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Modular Total Synthesis of Rhizopodin: A Highly Potent G-Actin Dimerizing Macrolide

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Abstract: A highly convergent total synthesis of the potent polyketide macrolide rhizopodin has been achieved in 29 steps by employing a concise strategy that exploits the molecule's C_2 symmetry. Notable features of this convergent approach include a rapid assembly of the macrocycle through a site-directed sequential cross-coupling strategy and the bidirectional attachment of the side chains by means of Horner–Wadsworth–Emmons (HWE) coupling reactions. During the course of this endeavor, scalable routes for synthesis of three main building blocks of similar complexity were developed that allowed for their stereocontrolled construction. This modular route will be amenable to the development of syntheses of other analogues of rhizopodin.

Keywords: macrocycles · natural products · polyketides · rhizopodin · total synthesis

Introduction

Myxobacteria are an extremely rich source of structurally unique and highly diverse natural products with a broad range of important biological properties.[1,2] In 1993, the groups of Höfle and Reichenbach introduced rhizopodin as a new compound from the myxobacterium *Myxococcus stipitatus* (strain Mx f164), which was obtained from a soil sample that was collected on San Andrés Island in the Caribbean Sea.[3] The original communication proposed a monomeric structure (**1**) for this compound, as shown in Figure 1.

It has been reported that cells undergo pronounced morphological changes on treatment with rhizopodin in low nanomolar concentrations, owing to the formation of a distorted cytoskeleton.[4] In detail, rhizopodin affects the polymerization process of monomeric G-actin to afford filamentous F-actin.

Actin polymerization not only plays a crucial role in cytoskeleton formation, but also in various other vital cell processes, such as adhesion, cell motility, and intracellular trans-

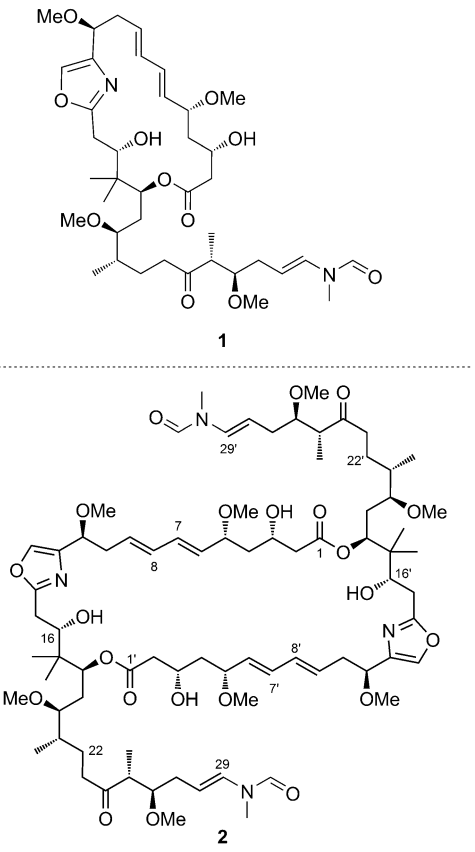

Figure 1. Originally reported monomeric structure (**1**) and revised dimeric structure of rhizopodin (**2**).

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portation.[5] A more fundamental understanding of the various processes that are involved in actin dynamics may lead to a more profound knowledge regarding cell organization, which might eventually be exploited for pharmaceutical purposes, for example, in cancer therapy.[6] In addition, it has been shown that the treatment of yeast cells with rhizopodin results in a dramatically decreased phagocytosis efficiency.[7]

Intrigued by this impressive biological profile, programs that were directed toward the determination of the absolute structure of rhizopodin were initiated. During their X-ray diffraction studies of actin-bound rhizopodin in 2008, in combination with advanced HRMS analysis, Jansen, Schubert, and co-workers realized that the originally proposed structure of rhizopodin needed to be revised to a C_2-symmetric dimer (**2**, Figure 1).[8] In a parallel study, the full relative and absolute stereochemistry of rhizopodin was assigned by ourselves by exploiting a variety of advanced NMR spectroscopic methods and molecular modeling, as well as chemical-derivatization experiments.[9] Simultaneously, the complete stereochemistry of rhizopodin was independently assigned by the group of Schubert.[10]

Altogether, the unique architecture of rhizopodin is characterized by a central 38-membered macrolactone core, which is comprised of two oxazole rings and two diene units, together with two stereotetrads adjacent to geminal dimethyl centers. Notably, the relative configuration within this specific type of hindered subunit appears to be unprecedented in nature. Attached to the central core are two side chains with *N*-vinyl-formamide termini. It became clear from the X-ray structure of actin-bound rhizopodin that these side chains were responsible for the formation of a very stable ternary complex with two G-actin units.

More recently, Pistorius and Müller proposed a biosynthetic pathway to rhizopodin by analyzing the respective gene clusters that are responsible for the synthesis of rhizopodin in *Stigmatella aurantiaca*.[11] Interestingly, they found a *trans*-polyketide synthase[12] that was involved in these bacteria, which meant that all of the methyl branches on the carbon skeleton must have resulted from methyl-transferase domains, such as in the biosynthesis of bryostatin. By applying the empirical models that were proposed by McDaniel and co-workers and Caffrey for the stereochemical outcome of ketoreductase activity,[13] they found a complete match between all of the hydroxy-bearing stereocenters and the initially proposed structure.

The intriguing and synthetically challenging architecture of rhizopodin, together with its sparse natural supply, piqued our interest in developing a total synthesis of this unprecedented dimeric macrolide, not only to enable the unambiguous confirmation of its initially uncertain stereochemistry, but also to support further biological evaluations and to enable structure–activity studies, as well as the development of simplified analogues to further understand and potentially utilize the unique biological profile of rhizopodin.

Rhizopodin has attracted considerable synthetic efforts from various groups and several syntheses of elaborate fragments,[14] as well as a preparation of the originally proposed monomeric structure, had been reported[15] before a first total synthesis was accomplished by our group.[16] During the preparation of this manuscript, Paterson and co-workers described an alternative synthesis of rhizopodin,[17] which relied on similar synthetic fragments and an endgame strategy that was originally discussed in our total synthesis.[16] Herein, we report the full details of the various strategies that we pursued, which eventually culminated in the first total synthesis of rhizopodin.[18]

Results and Discussion

Retrosynthetic analysis: As shown in Figure 2, our synthetic approach relied on the late-stage attachment of the side chains in a bidirectional manner to enable a modular connection of this critical part of the pharmacophore. We planned to introduce the side chains either through an aldol/elimination/reduction sequence (i.e., through the coupling of compound **3** with compound **4**)[19] or by applying a HWE coupling of compound **3** with compound **5** and subsequent 1,4-reduction.

Because we were concerned about the stability of compound **5**, we decided to use the OTES group as a synthetic equivalent of the enamide terminus, in contrast to a fully elaborate side chain (**4**). In both cases, macrocyclic dialdehyde **3** would serve as the coupling partner.[20] At this point, we planned to exploit the inherent symmetry in compound **3** and, thus, we dissected both ester motifs, thereby leading to their respective monomeric fragments (**6** and **7**). A distinctive structural feature in fragments **6** and **7** is the diene moiety, which could be forged by means of a suitable cross-coupling method. Then, ring-closure may either be achieved by means of a macrolactonization reaction or by employing a cross-coupling reaction, thereby rendering considerable flexibility into our synthetic plan. An inspection of these strategic considerations revealed that four fragments, namely C1–C7 building blocks **8** and **9** and C8–C22 building blocks **10** and **11**, could be suitable for the assembly of the macrocyclic core.

As shown in Figure 3, we considered various strategies for the synthesis of this central building block. To enable a short route, we intended to form the oxazole ring through a convergent cyclodehydration sequence, which required aminoalcohol **13** and an appropriate carboxylic acid as the key components. Our first approach envisaged a synthesis of compound **12** with all of the stereocenters between atoms C16 and C21 already in place before the ring-closure reaction.

As mentioned above, no method for the construction of the sterically hindered stereotetrad of compound **11** with the required relative configuration had been reported at the beginning of our campaign. Therefore, we planned a stepwise strategy, which relied on an Evans aldol reaction for the preparation of the C20/C21-*syn*-relationship, an asymmetric Sharpless epoxidation to install the stereocenter at the C18

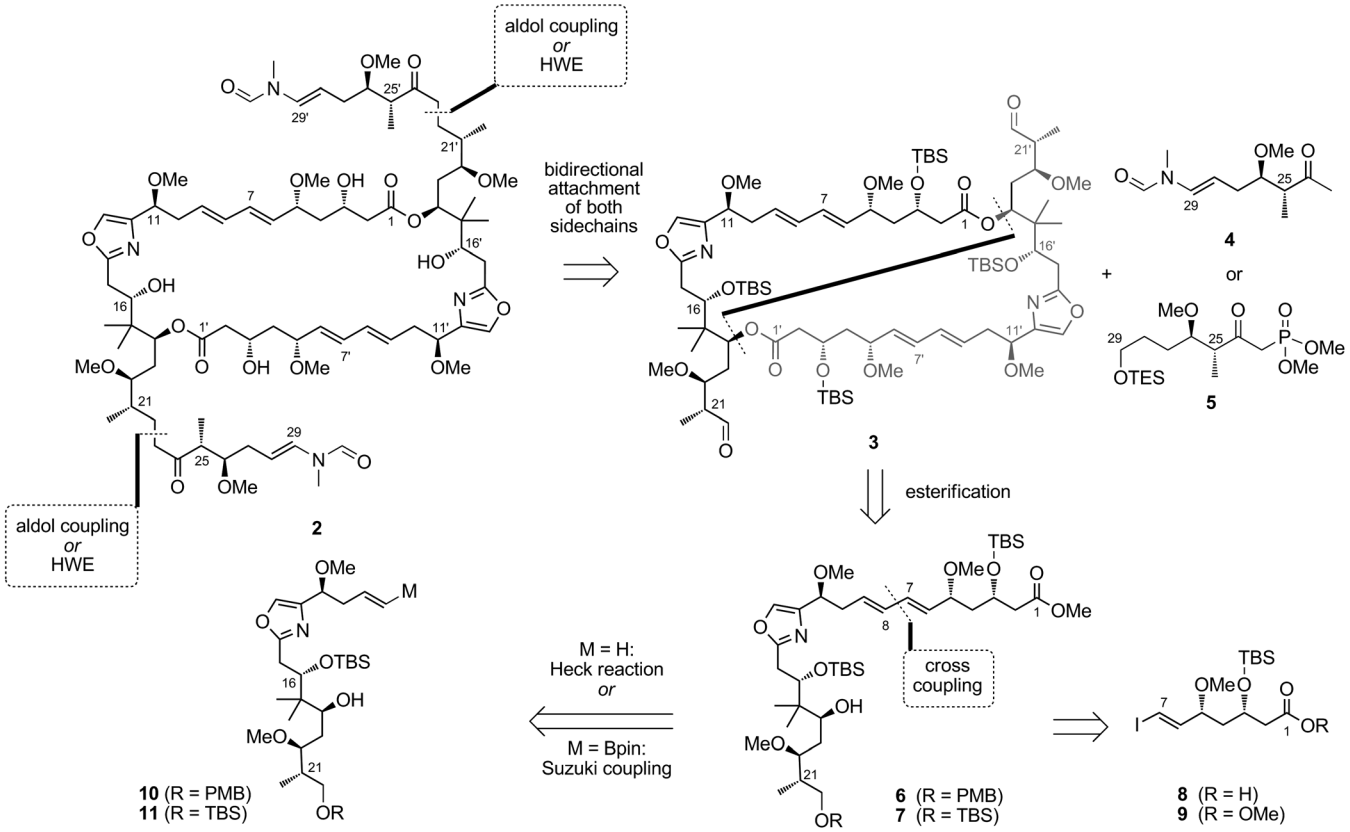


Figure 2. Retrosynthetic analysis of rhizopodin (**2**). Pin = pinacol, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

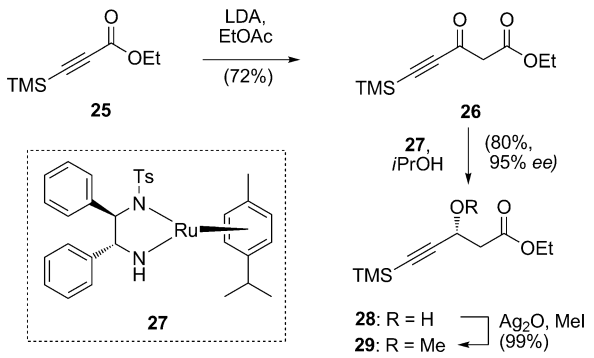
position, and either an asymmetric Mukaiyama aldol reaction or an iridium-catalyzed reverse-prenylation reaction as reported by Krische to gain access to the C16 stereocenter.

In parallel, we also evaluated a shorter approach to compound **11**, which relied on an early-stage oxazole ring-closure from chiral acid **23** (Figure 4). All of the remaining stereocenters would be installed by either applying an umpolung approach (by using epoxide **20**) or an aldol-coupling reaction with a methyl ketone of type **22**. This sequence would either require dithiane **19** or aldehyde **21**, which may be derived from compound **13** and acid **23**, which, in turn, should be accessible from (−)-pantolactone (**24**). This latter approach would be more convergent than the previous one described in Figure 3 and should allow a more rapid access to the desired fragment (**11**).

Synthesis of the C1–C7 building block: To set the stereocenters at the C3 and C5 positions, we envisioned an asymmetric reduction of β-keto compounds, according to the procedure reported by Noyori and co-workers. Our first attempt to introduce the vinyl iodine started from an alkyne by using a hydrometalation/iodination sequence.

Accordingly, commercially available alkyne **25** smoothly underwent a Claisen condensation reaction with lithiated ethyl acetate to furnish compound **26** in 72% yield (Scheme 1).[21] Then, various conditions for the stereoselective reduction step were tested and the standard conditions reported by Noyori and co-workers were found to work best on this substrate, thereby allowing access to compound **28** in 80% yield and 95% *ee*.[22] This result represents the first example in which a β-keto ester is used as a substrate for this powerful method. However, this reaction was difficult to scale-up, presumably owing to the presence of trace amounts of deprotected alkyne, which is known to inhibit the reduction reaction.

Despite these problems, compound **28** was efficiently accessible by using this sequence and was subsequently trans-



Scheme 1. Transfer hydrogenation reaction of β-keto ester **26** under the conditions reported by Noyori and co-workers. LDA = lithium diisopropylamide, Ts = *para*-toluenesulfonyl.

