **17** in roughly 70% yield; this material still contained some impurities, mainly isopinocampheol, which could only be separated after the following step. Reduction of **17** with $(NMe_4)BH(OAc)_3$[19] gave the desired 1,3-*anti* diol **18** as the only isolable isomer in 66% yield (from **9**). Treatment of **18** with TIPSOTf at −78°C provided the C13 TIPS-ether (rhizoxin numbering) in 97% yield as a single regioisomer. Carbodiimide-mediated esterification of this intermediate with diethylphosphonoacetic acid finally furnished building block **7** in good yield (82%).

The synthesis of building block **8** departed from butane-1,4-diol, which was monobenzylated;[20] monobenzyl ether **19** was oxidized and the resulting aldehyde was α-methylenated in situ (CH_2NMe_2Cl, DBU) in excellent yield (86%), employing a modification of a procedure originally developed by Ogasawara and co-workers (Scheme 4).[21] Reduction with $LiAlH_4$ to give alcohol **20**, followed by Appel reaction then furnished the allylic chloride **21**. Conversion of the latter into the corresponding stannane **12** was achieved by an ultrasound-promoted Barbier-type reaction[22] of **21**, Mg turnings, and tributyltin chloride (quantitative, 80% purity by ^1H NMR analysis). Stannane **12** proved to be extremely prone to protodestannylation even on exposure to buffered silica gel, which precluded chromatographic purification. Fortunately, the purity of the material obtained after simple extractive workup was sufficient for the next step. Thus, transmetalation of **12** with Corey's bromoborane complex (prepared from BBr_3 and bistosylated (*R*,*R*)-DPEN (**22**))[23] under conditions elaborated by Williams et al.[24] and subsequent reaction with aldehyde **11** at −78°C furnished secondary alcohol **23** in very good yield and with high diastereoselectivity (74% over 2 steps, d.r. 10:1, 94% recovery of **22**). In contrast, conditions relying solely on Felkin–Anh control ($BF_3{\cdot}Et_2O$) led to poor diastereoselectivity (d.r. 1.9:1).[25] Esterification of **23** with acryloyl chloride and subsequent RCM with the Hoveyda–Grubbs II catalyst[11] (10 mol%) gave dihydropyrone **24**; hydrogenation of the latter with Pearlman's catalyst (5 mol%) then furnished δ-lactone **25** as a single isomer in 74% overall yield for the three-step sequence from **23**.[26] The elaboration of **25** into alkyne **8** was only possible after conversion into the corresponding (protected) lactol **26**, while all attempts to install the triple bond by Corey–Fuchs chemistry in the presence of the lactone moiety led to complete decomposition of starting material. Tris(silyl ether) **26** was obtained from **25** by DIBALH reduction followed by treatment with TBDPSCl in 90% yield (2 steps) as a single isomer (all substituents on the tetrahydropyran ring in equatorial positions).[27] Selective cleavage of the primary TBS ether with $NaIO_4$ in aqueous THF[28] followed by Swern oxidation, Corey–Fuchs alkynylation, and in situ trapping of



Scheme 4. a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C→0 °C, then CH_2NMe_2Cl, DBU, RT, 86%; b) $LiAlH_4$, THF, 0 °C, 96%; c) CCl_4, PPh_3, MeCN, RT, 95%; d) Mg, Bu_3SnCl, THF, ultrasound, 0 °C→RT, quant., 80% purity; e) BBr_3, ligand **22**, CH_2Cl_2, RT, then **12**, RT, 18 h, then **11**, −78 °C, 74% (2 steps, d.r. 10:1); f) acryloyl chloride, DIEA, CH_2Cl_2, −40 °C, 85%; g) Hoveyda–Grubbs II catalyst, DCE, reflux, 89%; h) H_2 (9 bar), $Pd(OH)_2$-C, EtOAc, RT, 98%; i) DIBALH, CH_2Cl_2, −78 °C; j) TBDPSCl, imidazole, CH_2Cl_2, RT, 90% (2 steps); k) $NaIO_4$, THF/water (4:1), RT, 87%; l) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C→RT, 96%; m) CBr_4, PPh_3, CH_2Cl_2, −78 °C, 99%; n) *n*BuLi, MeI, THF, −78 °C to RT, 94%; o) TBAF, AcOH, THF, 0 °C→RT, quant. (**28**/**29**, 2:1); p) TEMPO, BAIB, $Yb(OTf)_3$ (cat.), CH_2Cl_2, 0 °C→RT, 62%. BAIB = bis-(acetoxy)iodobenzene, Bn = benzyl, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DCE = 1,2-dichloroethane, DIBALH = diisobutylaluminum hydride, DIEA = *N*,*N*-diisopropyl ethyl amine, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.



