A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

Title: Metathesis at an Implausible Site: A Formal Total Synthesis of Rhizoxin D

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201812096
Angew. Chem. 10.1002/ange.201812096

Link to VoR: http://dx.doi.org/10.1002/anie.201812096
http://dx.doi.org/10.1002/ange.201812096

WILEY-VCH

10.1002/anie.201812096

Metathesis at an Implausible Site: A Formal Total Synthesis of Rhizoxin D

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Supporting Information and ORCHID identification number(s) for the author(s) of this article can be found under: http://doi.org/10.1002/anie. 201812096.

10.1002/anie.201812096

Abstract: *The new approach to the anticancer agent rhizoxin D described herein does not cohere with the conventional logic of metathesis, according to which macrocycles are best closed at a disubstituted olefinic site; rather, the trisubstituted C11-C12 alkene flanked by an allylic –OH group served as the pivot point for synthesis. This motif was attained in good yield and excellent selectivity by a sequence of alkyne metathesis, trans-hydrostannation and cross coupling. Because the exact same substructure is prominently featured in numerous other natural products, the underpinning strategy, though unusual, might bear more general relevance.*

Rhizoxin (**3**) was originally isolated as an antifungal agent from cultures of the rice pathogenic fungus *Rhizopus chinensis*.[1] It was later recognized, however, that it is not the fungus itself but a bacterial endosympiont of the genus *Burkholderia* which is the actual producer of this macrolide and numerous congeners such as **1** and **2**.[2] Endowed with remarkable *in vitro* cyctotoxicity and *in vivo* antitumor activity, this class of compounds spawned massive investigations into its chemistry, biological properties and medicinal significance.[3] Importantly, **3** had been selected for phase II clinical trials: activity against non-small-cell lung cancer was recorded with apparently only modest symptomatic and hematological toxicity;[4] unfortunately, however, the response rate of patients with advanced melanoma, breast, ovarian, colorectal or renal cancer was rather disappointing and the studies were therefore discontinued.[5] In mechanistic terms, the rhizoxins act as spindle poisons targeting the maytansine binding site on eukaryotic tubulin.[6-8] In this context, it is perhaps relevant to note that maytansine had also proven inadequate as a chemotherapeutic agent but now plays a preeminent role as warhead of clinically approved antibody-drug-conjugates (ADC's).[9] It needs to be seen whether or not rhizoxin qualifies for similar applications.

The unsaturated variant rhizoxin D (**1**), derived from the same source organism,[2, 10] is the likely biosynthetic precursor of **3**; it can also be transformed by chemical means into WF-1360F (**2**) and **3**.[3] Since the biological activity of **1** is similar to that of **2** and **3**, this polyunsaturated compound served as focal point for total synthesis in the past (Scheme 1).[3] Though rather diverse in detail, the different approaches reported in the literature are surprisingly conservative as to the closure of the macrocyclic ring, in that most of them converged to an intramolecular Horner-Wadsworth-Emmons

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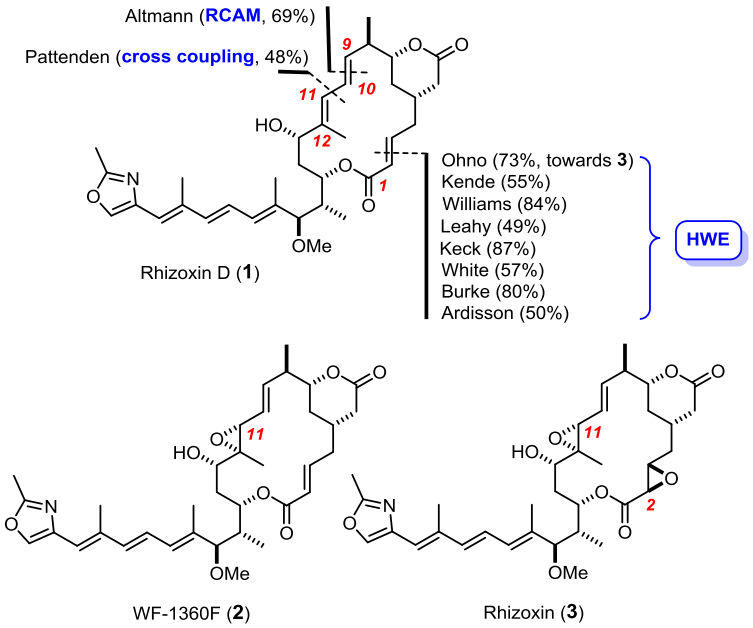
(HWE) olefination for the formation of the C2-C3 enoate bond.[11-18] Only a single total synthesis relied on macrocyclization at the 1,3-diene subunit via a modestly efficient intramolecular Stille cross coupling.[19]