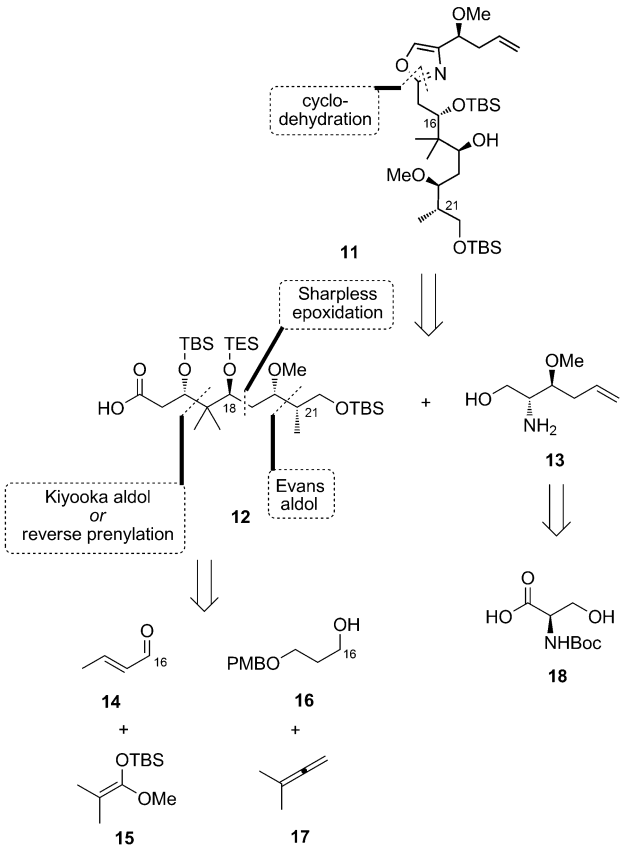


Figure 3. Further dissection of fragment **11**: late-stage oxazole formation. Boc = *tert*-butoxycarbonyl.

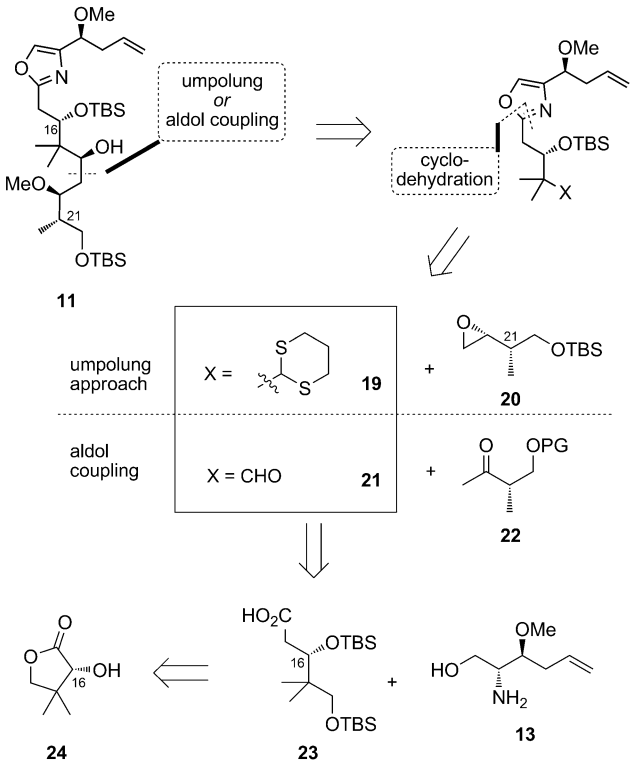
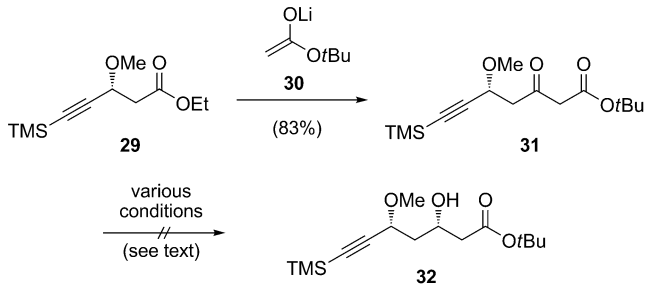


Figure 4. Alternative retrosynthetic analysis of compound **11**: early-stage oxazole formation. PG = protecting group.

formed into methyl ether **29**, which could then be subjected to the same condensation/reduction sequence as before (Scheme 2). Accordingly, compound **29** was treated with the lithium enolate that was derived from *tert*-butyl acetate (**30**), thereby enabling access to compound **31** in 83% yield, together with the formation of a byproduct that resulted from the double addition of the enolate (6%).[23] We found that the use of *tert*-butyl acetate instead of ethyl acetate was beneficial for the suppression of this undesired byproduct. Next, a second asymmetric reduction of compound **31** was examined. However, on applying Noyori's catalyst anew, the reaction was sluggish and only gave a moderate selectivity of 2:1

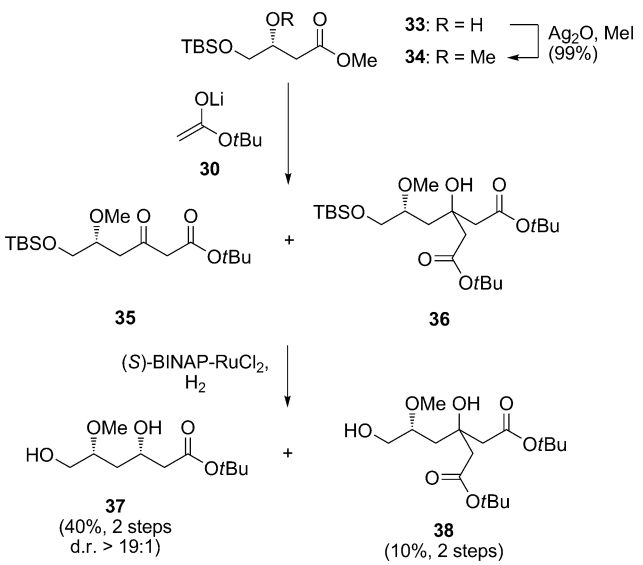


Scheme 2. Attempted diastereoselective reduction of β-keto ester **31**.

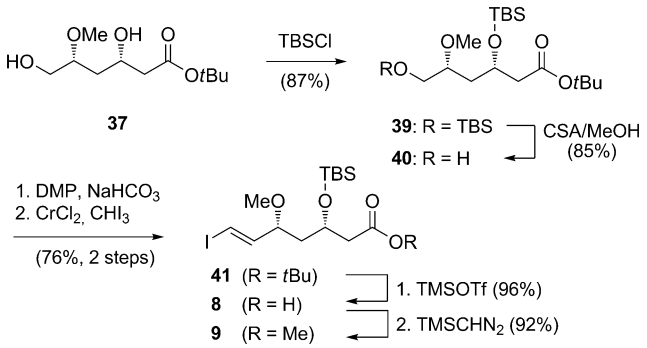
for the desired isomer (**32**), as did other conventional reducing agents ($NaBH_4$, $LiBH_4$, $Zn(BH_4)_2$, DIBAL). Disappointingly, our last option, namely an asymmetric hydrogenation reaction with $[RuCl_2(benzene)_2]$ as a catalyst and (*S*)-BINAP as a chiral ligand, resulted in over-reduction of the triple bond.[24]

These results prompted us to revise our synthetic plan. Because the alkyne motif seemed to be responsible for the problems that we encountered in the asymmetric reduction reactions, we chose an alcohol as a synthetic equivalent of the desired vinyl iodine, which would then be installed at a later stage by means of a Takai olefination reaction. The initial steps in this successful strategy are shown in Scheme 3. Starting from known ester **33**, which was available in three steps from D-malic acid,[25] ether **34** was obtained by treatment with methyl iodine in almost quantitative yield, which was then directly exposed to lithiated *tert*-butyl acetate.

This Claisen condensation reaction gave an inseparable mixture of compounds **35** and **36** in a 2.8:1 ratio, in which compound **36** was again the result of a double addition of the enolate.[26] Next, various attempts were made to improve this ratio, such as reversing the order of addition of the reaction partners to minimize the concentration of the enolate or employing other bases. In detail, the use of NaHMDS led to the formation of a considerable amount of a side-product that resulted from the elimination of the methoxy group of compound **34**. Alternatively, more LDA was added once the



Scheme 3. Successful route to the C3/C5 stereocenters of the C1–C7 fragment. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.



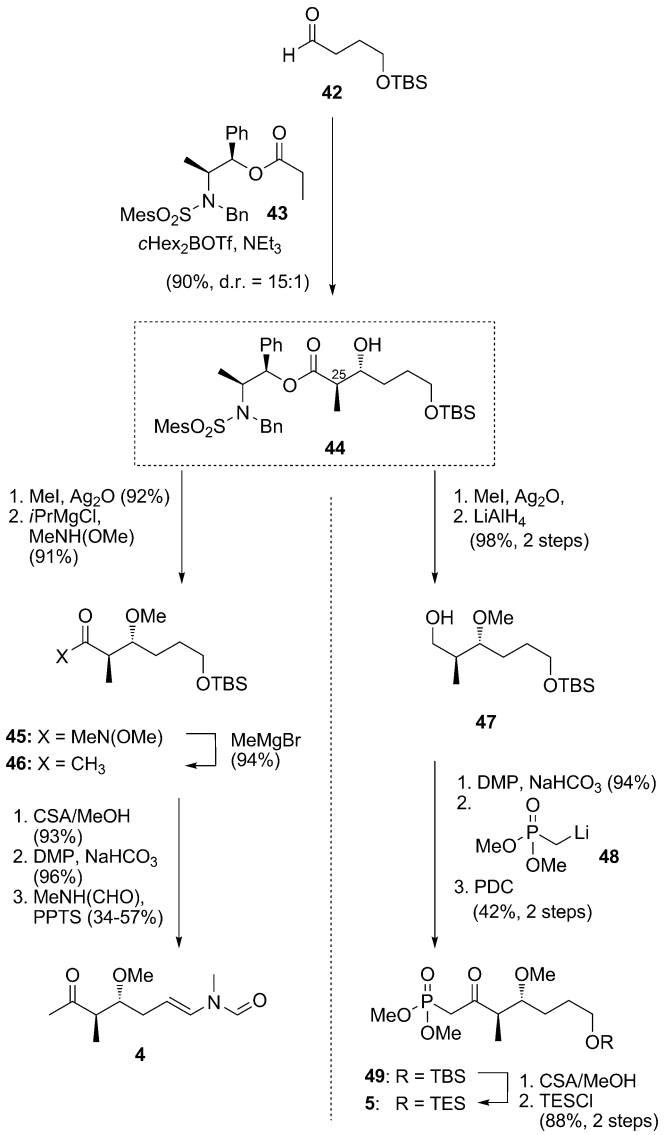
Scheme 4. Synthesis of the C1–C7 building block. DMP = Dess–Martin periodinane.

reaction had been judged to be complete by TLC to trigger a retro-aldol process to convert compound **36** back into compound **34**; however, this attempt was unsuccessful and no increase in the formation of compound **35** was observed. Another idea was the addition of a second, weaker base, such as DBU, to transform compound **35** in situ into the corresponding enolate, which should be unreactive towards a second attack of the nucleophilic enolate, but this was also unsuccessful. At this point, we decided to directly use the mixture in the subsequent asymmetric hydrogenation reaction and, much to our delight, the application of H_2 (4 bar) in the presence of $[RuCl_2(benzene)_2]$ and (*S*)-BINAP[23] gave a separable mixture of compound **37** with the concomitant loss of the TBS groups (40% over two steps) as a single diastereomer, together with compound **38** (10% over two steps). At this stage, the stereochemistry at the C3 position was confirmed by analysis of the Mosher's ester derivatives. Then, we proceeded with the elaboration of compound **37** into the desired vinyl iodine motif (Scheme 4). First, we investigated a selective primary oxidation reaction,[27] but unfortunately it resulted in the formation of the corresponding lactone from an intramolecular attack of the C3–OH group onto the newly formed aldehyde and a second oxidation process. To circumvent this problem, we transformed compound **37** into bis-TBS-ether **39**, which was then selectively deprotected in high yield at the primary position by using carefully controlled conditions (CSA in MeOH at −10 °C). Oxidation to the aldehyde was uneventful and subsequent treatment with iodoform in the presence of chromium(II) chloride, following the original procedure reported by Takai et al., gave compound **41** as an inseparable mixture of isomers (*E*/*Z* = 7:1, 76% upon scale-up).[28]

With regard to the upcoming assembly of the macrocycle, two aspects were considered at this stage. Firstly, the corresponding acid (**8**) was required as a coupling partner for the anticipated esterification reactions and, secondly, the protecting group at the C1 terminus had to be chosen carefully to allow for its selective removal at a later stage of the synthesis under mild conditions. During the assembly of the macrocycle of rhizopodin, we realized that selective cleavage of the *tert*-butyl ester was problematic, which motivated us to also synthesize the corresponding methyl ester. Accordingly, acid **8** was obtained by the treatment of compound **41** with TMS triflate and hydrolysis of the intermediary silyl ester during work-up (96%). Then, transformation into methyl ester **9** was effected through the in situ generation of diazomethane from $TMSCHN_2$ in the presence of MeOH.[29] The whole sequence was found to be reliable and allowed access to compounds **8** and **9** on a gram-scale in 11 and 12 steps, respectively.

Synthesis of the C23–C29 building block: For the construction of the *anti*-propionate motif in the C25/C26 region of rhizopodin, we used an auxiliary-based approach, as described by Abiko, Masamune, and co-workers.[30,31] As shown in Scheme 5, the treatment of ephedrine derivative **43** with dicyclohexyl boron triflate and triethylamine and coupling of the resulting *E* enolate to aldehyde **42** (derived in two steps from 1,4-butanediol) gave the desired C25/C26 *anti* isomer in high yield and good selectivity (95%, d.r. = 15:1). Following careful chromatography on silica gel, removal of the undesired diastereomer was possible and compound **44** now served as a common intermediate for the preparation of both compounds **4** and **5**.