Scheme 5. a) LiCl, DBU, THF/MeCN 3:1, 0 °C→RT, 81% (88% brsm); b) catalyst **30a** or **30b**, $MnCl_2$, toluene, 5 Å molecular sieves, 125 °C, **30a**: 69%, **30b**: 63% (67% brsm); c) 1. $[Co_2(CO)_8]$, CH_2Cl_2, RT; 2. 1-ethylpiperidine hypophosphite, benzene, reflux, 74% over 3 cycles, *Z* only; d) AIBN, PhSH, benzene, reflux, 88%, *E*/*Z* = 20:1; e) $[PdCl_2(MeCN)_2]$, DMF, RT, 68%; f) HF·py, py, THF, 0 °C→RT, 54%; g) *t*BuOOH, $[VO(acac)_2]$, benzene, 0 °C→RT, 65%, 29% after preparative RP-HPLC. acac = acetylacetonato, AIBN = azobisisobutyronitrile, brsm = based on recovered starting material, py = pyridine.

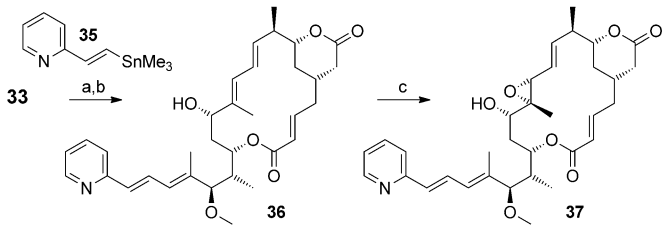
the intermediate lithium acetylide with MeI then afforded alkyne **27** in excellent overall yield (78% over 4 steps). Simultaneous cleavage of both silyl ethers with TBAF/AcOH produced an inseparable mixture of lactols **28** and **29** (each as a pair of diastereoisomers; 2:1 ratio in favor of the desired regioisomer **28**), which was treated with bis-(acetoxy)iodobenzene (2.2 equiv) in the presence of catalytic amounts of TEMPO (19 mol%) and $Yb(OTf)_3$ (4 mol%)[29] to produce the desired building block **8** as a single isomer in 62% yield (based on bis(TBDPS ether) **27**).[30]

Building blocks **7** and **8** were connected in a high-yielding HWE reaction (DBU/LiCl)[31] to afford diyne **6** as the substrate for ring-closure by RCAM (Scheme 5). Gratifyingly, treatment of **6** with 10 mol% of the Fürstner catalyst **30a**[14,15] (Scheme 5) gave the desired macrocycle **31** in an impressive 69% yield. A somewhat lower yield of **31** was obtained with catalyst **30b** (63%), although this may not be statistically significant; alternatively, the difference may be related to the larger scale of the reaction with **30b** (900 μmol of **6** vs. 45 μmol for **30a**). For the ring-closure to proceed efficiently, a temperature of at least 120 °C was mandatory (with reaction times between 3 h and 27 h), which in turn highlights the exceptional thermal stability of catalysts **30a** and **30b**.

The subsequent reduction of the alkyne moiety in **31** proved to be more challenging than expected. While all attempts at transition-metal-catalyzed hydrogenation, hydrostannylation, hydroboration, and hydrozirconation of the triple bond met with failure, hydrosilylation was possible with $(EtO)_3SiH$ and Trost's $[CpRu(MeCN)_3]PF_6$ catalyst (Cp = cyclopentadienyl) but not with the $[Cp^*Ru(MeCN)_3]PF_6$ complex (Cp^* = pentamethylcyclopentadienyl).[32] However, yields after protodesilylation with AgF[33] were low (30–40% over 2 steps), selectivities were unsatisfactory (*E*:*Z* = 1:4.7 to 1:2.6), and the reaction lacked reproducibility. Ultimately, the most efficient way of processing alkyne **31** was its conversion into *Z* olefin **32** by in situ reductive decomplexation of the corresponding acetylenehexacarbonyl dicobalt complex with ethylpiperidine hypophosphite (EPHP).[34,35] Using this approach, **32** was ultimately obtained in 74% yield as a single isomer after three reaction cycles, which were required to achieve complete consumption of the starting

alkyne **31**; full consumption of **31** was mandatory, as **31** and **32** were inseparable. The subsequent *Z* to *E* isomerization proceeded smoothly with AIBN/PhSH in benzene at reflux and delivered *E* olefin **33** in 88% yield ($E/Z = 20:1$).[36] The overall yield of **33** from **19** (longest linear sequence) was 6.8% (20 steps).