Scheme 1. Three representative and biosynthetically related rhizoxin derivatives; analysis of prior total syntheses (site and yield of macrocyclization).

One might expect that the rhizoxins also lend themselves to ring closing olefin metathesis (RCM), which is arguably one of the most successful entries into macrocyclic rings since the advent of highly active and functional group tolerant catalysts.[20, 21] This anticipation, however, proved premature: it was reported by the Altmann group that attempted closure of the 16-membered core at the disubstituted C9–C10 olefin by RCM failed, despite extensive experimentation (Scheme 2).[22] In striking contrast, ring closing alkyne metathesis (RCAM) worked exceedingly well at this demanding site, affording the ostensibly more strained cycloalkyne in appreciable 69 % yield.[22] Unfortunately, however, the congested microenvironment precluded direct *trans*-reduction of the acetylenic entity to the *E*-alkene from occurring. Rather, an indirect solution had to be found, commencing with formation of the corresponding hexacarbonyl dicobalt complex, which was

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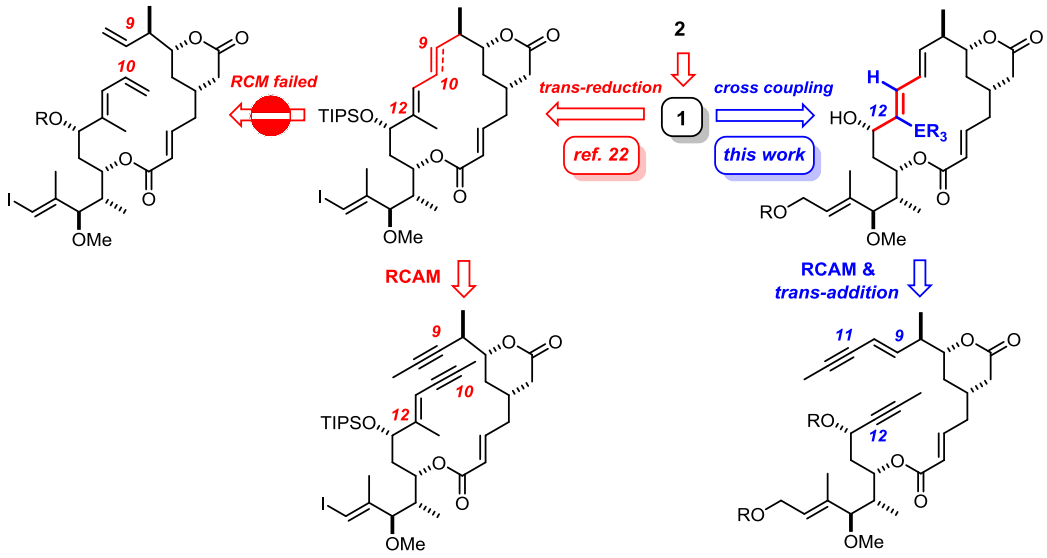
subjected to reductive decomplexation, followed by isomerization of the resulting *Z*-alkene to the required *E*-isomer under free radical conditions.[22]



Scheme 2. Different metathesis-based approaches to rhizoxin D (and WF-1360F); E = Si, Ge, Sn.