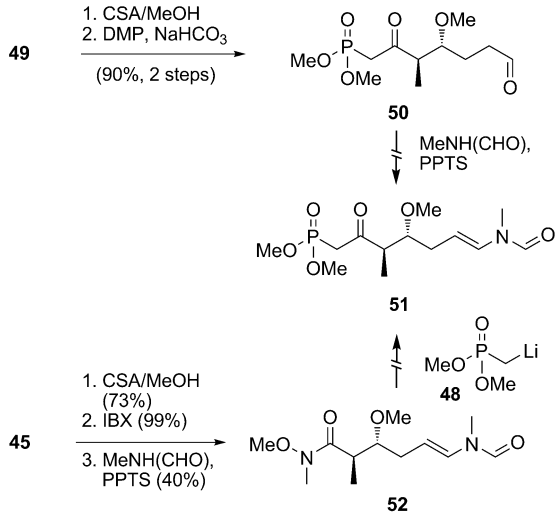
To this end, compound **44** was methylated and the auxiliary moiety was elaborated into Weinreb amide **45**[32] following a method developed in our group, and was then easily transformed into the desired methyl ketone (**46**) in almost quantitative yield (Scheme 5, left). Although the formation of the Weinreb amide was accompanied by small degrees of elimination along the methoxy group and the formation of the corresponding enone (about 10%), it was still found to be more effective than a likewise-tested sequence that involved the reductive removal of the ephedrine ester and a subsequent oxidation/addition/oxidation sequence. Next, the TBS group was removed under acidic conditions by treatment with CSA (93%), because basic media led to con-



Scheme 5. Preparation of side chains **4** and **5**. PDC = pyridinium dichromate, PPTS = pyridinium *para*-toluenesulfonate.

siderable formation of the elimination product. The by-product that resulted from elimination could be easily removed at this stage, which secured access to compound **4** after oxidation with DMP (96%) and Brønsted-acid-mediated condensation with *N*-methyl formamide. Notably, no reliable conditions for this condensation step could be established, that is, neither variation of reaction time, solvent, or acid gave satisfactory results. Finally, moderate yields (34–57%) were accepted, which allowed the isolation of compound **4** as a 2:1 mixture of rotamers.

In a rationale for the preparation of compound **5**, the direct replacement of the auxiliary with lithiated compound **48** was also tested, but met with failure.[31] Instead, treatment of compound **44** with MeI and Ag_2O, followed by reduction with $LiAlH_4$, gave alcohol **47** in 98% yield over two steps (Scheme 5, right). Oxidation with DMP furnished an instable aldehyde, to which compound **48** was smoothly added. The obtained mixture of diastereomers was directly oxidized with PDC in an efficient manner. This sequence proceeded with a typical yield of 40% over three steps. To allow for the selective liberation of the primary alcohol at a late stage of the synthesis, we decided to convert the primary TBS group of compound **49** into its more labile TES congener (**5**), which was accomplished by treatment with CSA and re-protection with TESCl (88% over two steps). In principle, the TES analogue of compound **42** could have been used directly, but in this case the first aldol reaction (Scheme 5) only gave a yield of 64%, which prompted us to rely on this somewhat longer sequence. Ultimately, attempts were made to prepare phosphonate **51** with a fully elaborated enamide terminus (Scheme 6). Not unexpectedly, all of



Scheme 6. Failed attempts towards fully functionalized β-keto phoshonate **51**. IBX = 2-iodoxybenzoic acid.

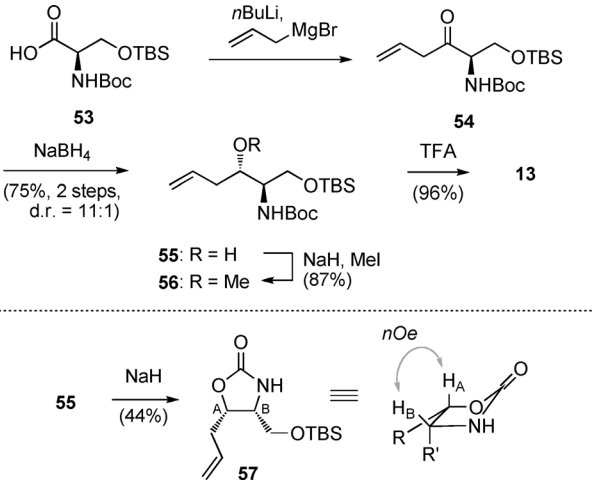
these attempts were unsuccessful, presumably owing to the harsh reaction conditions that were required. First, the intermediate alcohol that resulted from the removal of the TBS group from compound **49** was oxidized by treatment with DMP and the aldehyde was heated in the presence of PPTS and *N*-methylformamide. However, this reaction resulted in extensive decomposition of the starting material. Alternatively, the sequence for the conversion of compound **46** into compound **4** (Scheme 5, left) was applied to compound **45** and successfully furnished compound **52**. Disappointingly, treatment of the latter compound with the appropriate lithiated phosphonate (**48**) only led to decomposition.

These results made us aware of the instability of the vinyl-formamide motif and we integrated this knowledge in our future synthetic considerations.

Synthesis of the C8–C22 building block: Next, our efforts were directed towards the preparation of the C8–C22 building block. The oxazole ring should be closed in a convergent manner, following a cyclodehydration strategy. To enable

a simultaneous deprotection at a late stage of the synthesis, a TBS group was chosen to protect the C16 alcohol group, in analogy to the protecting group on the C3-hydroxy function. The C22 terminus needed to be transformed into the desired aldehyde, so our initial idea was to orthogonally protect it as a PMB-ether. Likewise, a TBS-protected congener was considered (**10** and **11**, Figure 2).

Synthesis of amino alcohol 13: Common to all of these routes was the requirement of amino alcohol **13** for the formation of the oxazole ring, the preparation of which is summarized in Scheme 7. Starting from commercially available



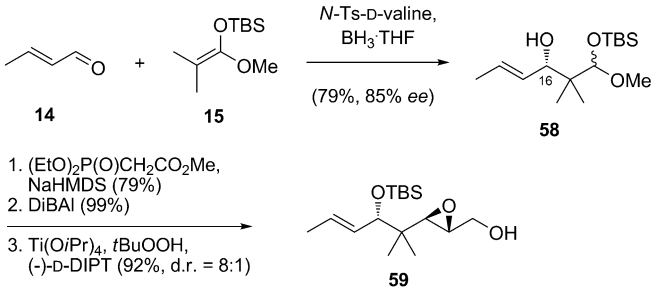
Scheme 7. Preparation of aminoalcohol **13** and verification of the 1,2-*anti*-aminoalcohol relationship of **55.**

N-Boc-D-serine, TBS protection of the hydroxy group proceeded in good yield (79%, not shown), thus allowing the formation of the lithium carboxylate of compound **53** and the subsequent addition of allylmagnesium chloride, as described by Knudsen and Rapoport.[33] This reaction afforded homoallylic ketone **54**, which was prone to isomerization and, hence, was directly reduced to the corresponding alcohol (**55**). According to a report by Evano and co-workers, this transformation proceeded smoothly by using sodium borohydride at −78 °C.[34] Presumably owing to internal chelation of the amino group, the shown diastereomer was formed in a ratio of 11:1. The undesired isomer was easily removed by column chromatography on silica gel and gave access to compound **55** on a multigram scale. The stereochemical outcome of this reaction was confirmed by transforming compound **55** into the corresponding oxazolidinone (**57**), which showed a characteristic nOe correlation (Scheme 7, bottom).

After having verified the correct stereochemistry of compound **55**, selective O-methylation of compound **55** was required, which required some optimization. Although a variety of bases (NaHMDS, 2,6-lutidine, etc.) and methylation agents (MeOTf, $Me_3O{\cdot}BF_4$) were tested, NaH/methyl iodide gave superior results if the deprotonation step was conducted carefully. Reaction time and temperature were crucial for preventing either N-methylation or the formation of oxazolidinone **57**. Under these optimized conditions, the synthesis of methyl ether **56** was possible in reproducibly high yield (87%). Finally, both protecting groups could be simultaneously cleaved with aqueous TFA, with special attention to the high polarity of the target compound (**13**) during work-up and isolation. In summary, gram-quantities of compound **13** were accessed in 49% yield over five steps.

Late-stage oxazole ring-closure: As mentioned earlier (Figure 3), we next focused on the synthesis of carboxylic acid **12**, with all of the stereocenters between atoms C16 and C21 already in place, which should all be installed in a stepwise, stereocontrolled manner.

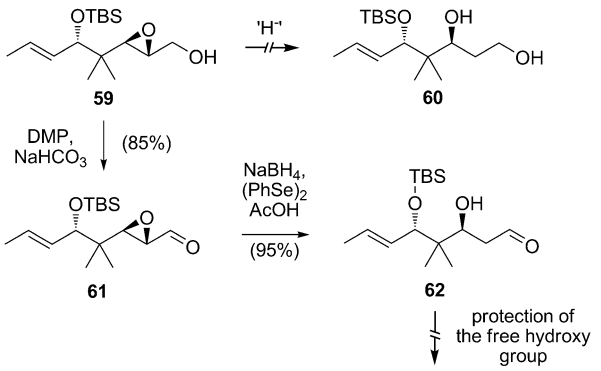
Kiyooka aldol approach: First, we adapted a strategy developed by Meyers and co-workers.[35] Starting with an asymmetric Mukaiyama aldol reaction reported by Kiyooka et al.[36] between crotonaldehyde (**14**) and compound **15**,[37] silylacetal **58** was afforded in high yield in an enantiomeric excess of 85% with respect to the C16 stereocenter (Scheme 8).



Scheme 8. Kiyooka aldol reaction and further elaboration of compound **58** to obtain the desired C16/C18 configuration. (−)-D-DIPT = (−)-D-diisopropyltartrate.

Upon treatment with base in the presence of methyl diethylphosphonoacetate, a 1,5-*O*-silyl migration took place to afford an aldehyde intermediate, which was converted without isolation into the corresponding unsaturated ester in 79% yield.[38] Reduction of the ester with DIBAL proceeded smoothly and the resulting allylic alcohol was subjected to Sharpless asymmetric epoxidation conditions[39] to furnish epoxide **59** in 92% yield in a diastereomeric ratio of 8:1 in favor of the desired isomer.

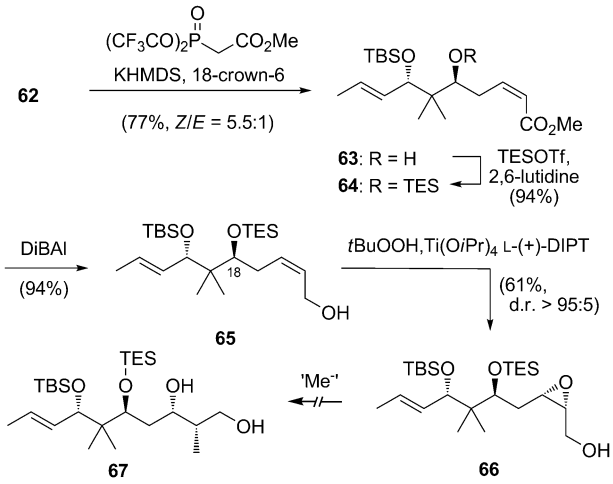
Next, our efforts were directed towards the transformation of compound **59** into a 1,3-diol equivalent (Scheme 9). To this end, various hydride sources were examined for the regioselective opening of the epoxide, including RedAl, $LiAlH_4$, DIBAL, and AlH_3, but all of them resulted in either decomposition of the starting materials or afforded mixtures of diols as a result of silyl migration under the basic reaction conditions, with the formation of only trace amounts of the desired compound (**60**). Ultimately, we oxi-



Scheme 9. Attempted regioselective opening of epoxide **59**.

dized compound **59** to the respective epoxyaldehyde (**61**) by treatment with DMP, for which a method to convert it to a β-hydroxyaldehyde has been described.[40] Indeed, treatment of compound **61** with $NaB(OEt)_3SePh$ furnished compound **62**; however, the hydroxy group in the product could not be orthogonally protected under a variety of conditions (Ac_2O/pyridine, PivCl/NEt_3, TESOTf/2,6-lutidine, etc.).

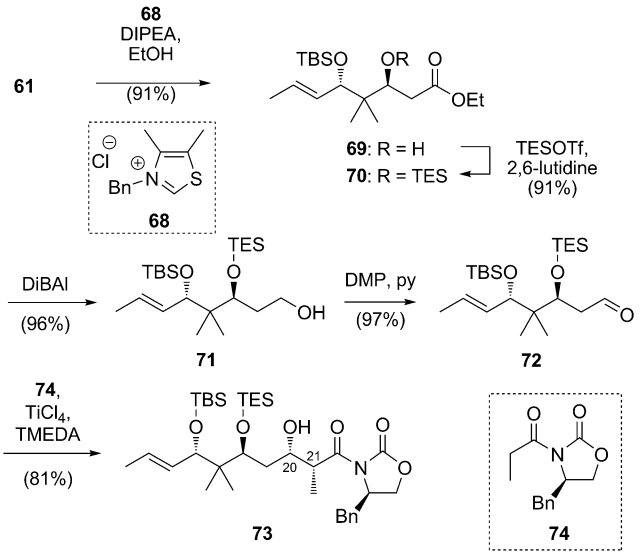
In contrast, compound **62** smoothly underwent a Still–Gennari olefination reaction[41] to afford the pure *Z* isomer (**63**) in 77% yield after chromatography on silica gel (Scheme 10), which was subsequently protected as a TES-ether and reduced by treatment with DIBAL to afford compound **65** in excellent yield.



Scheme 10. Still–Gennari olefination of compound **62** and attempted selective epoxide opening to afford compound **67**.

In agreement with previous reports that *Z*-allylic alcohols are poor substrates for asymmetric epoxidation reactions,[38] the standard conditions described by Sharpless did not allow complete conversion, but compound **66** could be isolated in 61% yield as a single diastereomer. It should be noted that protection of the C18-alcohol group was crucial, otherwise a 4:1 mixture of both epoxides was observed. With compound **66** in hand, we were confident of establishing conditions for a selective copper-mediated opening of the epoxide with one of the many reported methyl nucleophiles to gain access to compound **67**.[42] Thus, we examined various copper(I) sources (CuI, CuCN) with different nucleophiles (MeLi, MeMgCl, MeMgBr), as well as the reagent combination *n*BuLi/$AlMe_3$, which was only recently described.[43] However, disappointingly, all of these conditions either resulted in decomposition (CuI/MeMgBr) or no conversion, so we had to revise our strategy.