The conversion of **33** into rhizoxin D (**3**) by means of Stille coupling with stannane **34** and subsequent removal of the TIPS protecting group with HF·pyridine has been described previously.[18,37] Following the corresponding literature procedures, **3** could be obtained in 37% overall yield, which is somewhat lower than the yields that have been reported for this two-step sequence (50%[18] and 76%[37]). No attempts were made to optimize the transformation of **33** into **3**, but we note that both the protected Stille coupling product as well as **3** were prone to decomposition and thus difficult to purify.[27,38] In a final step directed epoxidation of the 11,12 double bond in **3** with *t*BuOOH/$[VO(acac)_2]$[39] provided the natural product WF-1360F (**2**) in 65% yield and approximately 73% purity. Purification by preparative RP-HPLC gave analytically pure **2**. The NMR data for **3** and **2** were in perfect agreement with literature data on natural rhizoxin D[7] and WF-1360F,[8] respectively. Stannane **35** was employed to elaborate vinyl iodide **33** into the side-chain-modified rhizoxin analogues **36** and **37**; the overall yield of **36** was significantly higher than that of **3** (65% vs. 37%; Scheme 6).



Scheme 6. a) $[PdCl_2(MeCN)_2]$, DMF, RT, 97%; b) HF·py, py, THF, 0°C→RT, 67%; c) 1. *t*BuOOH, $[VO(acac)_2]$, benzene, 0°C→RT; 2. preparative RP-HPLC, 34%.

The antiproliferative activity of **2**, **3**, **36**, and **37** was assessed against the human pancreatic and colon cancer cell lines MiaPaCa and HCT116, respectively (Table 1). For WF-1360F (**2**), IC_{50} values were in the single-digit nanomolar range, which is in general agreement with the data reported for natural **2** on K-562 and L929 cells;[8] a sub-nanomolar IC_{50} value has been reported against the P388 mouse leukemia cell line.[5a] Deletion of one alkene unit in the side chain with concomitant replacement of the oxazole heterocycle by a pyridine moiety resulted in only a moderate increase in IC_{50} values (6- to 10-fold) for **37**, which indicates that analogues with truncated (and potentially more stable) side chains can retain relevant biological activity.[40] Desoxy analogues **3** and **36** both proved to be significantly less active than their corresponding epoxide-containing congeners (more than 10-fold less active). This is somewhat surprising, as the activity of rhizoxin D (**3**) has been implied to be comparable to that of rhizoxin (**1**);[9] however, to the best of our knowledge, no original data on the effects of **3** on mammalian cells are available in the literature.[41]

Table 1: Antiproliferative acitivity of WF-1360F (**2**), rhizoxin D (**3**), and analogues **37** and **36** (IC_{50} values [nM]).[a]

Compd.	MiaPaCa	HCT116
2	5.1 ± 0.74	4.5 ± 0.38
3	75 ± 6.9	49 ± 6.6
37	45 ± 1.8	29 ± 6.1
36	1432 ± 246	297 ± 2.4

[a] Cells were exposed to the tested compound for 72 h. Data are average values ± standard error of the mean. For details see the Supporting Information.

In summary, we have accomplished the total synthesis of the antimitotic natural product WF-1360F (**2**), based on macrocyclic ring-closure by RCAM and the efficient conversion of the ensuing alkyne moiety into the required *E*-configured double bond. The successful implementation of this strategy is highly remarkable, as all attempts to achieve the corresponding ring-closure by RCM had failed in our hands. Our approach provides efficient access to vinyl iodide **33**, which can serve as a common precursor for the synthesis of side-chain-modified rhizoxin analogues for structure–activity studies and lead optimization.

Received: January 22, 2013
Published online: April 22, 2013

Keywords: drug discovery · metathesis · natural products · rhizoxin · total synthesis

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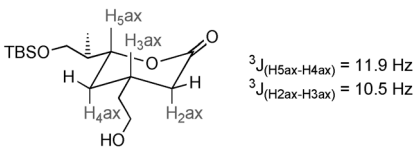

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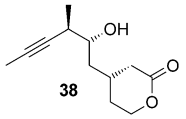

38

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