This surprisingly involved situation encouraged us to pursue an arguably counterintuitive solution: Rather than targeting the disubstituted C9-C10 double bond as the deceptively obvious site for metathetic ring closure,[20-23] we contemplated that the trisubstituted C11-C12 alkene might actually be more appropriate: This stratagem – although very much in dissent with conventional wisdom[24, 25] – builds upon recent advances in directed *trans*-addition reactions to internal alkynes.[26] Most notably, propargylic alcohols lend themselves to highly regio- and stereoselective *trans*-hydrometalation, whereby an R_3E- residue (E = Si, Ge, Sn) is faithfully delivered to the more crowded site proximal to the –OH function.[27] This course is rooted in cooperativity between the protic group and the polarized [Cp*Ru–Cl] unit of the catalyst: the resulting hydrogen bond increases the affinity of the substrate to the ruthenium center and imposes directionality onto the ensuing transition state.[26, 28] From the synthetic vantage point, this methodology opens a concise gateway to trisubstituted alkenes, not least of the type featured in the macrocyclic frame of **1**.[29, 30] For its illustrious pedigree,[11-19, 22] this target was deemed an ideal testing ground that allows the competitiveness of this approach to be tested. Although not pursued herein, we like to mention that

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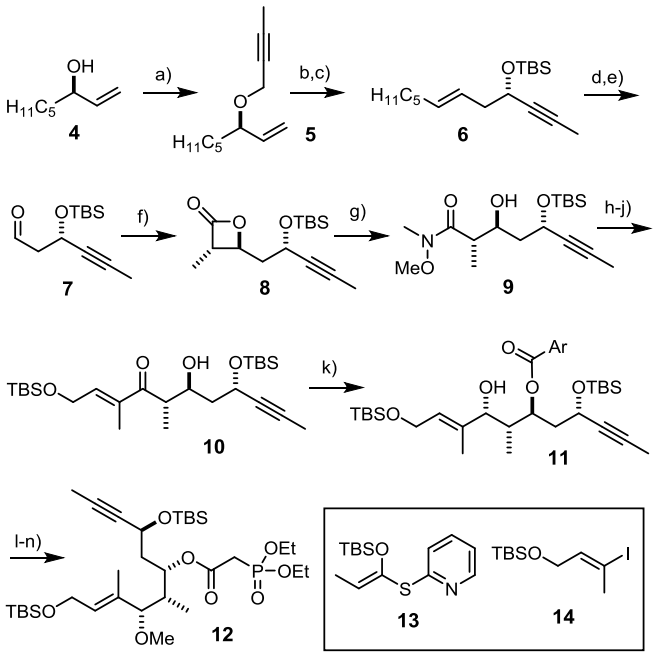
a strategically placed R_3E-substutent at the C12 position of the carbon framework potentially provides access to various analogues too;[29, 31] differing from the parent natural product at a site that has not yet been addressed in previous structure/activity relationship (SAR) studies.



Scheme 3. a) 1-bromo-2-butyne, NaH, THF, 93 %; b) *n*BuLi, THF, −78 °C; c) TBSCl, imidazole, CH_2Cl_2, 0 °C → RT, 79 % (over two steps); d) OsO_4 (0.22 mol%), NMO, CH_2Cl_2, acetone; e) $NaIO_4$, pyridine, 1,4-dioxane/water, 69 % (over two steps); f) **13**, $ZnCl_2$, CH_2Cl_2, 90 % (dr = 6:1); g) MeNH(OMe)·HCl, $AlMe_3$, CH_2Cl_2, 0 °C → RT, 67 % (pure diastereomer); h) TMSCl, imidazole, CH_2Cl_2, pyridine, 0 °C → RT; i) **14**, *t*BuLi, $CeCl_3$·2LiCl, THF, −78 °C; j) camphorsulfonic acid (cat.), CH_2Cl_2/MeOH, 0 °C (87 % over three steps); k) 4-nitrobenzaldehyde, SmI_2 (40 mol%), THF, −25 °C, 80 %; l) $Me_3O{\cdot}BF_4$, proton sponge, CH_2Cl_2, 0 °C → RT; m) K_2CO_3, THF/MeOH, 63 % (over both steps); m) diethyl phosphonoacetic acid, EDC·HCl, DMAP, CH_2Cl_2, 72 %; Ar = 4-nitrophenyl; DMAP = 4-dimethylaminopyridine; EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; NMO = *N*-methylmorpholine-*N*-oxide; TBS = *tert*-butyldimethyl-silyl; TMS = trimethylsilyl.