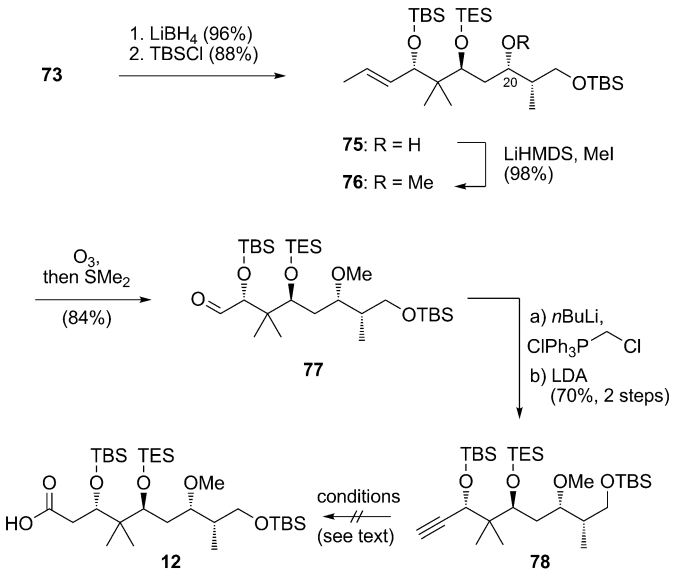
Alternatively, Bode and co-workers described an organocatalytic internal redox-isomerization reaction of 2,3-epoxyaldehydes, such as compound **61** (Scheme 9), to afford the corresponding β-hydroxyesters.[44] Application of these conditions allowed the preparation of compound **69** in high yield, without losing any stereochemical information, even on a gram scale (Scheme 11). Following the routine adjustment of the oxidation states and protecting groups, aldehyde **72** was finally obtained in high yield over these three steps and also allowed the partial removal of the undesired diastereomer by careful chromatography on silica gel. From a strategic point of view, compound **72** was a well-suited precursor for installing the missing stereochemical C20/C21-*syn* relationship by using an auxiliary-controlled aldol reaction, as described by Evans et al.[45] Consequently, compound **72** was treated with different enolates that were derived from compound **74**, of which the titanium enolate as described by Crimmins and co-workers was most reliable and allowed the formation of compound **73** in 81% yield as a single isomer.[46]



Scheme 11. Organocatalytic redox-isomerization of compound **61** and Evans aldol reaction to install the full C16–C21 stereotetrad. DIPEA = *N*,*N*-diisopropylethylamine, py = pyridine, Bn = benzyl.

Next, the auxiliary was removed upon treatment with $LiBH_4$, as reported by Soai and Ookawa,[47] and the resulting diol was selectively protected as a primary TBS-ether before

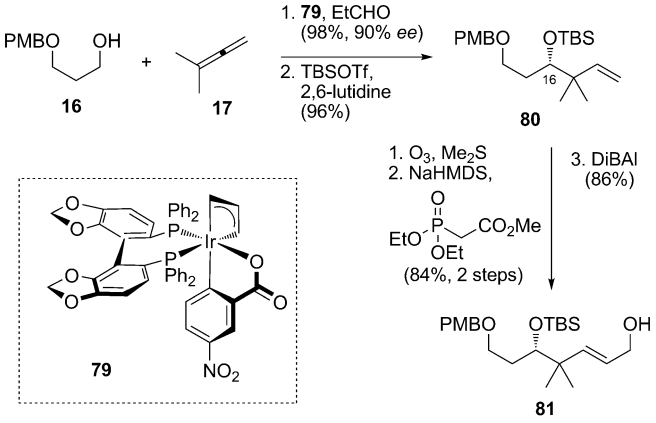
the remaining hydroxy group at the C20 position was transformed into the corresponding methyl ether (**76**, Scheme 12). This strategy was found to be superior to an inverted order of these steps, that is, methylation/reduction/TBS protection.



Scheme 12. Attempts to synthesize acid **12**.

To advance compound **76** into compound **12**, our synthetic plan now demanded the elaboration of the vinyl unit into a carboxylic acid. To this end, the olefin was oxidatively transformed into aldehyde **77**. At this stage, several methods were considered. Because compound **77** was extremely sterically hindered and, hence, was unreactive toward a variety of nucleophiles, we took note of a method that was used by Körner and Hiersemann to solve a related problem, which allowed the formation of an alkyne from sterically congested aldehydes.[48] Thus, the treatment of compound **77** with an ylide that was derived from chloromethyltriphenylphosphonium chloride smoothly resulted in the formation of a mixture of *E*/*Z*-vinyl chlorides, which, upon treatment with LDA, collapsed in a Fritsch–Buttenberg–Wiechell-like rearrangement into compound **78**. With alkyne **78** in hand, numerous conditions for its transformation into acid **12** were examined (most likely through a two-step process that involved the initial formation of an aldehyde). Among these conditions were an *anti*-Markovnikov hydration,[49] various hydroboration/oxidation methods, and a hydrosilylation reaction followed by a Tamao–Fleming oxidation.[50,51] Disappointingly, all of these efforts were unsuccessful and only gave trace amounts of compound **12** at best. Mostly, decomposition of starting materials was observed.

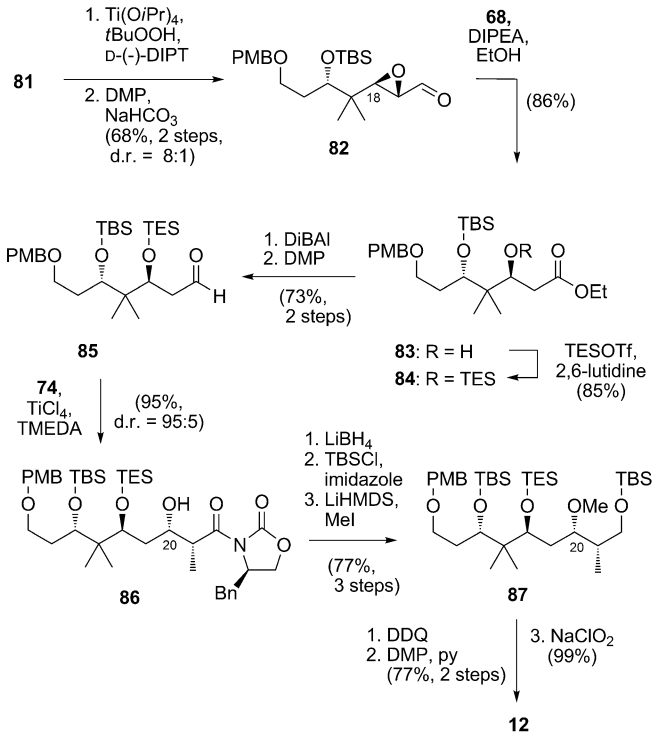
Reverse-prenylation approach: Despite this highly unsatisfying outcome, we had established a sequence for the construction of the C16–C21 stereocenters and we felt that a slight variation of the starting material should enable access to acid **12**. Our revised strategy is shown in Scheme 13 and commenced with an asymmetric reverse-prenylation reaction, following a procedure reported by Krische and co-workers.[52]



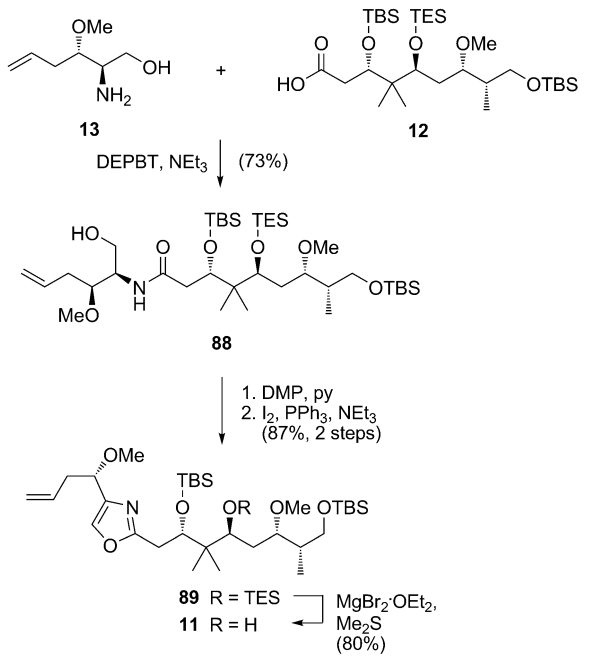
Scheme 13. Reverse-prenylation approach.

We identified PMB-protected alcohol **16**[53] as a suitable precursor for the installation of the required carboxylic acid, which was treated with 1,1-dimethyl allene (**17**) in the presence of propionaldehyde and a catalytic amount of Ir-catalyst **79** to afford compound **80** in quantitative yield. The enantiomeric excess could be improved from 82 to 90% if compound **79** was purified by column chromatography prior to use[54] and the configuration of the new stereogenic center was validated by analysis of the Mosher esters. Next, the free OH group was protected as a TBS-ether (96%) before oxidative cleavage of the double bond afforded an aldehyde, which was directly homologated by means of a HWE reaction and reduced to the corresponding allylic alcohol (**81**) in high yield. Whereas an ozonolysis reaction was feasible on a small scale (Scheme 13), problems arose during scale-up, with partial cleavage of the PMB group upon prolonged exposure to ozone. However, this problem could be easily circumvented by applying a two-step procedure of bis-hydroxylation, followed by glycol cleavage with $NaIO_4$.[55]

Inspection of compound **81** unambiguously revealed its similarity to an intermediate in the route presented above and we hoped that the sequence that we had developed for the installation of the missing stereocenters could be easily adapted. As shown in Scheme 14, this was indeed the case. Epoxidation of compound **81** under the previously described conditions was performed to afford an epoxyalcohol as an 8:1 mixture in favor of the expected C18 diastereomer. Oxidation with DMP furnished aldehyde **82**, which then underwent an internal redox-isomerization[43] into the respective β-hydroxyester (**83**), which was elaborated as described above. Aldehyde **85** now served as a starting material for an Evans-aldol reaction. Treatment with the titanium enolate



Scheme 14. Final successful route to acid **12**.



Scheme 15. Completion of the late-stage oxazole formation approach to building block **11**. DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one.

of compound **74** provided compound **86** as a sole product in 95% yield, which was found to be the C20/C21-*syn* isomer, as expected. With the lessons that were learned from our previous efforts, reductive removal of the auxiliary ($LiBH_4$, 88%), introduction of the primary TBS-ether (TBSCl), and methylation (LiHMDS, MeI, 88% over two steps) proceeded uneventfully and afforded compound **87**. In sharp contrast to the problems discussed above, the PMB group was removed under standard conditions (DDQ in buffered aqueous solution) and the liberated alcohol was oxidized to the required carboxylic acid (**12**) in two steps with DMP and $NaClO_2$.

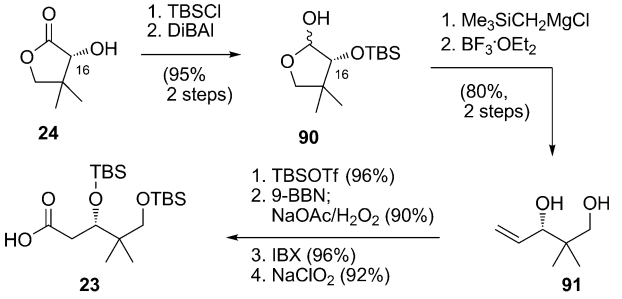
With efficient access to both compounds **12** and **13** in hand, we proceeded with their assembly. A few coupling conditions were examined, of which treatment with DEPBT[56] in the presence of NEt_3 was found to be most reliable and allowed the formation of amide **88** in 73% yield (Scheme 15).

Next, we successfully realized the planned convergent ring-closure of the oxazole by applying slightly modified Robinson–Gabriel conditions reported by Wipf and Miller,[57] which involved oxidation of the hydroxyamide and treatment of the intermediate aldehyde with triphenylphosphine/iodine in the presence of triethylamine. Much to our delight, these reagents resulted in the formation of compound **89** in 87% yield over both steps. Our final task was the selective removal of the TES group. Whereas HF/pyridine cleaved both the primary TBS- and the TES-ether, surprisingly, treatment with $MgBr_2{\cdot}OEt_2$ and SMe_2 exclusively deprotected the TES group as desired (80%),[58] thus affording the complete C8–C22 fragment (**11**) in a longest linear sequence of 23 steps in 8.1% yield.

Early-stage oxazole formation: The route described in the previous section allowed access to compound **11**, but it was, nevertheless, lengthy and difficult to scale-up. This drawback prompted us to address this problem by developing an alternative approach that was more convergent and, thus, allowed a more practical synthesis of the C8–C22 fragment.[16]

As discussed in the retrosynthetic analysis (Figure 4), acid **23** was required, which we anticipated could be available from (−)-pantolactone (**24**). In the forward sense, compound **24**, which already contained the stereocenter at the C16 position, was first protected as the TBS-ether and, subsequently, reduced to the corresponding lactol (**90**, Scheme 16).

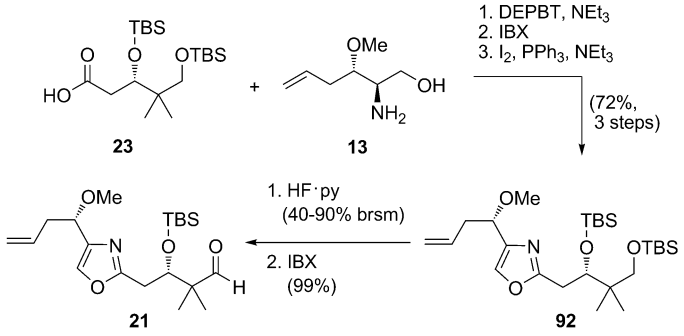
Next, we examined conditions to convert compound **90** into olefin **91**. Although all efforts to perform a Wittig olefination failed, in accordance with a literature precedent,[59] the desired methylene unit could successfully be installed by using the Tebbe reagent.[60] However, this reaction was very expensive when performed on a large scale. Therefore, we employed a two-step Peterson olefination procedure as described by Ley and co-workers.[61] The addition of a commercially available Grignard reagent and subsequent treatment with $BF_3{\cdot}OEt_2$ triggered the desired elimination reaction and afforded compound **91** on a multigram scale. Moreover, only a single chromatographic purification step was needed. Diol **91** was conveniently protected with two TBS groups and the double bond could be elaborated into the carboxylic acid in a straightforward manner. Hydroboration/oxidation



Scheme 16. Elaboration of acid **23** from (−)-pantolactone (**24**). 9-BBN = 9-borabicyclo[3.3.1]nonane.

using mild conditions developed by Trost et al. provided an alcohol (90%, not shown),[62] which was oxidized to the respective acid (**23**) by using IBX at reflux in EtOAc (96%)[63] and a subsequent Pinnick oxidation (92%). It is noteworthy that the intermediate aldehyde was susceptible to decomposition upon chromatography on silica gel. This decomposition could be omitted if the aforementioned conditions were used, which only required simple filtration.

With acid **23** and amino alcohol **13** (Scheme 7) in hand, these two fragments were coupled together by using DEPBT/NEt_3 through our previously developed sequence (Scheme 17). Oxidation with IBX, followed by treatment

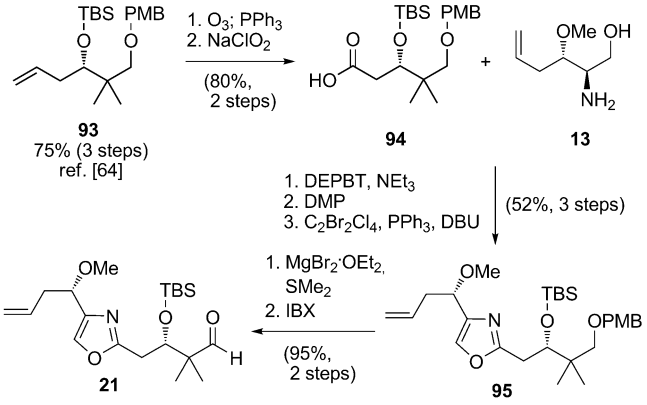


Scheme 17. Early-stage oxazole formation and synthesis of aldehyde **21**.

with PPh_3/I_2 and NEt_3, triggered the desired cyclodehydration and resulted in the smooth formation of oxazole **92** (72% over three steps).[56a] Because our synthetic plan envisaged the formation of aldehyde **21** as an intermediate for the application of either umpolung or aldol-coupling strategies, compound **92** needed to be selectively deprotected at the primary position. After considerable experimentation, we eventually found that HF/pyridine in buffered THF were the optimal conditions, which afforded the respective alcohol in various yields (40–90%, based on 75% conversion). Oxidation to aldehyde **21** was unproblematic and proceeded in quantitative yield.

We used this route (early-stage oxazole formation) to gain access to multigram quantities of aldehyde **21**. Nevertheless, during further investigations, we could optimize this route in terms of step count and reproducible overall yield (Scheme 18).

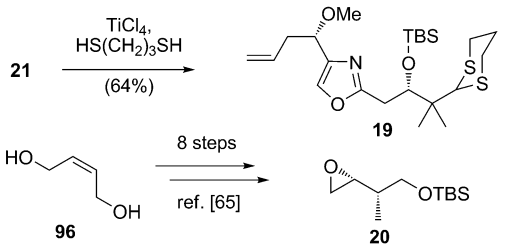
In 2009, Krische reported the facile and scalable synthesis of building block **93**, which was prepared by an iridium-cata-



Scheme 18. Optimized strategy leading to aldehyde **21**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

lyzed allylation reaction within three steps in high optical purity and excellent overall yield.[64] In our hands, this method was confirmed as a powerful tool for the allylation of extremely sterically hindered alcohols or aldehydes. We oxidized compound **93** by means of ozonolysis and Pinnick oxidation. Amide formation was again best performed by using DEPBT as a coupling reagent in 93% yield. *N*,*N*′-dicyclohexylcarbodiimide (DCC), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), and the corresponding acid chlorides that were generated by heated acid **94** at reflux in thionyl chloride or oxalyl chloride gave lower yields. After oxidation, oxazole building block **95** was most efficiently obtained under slightly different cyclodehydration conditions, as also described by Wipf and co-workers.[56a] The intermediate aldehyde (not shown) was treated with 1,2-dibromo-1,1,2,2-tetrachoroethane, PPh_3, and NEt_3 and subsequently exposed to DBU to give rise to compound **95** in good yield. It should be mentioned that the procedure as described above ($I_2/PPh_3/NEt_3$) suffered from highly varying yields. As depicted in Scheme 17, the selective deprotection of the primary TBS group was also problematic in terms of material throughput, because incomplete conversion and varying yields had to be accepted. Within the optimized route shown in Scheme 18, the orthogonal PMB protection of compound **95** was found to be advantageous, owing to the possibility of selectively deprotecting compound **95** in almost quantitative yield by employing mild Lewis acidic conditions ($MgBr_2{\cdot}Et_2O/SMe_2$). After oxidation with IBX, the desired aldehyde (**21**) was now accessible in only 10 steps and an overall yield of 30%.

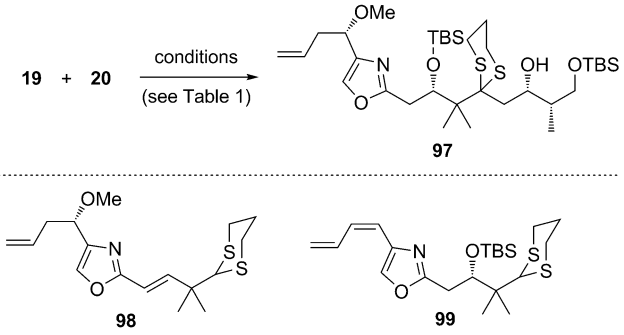
Umpolung approach: For the desired umpolung reaction, we required compound **20** as a coupling partner, whose mirror image was already literature-known (Scheme 19).[65] We



Scheme 19. Preparation of the precursors for the envisaged umpolung approach.

adapted the described sequence starting from commercially available diol **96** by using the enantiomeric tartrate for the initial Sharpless epoxidation, which furnished compound **20** in 8 steps. Then, aldehyde **21** was transformed into the desired dithiane (**19**) by treatment with 1,3-propanedithiol and catalytic amounts of $TiCl_4$.[66]

With compounds **19** and **20** in hand, we were poised to study the key umpolung step.[67] To this end, various bases and conditions were applied to form the anion that was derived from compound **19**, which should open epoxide **20** through a nucleophilic attack (Scheme 20).



Scheme 20. Umpolung approach.

Much to our disappointment, we observed either no conversion or the formation of several side-products that resulted from elimination processes. With *n*BuLi as a base (Table 1, entry 1), both starting materials were almost fully recovered. With *s*BuLi, the reaction proceeded sluggishly (Table 1, entry 2), that is, compound **19** decomposed and low yields of compound **99** were observed. In contrast, treatment of compound **19** with *t*BuLi resulted in the smooth formation of undesired compound **98** after 10 min (Table 1, entry 3). We anticipated that compounds **98** and **99** arose from E1cb mechanisms, which implied that protons adjacent to the heterocyle possessed pK_a values within the same range as the dithiane proton, which indeed might be the case. In addition, treatment of compound **19** with various bases and quenching with D_2O did not result in the formation of deuterated compound **19**, which gave rise to the conclusion that no deprotonation at the desired position occurred.

Table 1. Attempted umpolung reaction of dithiane **19**.[a]

Entry	Base	Additive	Result (yield [%])
1	*n*BuLi	HMPA	no conversion
2	*s*BuLi	TMEDA	**99** (15)
3	*t*BuLi	HMPA	**98** (96)

[a] HMPA = hexamethylphosphoramide, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine.

For a related system, Smith and co-workers extensively studied several sterically encumbered dithianes, which they were able to metalate without problem.[68] However, a related substrate to compound **19**, which contained an allyl-ether functionality, could not be deprotonated either. This result prompted us to further study this process. From literature precedents, we concluded that the equatorial proton in a dithiane was abstracted much more quickly;[69] this conclusion was rationalized by the assumption that the formed anion showed no disturbing interactions with the electron lone pair located on the sulfur atom, and the anion exhibited a favorable interaction with the σ* orbital of the carbon–sulfur bond.[70] This delocalization would result in a lengthening of the indicated carbon–sulfur bond. Although Lehn and Wipff confirmed this theory for thioacetals in a theoretical study,[71] to the best of our knowledge, no data for (cyclic) 1,3-dithianes were available. Consequently, we calculated the bond lengths in both neutral and anionic 2-*tert*-butyl-1,3-dithiane as models for compound **19**, which showed the anticipated result (Figure 5). The anion located at the C1 position transferred electron density into the σ* orbital, which resulted, on the one hand, in a substantial contraction of the indicated bond and, on the other hand, in an enlargement of the C–S bond of 0.03 Å, owing to partial occupancy of the antibonding orbitals. This result strongly underpins the importance of the σ* orbital for the stabilization of the anionic species, which is only possible in this conformation with the *tert*-butyl substituent being pseudo-axial.

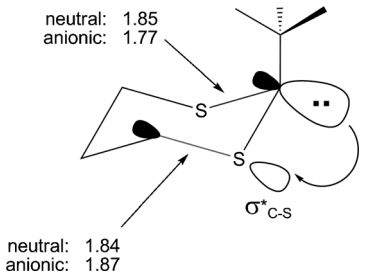


Figure 5. Orbital interactions in 2-*tert*-butyl-1,3-dithiane; bond lengths [Å] were calculated by using DFT at the B3LYP, 6-31G** level of theory.

According to the report by Smith et al., two conformations of compound **19** might, in principle, be involved. Presumably owing to the Thorpe–Ingold effect, compound **19** is expected to reside in either an axial or an equatorial arrangement with respect to the proton of the dithiane, as shown in Figure 6.[68] A second DFT study revealed that, un-

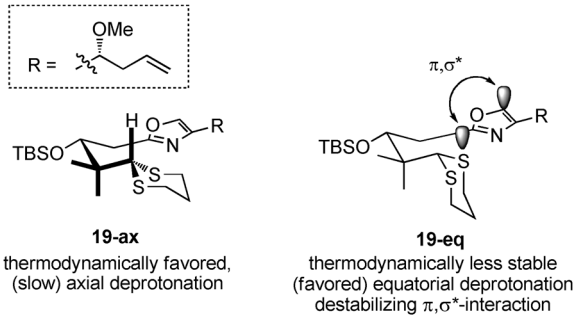
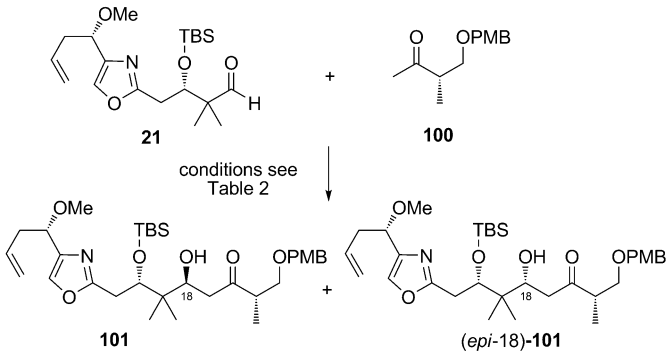


Figure 6. Possible conformations of dithiane **19**.



Scheme 21. Aldol coupling reaction of aldehyde **21** with methyl ketone **100**.

surprisingly, structure **19-ax** (left) was energetically favored, although it would only allow slow axial deprotonation. Conformation **19-eq** (right) indeed possessed the desired arrangement for effective proton abstraction, but it was less stable. Moreover, it could exhibit an interaction between the π system of the heterocycle and the empty σ* orbital. Although this explanation was originally devised for an olefin system, the heteroaromatic ring system has, in principle, the ability to exhibit a comparable stereoelectronic effect, which, in turn, might diminish the ability of this orbital to stabilize the required carbanion and, thus, impede deprotonation. These findings allow the conclusion that neither conformation allows an effective deprotonation at the desired position. Because compound **19** contained several protons of comparable acidity, namely those at the benzylic positions, these protons were preferentially abstracted instead of the desired dithiane proton, thus leading to the observed side-products.

Despite these unfruitful efforts, aldehyde **21** could serve as a coupling partner in an aldol-coupling reaction, which would allow an alternative option to install the missing stereocenters in a convergent manner.

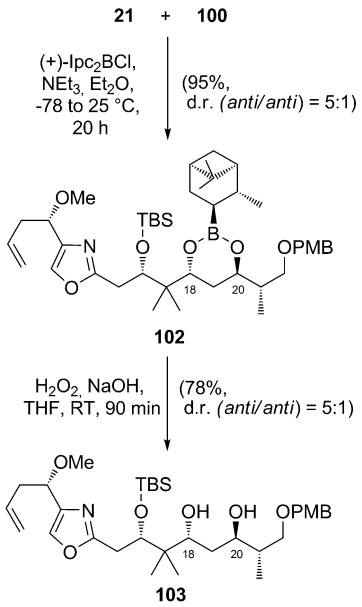
Aldol-coupling approach for the construction of the C8–C22 building block: After the disappointing results with the umpolung approach, we decided to pursue an aldol-coupling strategy between aldehyde **21** and methyl ketone **100**, which was derived from the (*S*)-Roche ester. This coupling process would open up a highly convergent route toward the desired C8–C22 building block and, hence, was promising for gaining access to multigram quantities of this compound. For this purpose, our efforts were aimed at establishing appropriate conditions that would deliver the desired coupling product (**101**) in acceptable yield and with the desired stereochemistry at C18 (Scheme 21).

However, implementation of this strategy was extremely challenging, owing to the high steric hindrance of aldehyde **21** and its strong preference for the formation of the undesired C18 epimer. Initially, the coupling reaction between the corresponding Li-, Na-, and K-enolates of methylketone **100** and aldehyde **21** only resulted in low to moderate yields of compound **101**, always in favor of the non-desired diastereomer, (*epi*-18)**-101**. To subvert this preference, we attempted (+)-/(−)-Ipc-boron aldol reactions, as well as Mukaiyama-type aldol reactions, but the yields of the isolated products were very low and the undesired diastereomer still remained the main product. Table 2 shows representative aldol reactions amongst a large variety of tested conditions within this project.[72] In terms of chemical yield, the Li-enolates that were formed from PMB-protected methylketone **100** were found to be the best after optimization (Table 2, entries 1 and 2). However, only mixtures of diastereomers in favor of the undesired (e*pi*-18)**-101** (determined by analysis of the Mosher esters) could be obtained. The use of chiral (+)-/(−)-Ipc-boron enolates could not overrule the preference for the formation of the ″undesired″ diastereomer (Table 2, entries 5 and 6 and Scheme 22), presumably owing to an inherent 1,4-*syn* substrate control of methylketone **100**. In all of these "closed-transition-state" aldol reactions,[73] the stereochemical outcome was clearly directed toward the undesired diastereomer. In contrast, a Mukaiyama aldol reaction of the in situ formed TMS-silyl enol ether of compound **100** proceeded with some preference for the desired diastereomer (Table 2, entry 7), which could be explained in contrast to earlier aldol attempts through an "open-transition-state" model. However, this Mukaiyama

Table 2. Conditions for the aldol-coupling reaction between compounds **21** and **100**.