The substrate that allowed this concept to be tested was assembled as shown in Scheme 3. Of the different routes to aldehyde **7** investigated, the sequence starting off with a [2,3]-Wittig rearrangement of the allyl propargyl ether **5** was found to be most practical,[32] not least because the

required alcohol precursor **4** is readily available in optically pure form (>99 % *ee*) on multigram scale by enzymatic resolution;[33] moreover, the alkyl tail renders **5** non-volatile and hence easy to work with. Oxidative cleavage of the double bond in the derived enyne **6** furnished aldehyde **7**, which was engaged in a Mukaiyama-type aldol reaction/lactonization sequence with the mixed ketene acetal **13** to give the corresponding β-lactone **8** in high yield and good diastereoselectivity in favor for the *anti*-aldol isomer;[34, 35] the observed 1,3-asymmetric induction concurs with the generally accepted model for Lewis acid mediated additions to β-silyloxy aldehydes.[36] Since opening of the strained ring of **8** with organometallic reagents proved erratic, the lactone was transformed into the corresponding Weinreb amide **9** prior to ketone formation;[37, 38] best results were obtained, after transient protection of the –OH group as a labile TMS-ether, when the organolithium species formed from **14**[39] and *t*BuLi was transmetallated with $CeCl_3 \cdot 2LiCl$ to temper the basicity of the reagent.[40] Subsequent Evans-Tishchenko redox esterification with *p*-nitrobenzaldehyde of the resulting hydroxy ketone **10** set the 1,3-*anti* diol motif in an appropriately differentiated format.[41-43] Product **11** thus formed was subjected to O-methylation before the *p*-nitrobenzoate was exchanged for a diethyl phosphonoacetate group to afford compound **12** in readiness for fragment coupling.

The required partner was attained by Sharpless epoxidation of crotyl alcohol (**15**),[44] followed by opening of the resulting product **16** with lithiated 1,3-pentadiyne[45] in the presence of Et_2AlCl (Scheme 4).[46] The high selectivity in favor of the desired product **17** (≥ 10:1) is best appreciated upon comparison with the rather poor regiochemical outcome (≈ 4:1) obtained with lithio trimethylsilylacetylide as the reagent under otherwise identical conditions. Diol **17** was elaborated into the terminal epoxide **18**, which reacted under copper catalysis with the Grignard reagent derived from 4-bromo-cyclopent-1-ene. The resulting compound **19** was transformed into ketal **20** prior to an exquisitely selective reduction of the homopropargylic triple bond with Red-Al.[47] Deprotection of the ketal, periodate cleavage of the released diol **21** and selective oxidation[48] of the resulting hemiacetal furnished the rather unstable aldehyde **22**. We acknowledge that this desymmetrization strategy echoes pioneering work in the rhizoxin arena by Williams and coworkers,[Fehler! Textmarke nicht definiert.][13] which had later also been elegantly adapted by other groups.[14, 17] As expected, the union of **22** with phosphonate **12** by HWE to give the cyclization precursor **23** was straightforward.