Entry	Base	Additive	Solvent	*T* [°C]	Yield [%]	d.r. (**101**/(*epi*-18)-**101**)
1	LiHMDS		THF	−40	95	1:1.7
2	LiHMDS		DMF	−40	19	1:1.1
3	NaHMDS		THF	−78	25–45	1:2.4
4	KHMDS		THF	−78	43	1:2.6
5	(+)-Ipc$_2$BCl	NEt_3	Et_2O	−78 to −20	17	1:4.0
6	(+)-Ipc$_2$BCl	NEt_3	Et_2O	−78 to +25	95	1:4.8[a]
7	TMSCl	NEt_3 then $BF_3{\cdot}OEt_2$	CH_2Cl_2	−78	5	2.2:1

[a] Cyclic boronate **102** was obtained as the product (also see Scheme 22). LiHMDS = lithium bis(trimethylsilyl)amide, (+)-Ipc$_2$BCl = (+)-chlorodiisopinocampheyl borane, TMSCl = trimethylsilyl chloride.

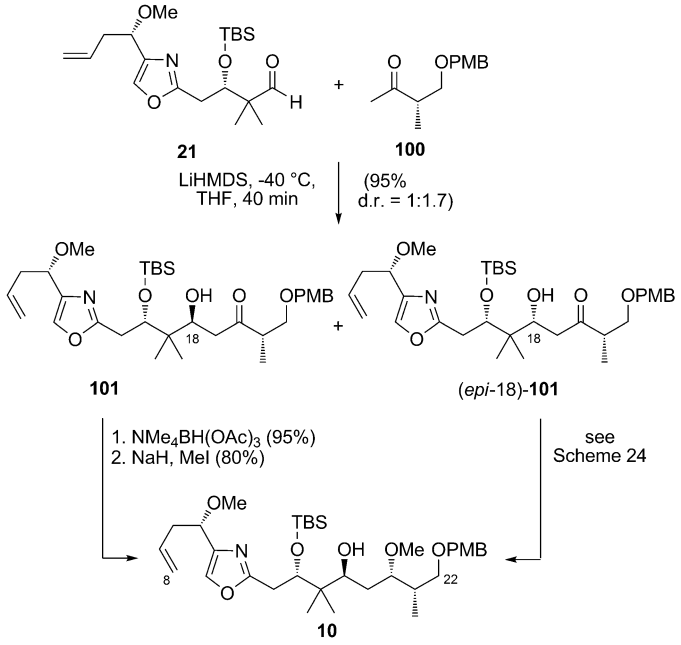


Scheme 22. Observed aldol-coupling/1,3-*anti*-reduction route to diol **103**.

reaction only proceeded in very low yield (5%), which could not be further improved.

During the course of these investigations, we also discovered a new type of domino aldol-coupling/1,3-*anti*-reduction sequence (Scheme 22), which has been described in detail elsewhere.[74] Because compound **21** only showed moderate reactivity upon treatment with the (+)-Ipc-boron enolate of compound **100** at −78 to −20 °C, the temperature was increased to 25 °C, which, surprisingly, resulted in the smooth formation of a single product, which was revealed to be compound **102** by using advanced NMR spectroscopic methods and chemical derivatization experiments (95% yield and a 5:1 ratio in favor of the *epi*-18/*epi*-20 isomer). The outcome of this reaction was rationalized to arise from the Ipc moiety acting as an internal reducing agent after the initially performed aldol coupling. Moreover, conditions for the effective removal of the boronate unit to afford compound **103** could be disclosed (basic H_2O_2 in THF at 25 °C). The scope of this newly developed domino process of an aldol coupling between a methyl ketone and an aldehyde and subsequent Ipc-mediated reduction to 1,3-*anti* diols was thoroughly explored and the stereochemical outcome could be shown to be independent from both substrate control and from the nature of the employed Ipc reagent. This method is expected to be efficiently applied in a diverse range of syntheses of polyfunctional substrates with 1,3-diol motifs.

Disappointingly, this new method did not help us to devise a route for the selective preparation of compound **101** either, which forced us to accept the undesired diastereoselectivity at this stage. However, due to its high convergence, this aldol approach proved to be superior in terms of overall material throughput, which prompted us to further pursue this strategy. To this end, efforts were made to optimize the initial aldol reaction between aldehyde **21** and methylketone **100**, before developing independent routes for the preparation of compound **10** from both compounds **101** and (*epi*-18)-**101** after their separation. As shown in Scheme 23, this reaction could indeed be achieved. The use

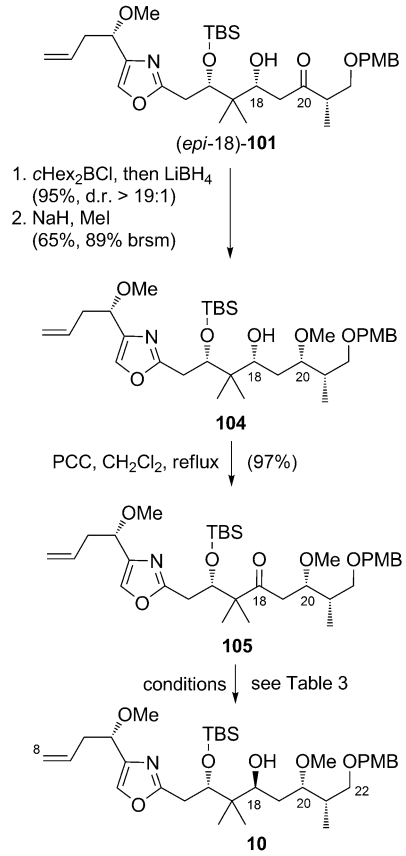


Scheme 23. Aldol-coupling approach and preparation of compound **10**.

of the Li-enolate of compound **100**, which was generated by using LiHMDS at −78 °C, followed by increasing the reaction temperature to −40 °C, and the subsequent addition of aldehyde **21** with a prolonged reaction time of 40 min enabled us to perform this reaction in almost quantitative yield (Table 2, entry 1). Following this procedure, we obtained a mixture of diastereomers that was slightly in favor of the undesired stereoisomer (*epi*-18)-**101**, 1:1.7 desired/undesired), which were separable by preparative HPLC. By using this route, we could obtain multigram quantities of both compounds **101** and (*epi*-18)-**101** (Scheme 23).

Next, the desired diastereomer (**101**) was transformed into building block **10** through a stereoselective 1,3-*anti* reduction reaction, according to the method described by Evans, Carreira, and co-workers (95%, d.r. > 19:1),[75] and a selective methylation of the less hindered C20-hydroxy group, which could be achieved in good yield after optimization. This mono-methylation reaction was best performed in a THF/MeI mixture (8:1, v/v) with an excess of sodium hydride (10 equiv) as a base and by careful adjustment of the reaction time and temperature (+10 °C, approximately 60 min with close monitoring by TLC). Within this two-step sequence, we could secure access to compound **10** in 76% yield. Alternatively, we tested the reduction of compound **101** by following the Evans–Tishenko procedure (SmI_2/acetaldehyde),[76] but this was not reliable in our hands and only led to a moderate yield of the expected product.

To likewise convert compound (*epi*-18)-**101** into compound **10**, a stereoselective 1,3-*syn* reduction of the β-hydroxy ketone moiety of compound (*epi*-18)-**101** was applied to first install the desired C20-hydroxy group (Scheme 24). This installation was best achieved by means of internal chelation with Cy_2BCl prior to the reduction with $LiBH_4$ (95%, d.r. > 19:1).[77] Subsequently, the C20-hydroxy group was selectively methylated under slightly modified conditions, as described above (MeI, NaH, THF, 0°C, 40 min, 65% yield, 89% brsm), to furnish compound **104** in good yield and selectivity.



Scheme 24. Conversion of the undesired (*epi*-18)-**104** into building block **10**: brsm = based on recovered starting material, PCC = pyridinium chlorochromate.

With compound **104** in hand, we aimed to invert the stereocenter at the C18 atom. Because Mitsunobu inversions are known to be hampered if the alcohol is sterically too burdened,[78] we envisaged an oxidation/asymmetric reduction sequence. The oxidation to ketone **105** was best achieved by heating compound **104** at reflux with pyridinium chlorochromate in CH_2Cl_2 (97%), whilst other oxidation methods, such as Swern or IBX, afforded lower yields. Next, the diastereoselective reduction of ketone **105** was examined, which was found to be difficult in the beginning (Table 3). Reduction with sodium borohydride, DIBAL, or (*R*)-Me-CBS oxazaborolidine and $BH_3{\cdot}SMe_2$[79] showed no conversion (Table 3, entries 1–3). Pleasingly, by using lithium aluminum hydride at −20°C, we were glad to observe ketone reduction in slight favor of the desired C18 diastereomer (**10**; Table 3, entry 4). This substrate control could be improved upon lowering the reaction temperature to −90°C, thereby allowing the selective formation of compound **10** (d.r. = 8:1) in good yield (Table 3, entry 5). Interestingly, application of Red-Al favored the undesired diastereomer (d.r.(**10**/**104**) = 1:2; Table 3, entry 6).

Table 3. Substrate-controlled diastereoselective reduction of ketone **105**.[a]

Entry	Reductant	Solvent	*T* [°C]	Yield [%]	d.r. (**10**/**104**)
1	$NaBH_4$	THF	−78 to 25	n.c.	–
2	DIBAL	THF	−78	n.c.	–
3	(*R*)-Me-CBS, $BH_3{\cdot}SMe_2$	CH_2Cl_2	0 to 25	n.c.	–
4	$LiAlH_4$	THF	−20	50	1.3:1
5	$LiAlH_4$	THF	−90	80	8:1
6	Red-Al	THF	−78	5–10	1:2

[a] n.c. = no conversion. (*R*)-Me-CBS = (*R*)-methyl oxazaborolidine, DIBAL = diisobutylaluminum hydride, Red-Al = sodium bis(2-methoxyethoxy)aluminumhydride.

In summary, the routes outlined in Scheme 18 and Scheme 23, which relied on an early-stage oxazole formation, allowed the effective preparation of building block **10** in a scalable and highly reproducible manner (13 steps, 20% overall yield).

Synthetic routes towards the macrocycle of rhizopodin:

Heck macrocyclization strategy: Figure 7 outlines our initial retrosynthetic plan to close macrocycle **106** of rhizopodin. We envisaged a chemoselective cross-coupling strategy by using sequential Suzuki and Heck coupling reactions. This plan required the C1–C7 fragment (**8**), the C8–C22 oxazole fragment (**10**), and boronate **107**, which was derived from oxazole **10**.

We planned to synthesize boronate **107** through the cross-metathesis of compound **10** with compound **108** (Scheme 25).[80] Given the complexity of compound **10**, some effort was necessary to obtain good results for this transformation. The results are summarized in Table 4.

Whereas Hoveyda–Grubbs 2nd-generation catalyst allowed the formation of compound **107** in good yield (Table 4, entry 1), the *E*/*Z* ratio varied over a broad range, whereas it remained more constant by applying Grubbs 2nd-generation catalyst (Table 4, entries 2–4). However, we found that an increased catalyst loading (10 mol%) was essential for ensuring reproducibly high yields and full conversion (Table 4, entry 4).

The next objective was the assembly of macrocycle **106**. As shown in Scheme 26, sterically hindered secondary alcohol **10** was first esterified with acid **8** by using Yamaguchi's reagent in excellent yield.[81] The obtained ester (**109**), which contained both vinyl iodine and terminal olefin groups, was connected to compound **107** by applying a Suzuki coupling

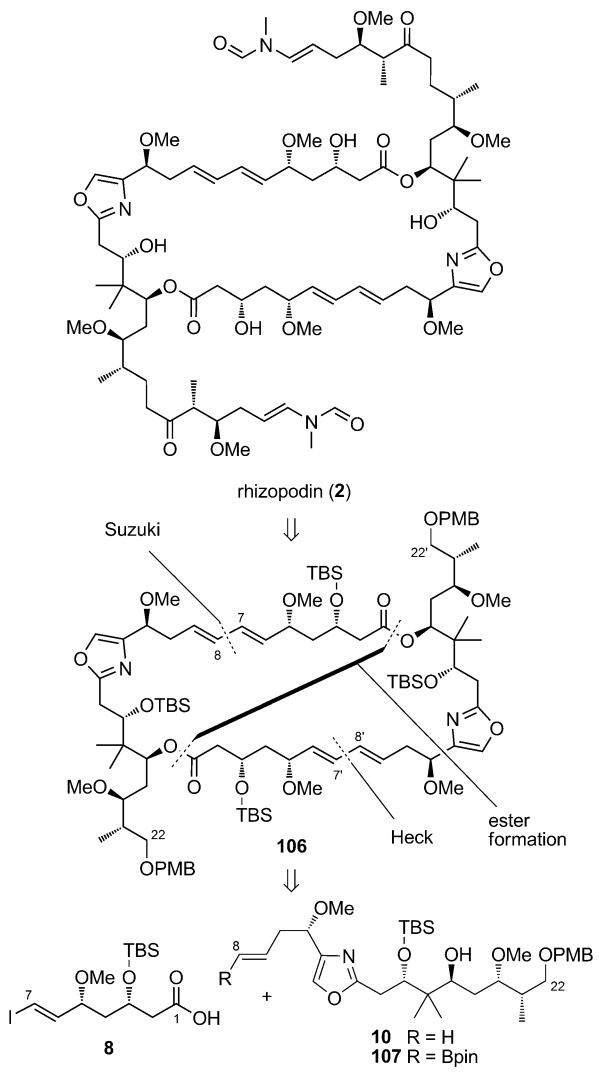
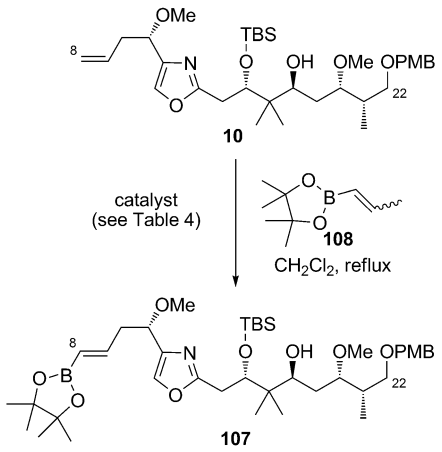


Figure 7. Retrosynthetic analysis of macrocycle **106**.

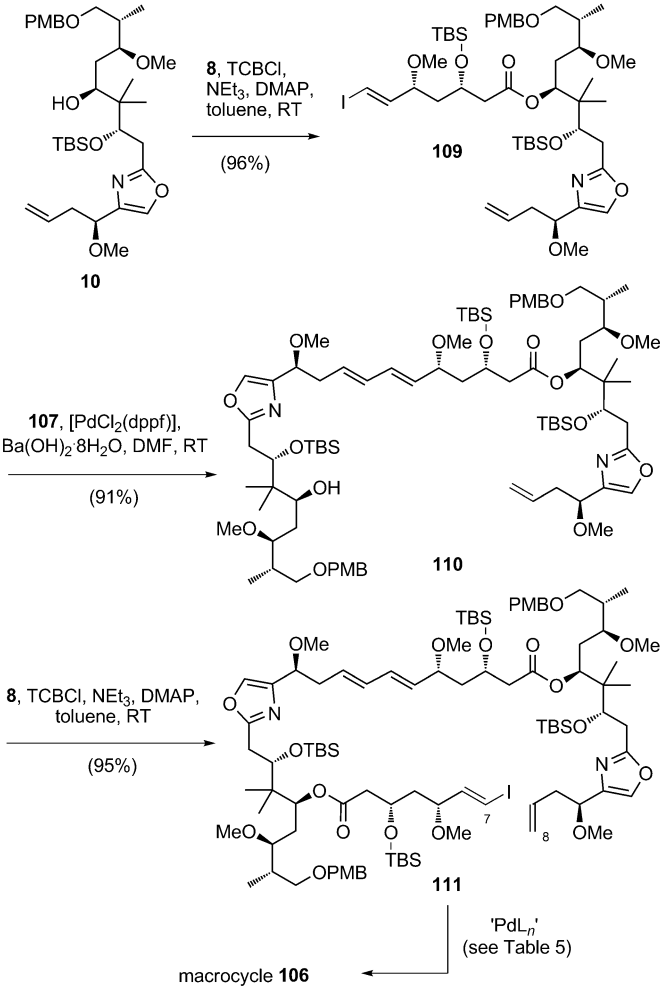


Scheme 25. Preparation of vinyl boronate **107**.

Table 4. Conditions for the cross-metathesis reaction between compounds **10** and **108**.

Entry	Catalyst	Catalyst loading [mol%]	Yield of **107** [%]	*E*/*Z* ratio
1	Hoveyda–Grubbs-II	5	64–77	5:1–24:1
2	Grubbs-II	2	11	8:1–16:1
3	Grubbs-II	5	60–80	8:1–16:1
4	Grubbs-II	10	80–95	8:1–16:1

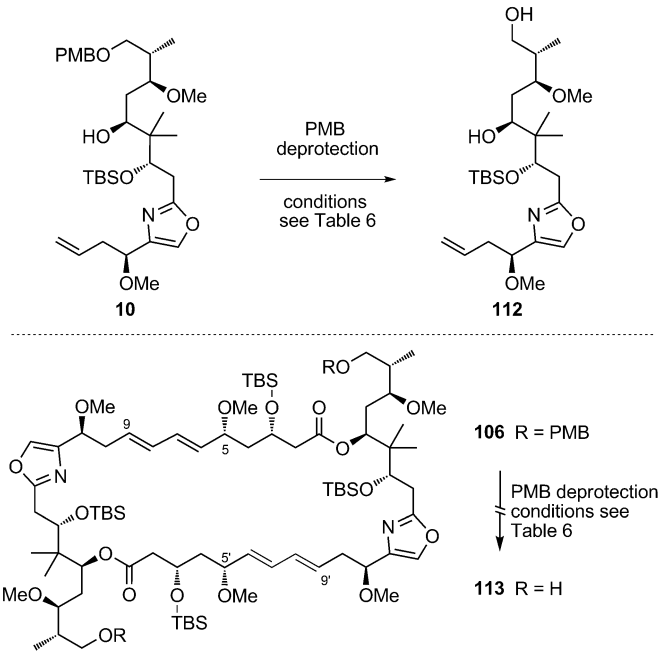
reaction with $[Pd(dppf)Cl_2]$ and $Ba(OH)_2{\cdot}8H_2O$ as a base to furnish diene **110** in high yield. The *E*/*Z* selectivity of this coupling process corresponded to the *E*/*Z* ratio of the employed vinyl boronate (**107**, *E*/*Z* = 16:1), as judged by ^1H NMR spectroscopy. Next, another Yamaguchi esterification reaction with acid **8** under the same conditions furnished cyclization precursor **111** in very good yield. Whilst these events proceeded without the need for optimization, the envisaged final intramolecular Heck macrocyclization was difficult in the beginning.



Scheme 26. Heck macrocyclization strategy to prepare macrocycle **106**. DMAP = 4-dimethylaminopyridine, TCBCl = 2,4,6-trichlorobenzoyl chloride.

A variety of conventional conditions[82,83] resulted in extensive decomposition of the starting material (Table 5, entries 1 and 2) and only trace amounts of the desired macrocycle (**106**) could be detected when the conditions described by Fu et al.[84] were used (Table 5, entry 3). Much to our delight, we found that optimized conditions described by Jeffery[85] in terms of temperature and reaction time allowed the formation of compound **106** in 77% yield and *E/Z* selectivity of 5:1 in favor of the desired product (**106**; Table 5, entry 4). In addition, the undesired *Z* isomer could be removed by careful column chromatography on silica gel. Notably, too-long reaction times or higher temperatures resulted in decomposition of the material.

The overall strategy towards compound **106** relied on an early-stage oxazole formation by employing Krische allylation, a highly convergent aldol-coupling reaction with further elaboration to building block **10**, and a sequential cross-coupling strategy, which provided macrocyclic compound **106** in 17 linear steps and an overall yield of 11%.[18b] Moreover, because only acid **8** was required for the C1–C7 building block, selective cleavage of the ester group was unnecessary, which added to the overall effectiveness of this entry to the macrocyclic core of rhizopodin. This route was scalable and considerable amounts of compound **106** could be prepared (100 mg).



Scheme 27. Attempted deprotection of the PMB groups on model system **10** and macrocycle **109**.

Table 5. Conditions for the Heck macrocyclization reaction of precursor **111**.

Entry	"PdL_n"	Additive(s)	Solvent[86]	T [°C]	t	Yield **106** [%]
1	$[PdCl_2(CH_3CN)_2]$	NEt_3, HCO_2H	MeCN	RT	2 h	dec.
2	$[PdCl_2(PPh_3)_2]$	K_2CO_3, NBu_4Cl	DMF	70	1 h	dec.
3	$[Pd_2(dba)_3]\cdot CHCl_3$/$t$$Bu_3P$	$c$$Hex_2NMe$	1,4-dioxane	RT	24 h	trace
4	$Pd(OAc)_2$	K_2CO_3, NBu_4Cl	DMF	60	50 min	77[87]

[a] dba = dibenzylideneacetone.

However, at this stage, all of our efforts to further advance compound **106** were thwarted by a seemingly impossible removal of the PMB group. In detail, we examined compound **10** as a simple model system to find suitable conditions for PMB deprotection, which could then be applied to macrocycle **106** (Scheme 27).

As shown in Table 6, PMB ether **10** could be easily deprotected under standard conditions by using oxidative (DDQ; Table 6, entry 1) or reductive methods (lithium naphthalenide, entry 13). High yields of compound **112** were also obtained by using mild Lewis acidic conditions (Table 6, entry 2). However, all of these methods, as well as many others, failed in the case of compound **106**.

We realized that the difficulty in deprotecting both PMB groups of macrocycle **106** resulted from the higher reactivity of the C5–C9 diene moiety, which was substituted with a homoallylic methoxy-ether group, as discussed elsewhere.[18b] In principle, various procedures exist for the deprotection of PMB-containing compounds in the presence of diene moieties.[81,88] However, these examples were performed with alkyl-substituted diene substrates, which might possibly have rendered them more stable.

Not only was the deprotection of macrocycle **106** problematic, additional difficulties arose in the reproducibility of good yields in the Heck macrocyclization step, depending on the source of the chemicals ($Pd(OAc)_2$, TBACl, K_2CO_3, DMF). In this case, yields of 10–30% of PMB-macrocycle **106** could be obtained without any reasonable explanation, which prompted us not only to re-evaluate the protection-group strategy, but also to slightly adopt our sequence to construct the macrocycle.

Suzuki macrocyclization strategy: To circumvent the deprotection problems, a terminal TBS group was chosen, which should be more readily removable. As shown in Scheme 28, we cleaved the PMB protecting group and transformed compound **10** into its TBS congener (**11**). The conditions of choice involved $MgBr_2\cdot OEt_2$ and dimethylsulfide and subsequent selective TBS protection of the primary C22 alcohol, which was best achieved by using TBSOTf and 2,6-lutidine at −78 °C in high yield. The corresponding vinyl boronate (**114**) could again be prepared from compound **11** by cross-metathesis with boronate **108**. This metathesis step required the same catalyst loading (10 mol%) as described for compound **10**; however, Grubbs 2nd-generation catalyst gave lower yields (53–65%) and some side-reactions, such as C=C isomerization, occurred. In contrast, Hoveyda–Grubbs 2nd-generation catalyst in the presence of 2,6-dichloroben-

Table 6. Attempted conditions for the deprotection of the PMB groups on model system **10** and macrocycle **106**.[a]

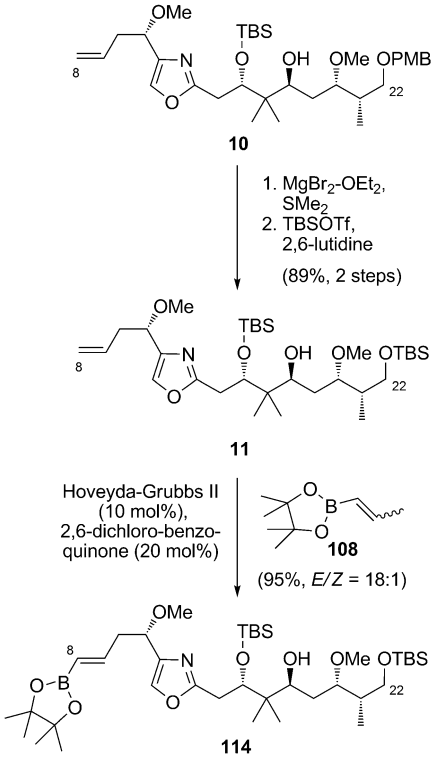
Entry	Reagent(s)	Solvent	*T* [°C]	Yield **10** [%]	Yield **106** [%]
1	DDQ	CH_2Cl_2/pH-buffer (1:1)	0	68	dec.
2	$MgBr_2{\cdot}OEt_2$, SMe_2	CH_2Cl_2	RT	95	n.c.
3	TMSOTf, lutidine	CH_2Cl_2	RT		n.c.
4	$SnCl_4$	CH_2Cl_2	RT		n.c.
5	$SnCl_4$, PhSH	CH_2Cl_2	−78		dec.
6	$SnCl_2$, TMSCl, anisole	CH_2Cl_2	RT		n.c.
7	CAN	$MeCN/H_2O$ (1:1)	0		dec.
8	CAN	MeCN/pH-buffer (1:1)	0		dec.
9	TFA (10% aq solution)	CH_2Cl_2	RT		dec.
10	TfOH, $tolSO_2NH_2$	1,4-dioxane	RT	40	dec.
11	CSI, Na_2CO_3, then NaOH	MeOH, then CH_2Cl_2	RT	30	n.c.
12	Ph_3CBF_4	CH_2Cl_2	RT	90	n.c.
13	$Li/C_{10}H_8$	THF	−78 to RT	75	dec.

[a] n.c. = no conversion. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TMSOTf = trimethylsilyltrifluoromethanesulfonate, CAN = ceric ammonium nitrate, TFA = trifluoroacetic acid, TfOH = trifluoromethanesulfonic acid, CSI = chlorosulfonyl isocyanate.

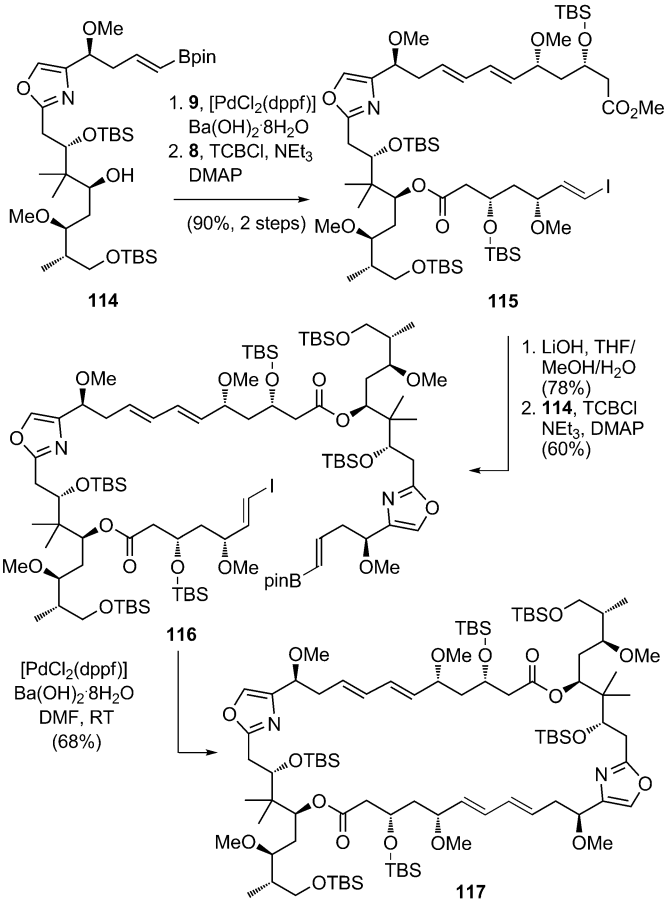
zoquinone[89] seemed to suppress side reactions and gave compound **114** in almost quantitative yield.

With regards to the good results that we had previously obtained for the Suzuki and Yamaguchi reactions, the second strategy for the construction of the macrocyclic core of rhizopodin now relied on an envisaged Suzuki macrocyclization step. For this purpose, vinyl boronate **114** was cross-coupled with vinyl iodine **9** and subsequently esterified with acid **8** to give compound **115** under the above-described conditions in excellent yield (Scheme 29).

We employed methyl ester **9** in this first Suzuki coupling reaction because earlier investigations had shown that the corresponding *tert*-butyl ester could not be cleaved under Lewis acidic conditions (TMSOTf, TESOTf, TBSOTf) or by using Brønsted acids (HCO_2H, AcOH) without extensive decomposition, again presumably owing to the instability of the α-methoxy-substituted diene moiety. With methyl ester **115** in hand, selective ester cleavage was achieved under basic conditions. Good yields were obtained by using lithium hydroxide in a mixture of THF/MeOH/H_2O 4:4:1 at ambient temperature overnight.[90] Milder conditions by using $Ba(OH)_2{\cdot}8H_2O$ gave comparable results, but required



Scheme 28. Transformation of compound **10** into its TBS-congener (**11**) and cross-metathesis to afford vinyl boronate **114**.