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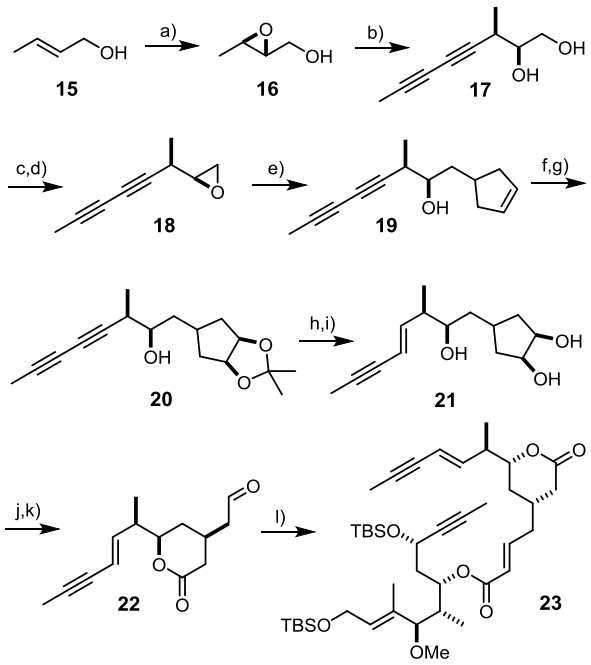

Scheme 4. a) Ti(O*i*Pr)$_4$ (4 mol%), D-(+)-diisopropyl tartrate (6 mol%), *t*BuOOH, MS 4Å, CH_2Cl_2, −20 °C, 78 % (er = 5:1); b) 1,3-pentadiyne, *n*BuLi, Et_2AlCl, CH_2Cl_2, −78 °C → 0 °C, 95 %; c) TsCl, pyridine, CH_2Cl_2, 0 °C → RT, 97 %; d) DBU, CH_2Cl_2, 0 °C → RT, 83 %; e) (i) 4-bromocyclopentene, Mg*, Et_2O; (ii) **18**, CuI, Et_2O, −40 °C, 78 %; f) OsO_4 (4 mol%), NMO, acetone/H_2O, 68 %; g) acetone, pyridinium *p*-toluenesulfonate (cat.), 83 %; h) Red-Al, THF; i) *p*TsOH (15 mol%), aq. MeOH, 40 °C, 93 % (over two steps); j) $NaIO_4$ adsorbed on SiO_2, CH_2Cl_2; k) PIDA, TEMPO (14 mol%), $Yb(OTf)_3$, CH_2Cl_2, 57 % (over two steps); l) **12**, LiCl, DBU, MeCN, then **22**, 0 °C, 86 %; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; PIDA = phenyliodine(III) diacetate; Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl radical; Ts = *p*-toluenesulfonyl.

With diyne **23** in hand, the project entered the critical assembly stage (Scheme 5). Gratifyingly, RCAM of this highly functionalized substrate proceeded well,[49] furnishing the desired product **24** in 67-70 % yield despite the considerable strain inherent to this polyunsaturated 16-membered ring. It is of note, however, that recourse to [Mo(N(*t*Bu)Ar)$_3$] (**30**)/CH_2Cl_2 as the catalyst system was necessary,[50] whereas the more convenient molybdenum alkylidyne complexes endowed with silanolate ligands gave mixtures of **24** and an acyclic dimer formed by homo-metathesis of **23**.

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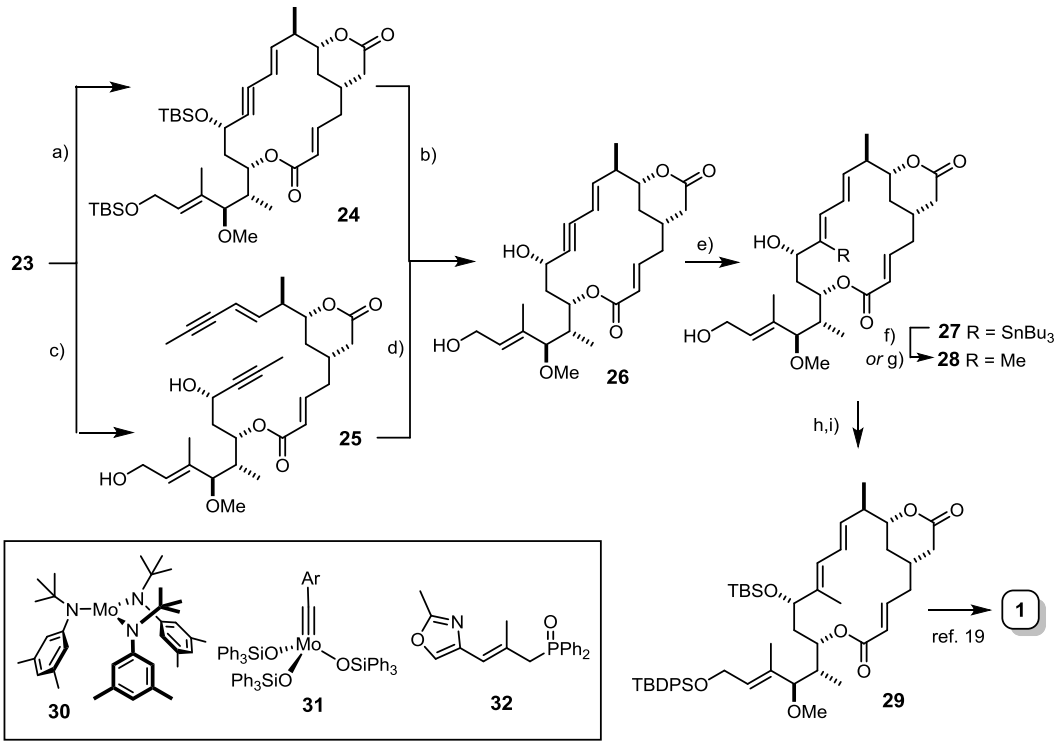

Scheme 5. a) **30** (10 mol%), toluene, CH_2Cl_2, 80 °C, 67-70 %; b) TBAF, THF, −50 °C → −10 °C, 90 %; c) TBAF, THF, −15 °C; d) **31** (15 mol%), MS 5 Å, toluene, 50 % (over two steps); e) $[Cp^*RuCl]_4$ (1.25 mol%), Bu_3SnH, 1,2-dichloroethane; f) MeI, CuTC, $[Ph_2PO_2][NBu_4]$, DMSO, 70 % (over two steps); g) [(cod)Pd(Me)(Cl)], THF, 56 % (over two steps); h) TBDPSCl, imidazole, CH_2Cl_2, −60 °C; i) TBSCl, imidazole, DMAP, CH_2Cl_2, 71 % (over two steps); Ar = 4-methoxyphenyl; cod = 1,5-cyclooctadiene; Cp* = pentamethylcyclopentadienyl; CuTC = copper thiophene-2-carboxylate; TBAF = tetra-*n*-butylammonium fluoride; TBDPS = *tert*-butyldiphenylsilyl.

This outcome is in line with earlier observations, which suggest that silanolate-based catalysts such as **31** (and variants thereof)[51, 52] are rather bulky and find limitations when it comes to metathesize sterically hindered triple bonds; propargylic alcohols protected with large O-substituents, as present in **23**, seem to fall into this category.[53]

To check this aspect, we deliberately cleaved both TBS-ether groups in **23** and subjected the resulting diol **25** to RCAM with complex **31** as the catalyst. In line with our expectations, this slimmer substrate did indeed afford the macrocyclic product **26**, although the overall yield was lower (50 % over two steps). This quantitative aspect notwithstanding, it is remarkable that a Schrock-type

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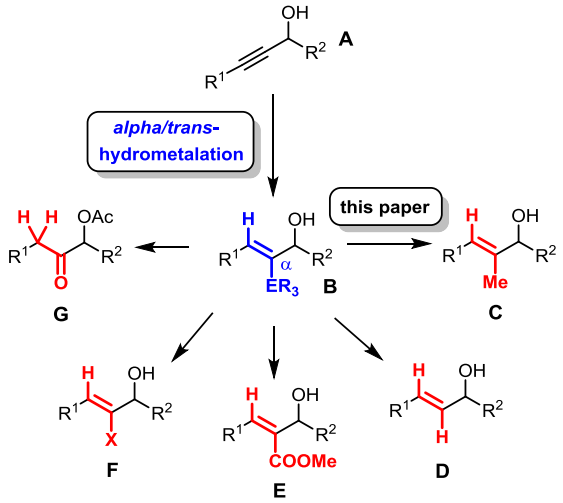
alkylidyne such as **31**, which is inherently nucleophilic and basic at the carbynyl carbon,[54] proves compatible with free primary and secondary –OH groups. Studies are underway in this laboratory to further evolve this striking yet arguably enabling chemical virtue.

With a robust entry into **26** in place, we were in the position to investigate the decisive downstream functionalization of this cycloalkyne. The key *trans*-hydrostannation reaction proved exquisitely selective when catalyzed by $[Cp^*RuCl]_4$[26, 27, 55] the resulting crude stannane **27** was directly subjected to C-methylation, which could be accomplished in two different ways by following protocols previously developed in our group: specifically, compound **27** was treated with MeI in the presence of CuTC as promotor and $[Ph_2PO_2][NBu_4]$ as an essentially neutral tin scavenger;[28] alternatively, it suffices to expose **27** to stoichiometric [(cod)Pd(Cl)(Me)]; this latter method mandates handling of a single reagent and is therefore recommended when working with small amounts of (precious) compounds.[56] Anyway, either procedure proved adequate, furnishing the required trisubstituted alkene **28** as a single regio- and stereoisomer in good yield. To complete the formal total synthesis of rhizoxin D (**1**), **28** was converted into the literature-known compound **29**, which intercepts the route described by the Pattenden group.[19] In parenthesis we note, that this detour might actually not be needed as diol **28** itself could probably be elaborated into **1** by selective oxidation followed by olefination of the resulting aldehyde with compound **32** (or an equivalent thereof). Because our investigation was mainly directed to provide proof-of-concept for a non-conventional metathesis strategy, we refrained from exploring this shortcut, as the rhizoxins had failed to find clinical approval.



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Scheme 6. Propargyl alcohols as gateway to common structural motifs

In conceptual terms, the results outlined above show that alkyne metathesis in concert with contemporary hydrometalation chemistry opens a reliable, selective and – by virtue of the rich chemistry of the C-ER_3 bond – inherently flexible entry into various types of (trisubstituted) alkenes and related motifs; some readily accessible patterns are depicted in Scheme 6. In addition to **C** pursued herein, the list includes substructures such as **D**,[57] **E**,[58] or **G**[59] as encountered in innumerous natural products, especially those of polyketide origin. The underlying strategy is hence likely of more general relevance since it might be translated to the synthesis of a very large number of (bioactive) target compounds. At the meta-level, one might even argue that motifs of type **C**-**G** deserve consideration as privileged assembly sites, although we certainly appreciate that this notion needs further scrutiny. In any case, the concept manifest in the present study is definitely distinct from the common reasoning that disubstituted rather than trisubstituted alkenes are necessarily the best sites for metathetic ring closure, especially when it comes to the formation of challenging macrocyclic rings.[20-25] Work is in progress that intends to test this non-traditional yet potentially enabling conclusion in other challenging settings.

Acknowledgements

Generous financial support by the MPG is gratefully acknowledged. We thank the analytical departments of our Institute for excellent cooperation.

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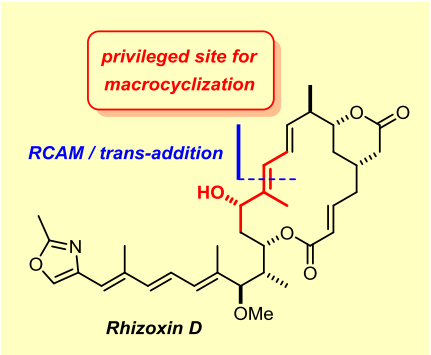

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Counterintuitive: The 1,3-diene region within the macrocyclic core of rhizoxin D is known to be crowded. Interestingly, ring closing alkyne metathesis (RCAM) proved better apt to meet this challenge than olefin metathesis (RCM); of particular note is the fact that the trisubstituted rather than the disubstituted alkene constitutes the more adequate assembly site. Either finding seems to violate common knowledge.

Keywords: Alkynes · 1,3-Dienes · *trans*-Hydrostannation · Macrocycles · Metathesis · Natural Products

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