Scheme 29. Suzuki macrocyclization strategy to access compound **117**.

longer reaction times (75%, 7 days).[87] Afterwards, the obtained acid was esterified with boronate **114** in acceptable yield (60%) to afford macrocyclization precursor **116**. After some optimization in terms of the catalyst and base loadings (Table 7), the desired macrocyclic compound (**117**) was received in reproducibly good yields (60–68%).

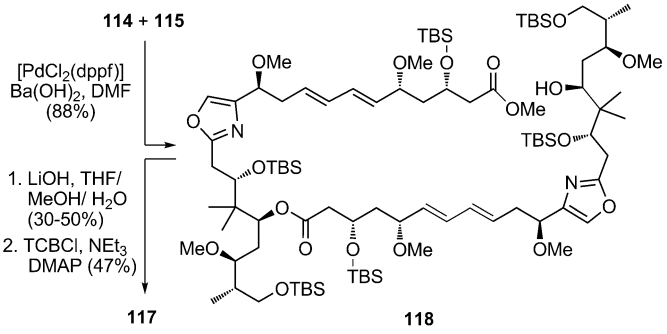
Table 7. Optimization of the Suzuki macrocyclization reaction of compound **116**.[a]

Entry	[$PdCl_2$(dppf)] [equiv]	Conditions ([equiv])[91]	Yield of **120** [%]
1	0.3	$Ba(OH)_2 \cdot 8H_2O$ (3.0)	20–43
2	0.5	$Ba(OH)_2 \cdot 8H_2O$ (5.0)	60–68
3	1.0	$Ba(OH)_2 \cdot 8H_2O$ (10.0)	35–50

[a] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

It should be mentioned that we also tried to synthesize the respective macrocyclic analogue of compound **117** bearing terminal TES protecting groups. To this end, the C22-TES-congener of compound **114** was prepared and an analogous strategy was pursued (Scheme 29). However, the lability of primary TES-ethers under basic conditions made the selective methyl-ester cleavage of the TES-analogue of compound **115** impossible in our hands and, thus, we discarded this approach.

Yamaguchi macrolactonization strategy: Likewise, an alternative Yamaguchi macrolactonization strategy was also evaluated. As shown in Scheme 30, vinyl iodine **114** was coupled

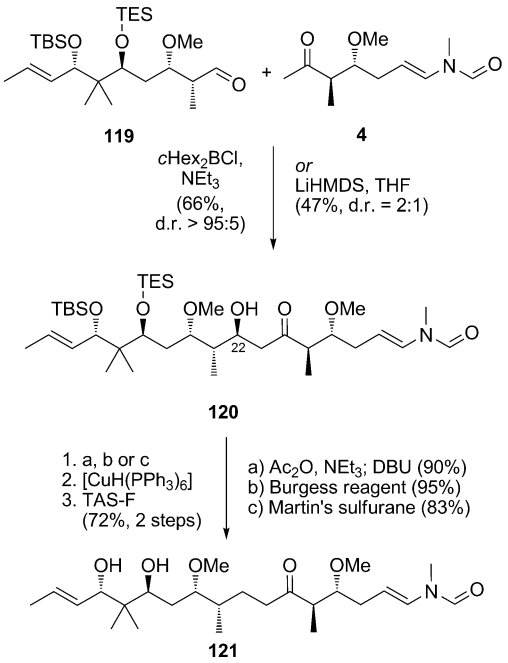


Scheme 30. Yamaguchi macrolactonization strategy to access compound **117**.

with vinyl boronate **115** to give methyl ester **118** in high yield. However, it turned out that cleavage of the methyl ester by using either lithium hydroxide or barium hydroxide gave consistently low to moderate yields. Essentially neutral conditions by using bis(tributyltin) oxide[92] resulted in decomposition of the material. The macrolactonization itself proceeded in good yield (47%).[93] However, this route was not pursued further, owing to the higher reliability of the Suzuki macrocyclization strategy as described above, which allowed the preparation of sufficient amounts of TBS-protected macrocycle **117** (120 mg).

Endgame strategies towards rhizopodin: Having accomplished the preparation of TBS-protected macrocycle **117**, we sought to attach both side chains in a bidirectional manner. The most convergent approach would rely on the introduction of an entire side chain that already contained the labile *N*-vinyl-formamide motif. We aimed to achieve this connection by means of an aldol-condensation reaction. As discussed above, a less convergent alternative would involve a HWE reaction with β-keto phosphonate **5** (Figure 2).

Model study of an aldol-condensation approach to attach the side chains: In view of the relatively small amount of compound **117** that was initially available, we decided to first use a truncated aldehyde (**119**, available from compound **73** in three steps) as a model substrate to examine the pivotal aldol coupling with side-chain fragment **4** (Scheme 31). By



Scheme 31. Model system to investigate the attachment of side chain **4** through an aldol-coupling strategy. Burgess reagent = methyl *N*-(triethylammoniumsulfonyl)carbamate. Martin sulfurane = bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur.

using conditions that had been previously described by Paterson and co-workers, we smoothly prepared compound **120** as a single diastereomer in 66% yield.[18,94] Likewise, compound **119** was treated with the lithium enolate of compound **4**, which also resulted in the formation of compound **120**, albeit in lower yield (47%, 75% over two cycles) and only modest diastereoselectivity.

Next, compound **120** needed to be dehydrated to afford the corresponding enone. First, we successfully applied a procedure that involved acetate formation with acetic anhy-

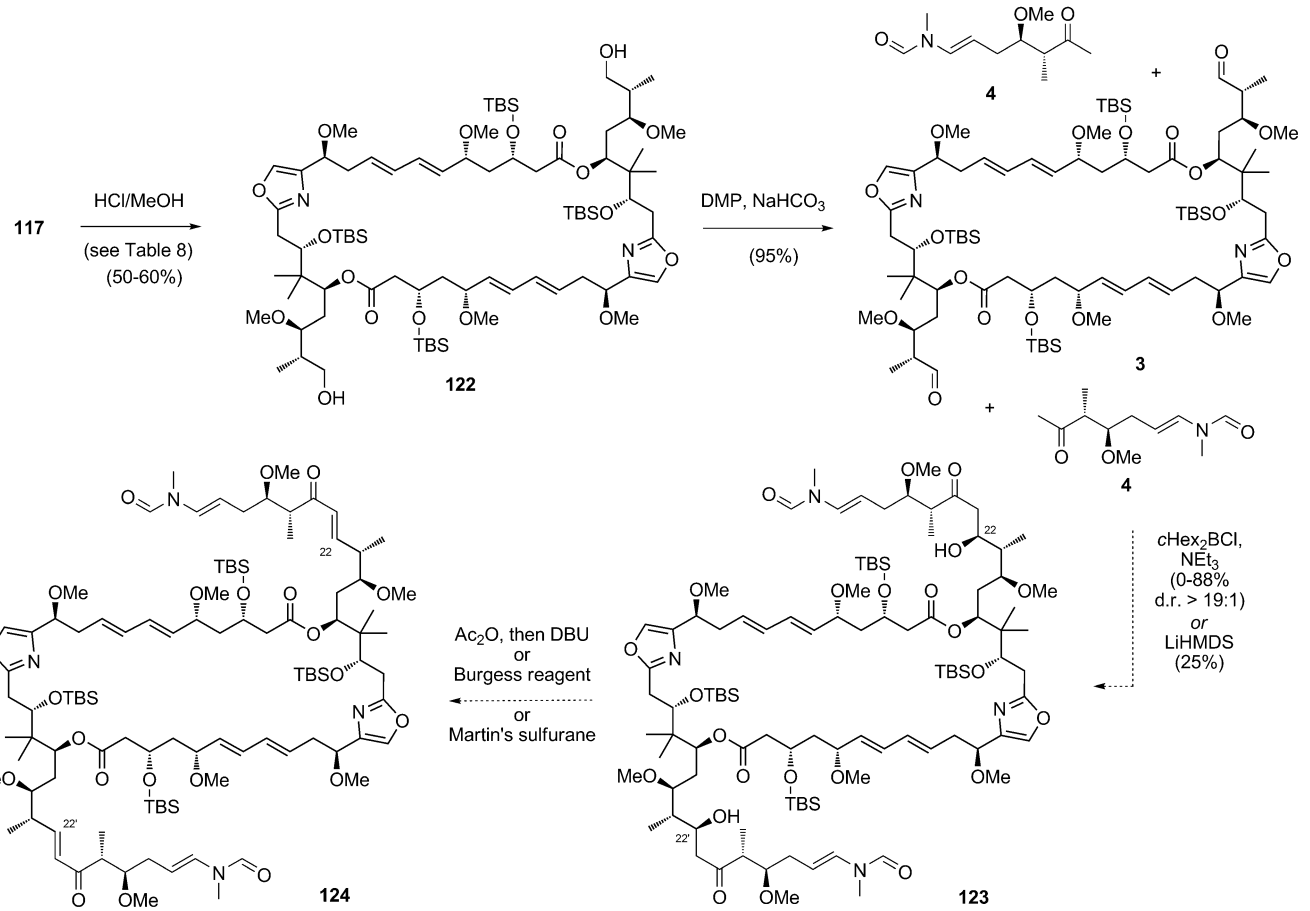
dride and DBU-mediated elimination.[81] Alternatively, we examined the feasibility of Burgess′ reagent[95] for this transformation. For successful application, it was of vital importance to use a freshly prepared reagent that could be stored at −20 °C for a maximum of about three weeks whilst the commercially available material resulted in decomposition of the starting material. Finally, we found that Martin's sulfurane[96] was also suitable for performing the desired elimination process.

For the subsequent selective 1,4-reduction of the respective enone, the application of Stryker′s reagent[97] was the method of choice and worked uneventfully. Because the separation of residual PPh_3 was tedious, we aimed to perform the direct deprotection of all of the remaining silyl groups. Because we expected the "real" system to be labile under basic conditions, we tested TAS-F, which is known to particularly tolerate base-labile substrates.[98] Treatment of the crude reduction product with excess TAS-F resulted in the clean formation of diol **121** in 72% yield over two steps.

Aldol condensation strategy towards rhizopodin: The successful development of an effective sequence to afford model compound **121** prompted us to apply this strategy to the final steps of the total synthesis (Scheme 32). To this end, we needed to selectively deprotect both primary TBS groups of macrocyclic compound **117**. Based on our earlier experiences with PMB deprotection, we mostly evaluated non-basic and non-Lewis acidic conditions, owing to the labile diene moiety, and turned our attention to Brønsted acidic methods. Pyridine-buffered HF/pyridine solution only allowed the detection of trace amounts of the desired macrocyclic diol (**122**) by using ESI-HRMS (Table 8, entry 1). Moreover, treatment with CSA, both in catalytic amounts and in excess, only resulted in very small quantities of the desired product besides decomposition of the material (Table 8, entries 2 and 3). Less basic TBAF buffered with acetic acid[99] gave compound **122** in low yield, besides decomposition (Table 8, entry 4). Gratifyingly, the use of 3 M HCl in MeOH at −20 °C resulted in

Table 8. Selective deprotection of the terminal TBS groups of macrocycle **117**.

Entry	Reagent ([equiv])	Solvent	T [°C]	t	Yield **122** [%]
1	HF-pyridine	pyridine/THF (1:1)	0	24 h	trace
2	CSA (0.3)	MeOH	0	1.5 h	trace
3	CSA (3.0)	MeOH	0	5 h	5
4	TBAF/AcOH (1:1, 10.0)	THF	RT	24 h	30–40
5	3 M HCl/MeOH	THF	0	30 min	10–20
6	3 M HCl/MeOH	THF	−20	60 min	50–60



Scheme 32. Attempted aldol-condensation strategy with macrocyclic compound **117**.

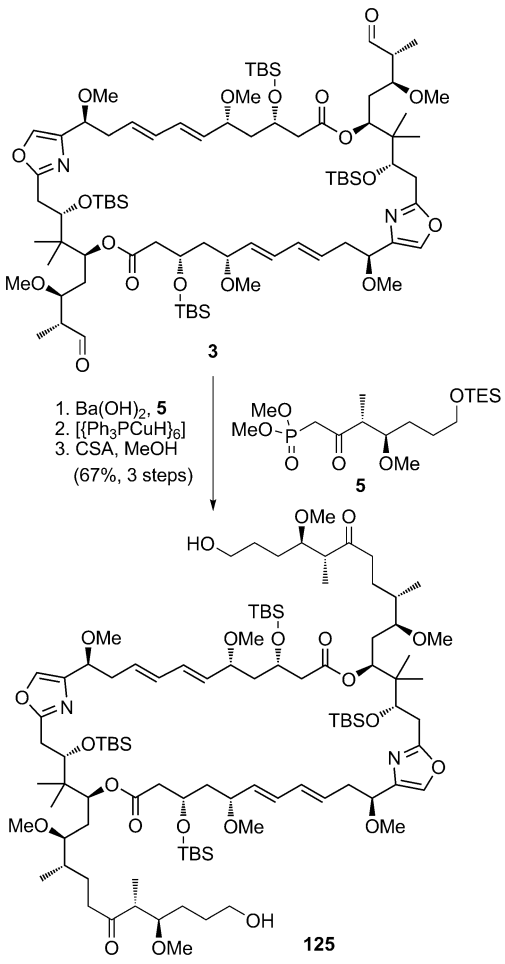
the formation of compound **122** in acceptable yield (50–60%), following careful adjustment of the amount of that was HCl added (Table 8, entry 6). If the temperature was increased to 0°C, undesired deprotection of presumably the C3-OTBS groups and decomposition were observed, with the formation of only small amounts of the desired compound (**122**; Table 8, entry 5). As mentioned above, we also tried to prepare the corresponding terminal TES-protected macrocycle. However, several of our established synthetic methods failed or gave significant lower yields, presumably owing to the lability of primary TES groups.

Then, macrocyclic diol **122** was oxidized to bis-aldehyde **3**, which was best accomplished by using buffered Dess–Martin periodinane, which proceeded in excellent yield. Notably, to obtain good and reproducible yields, the reagent had to be freshly prepared and used within about four weeks.[100] Parikh–Doering oxidation or treatment with TPAP/NMO only gave low yields of the desired compound (**3**).

With bis-aldehyde **3** in hand, the bidirectional aldol coupling reaction with compound **4** could be tackled (Figure 2).[18] However, the boron-mediated coupling of compound **3** with compound **4** under the above-evaluated conditions was extremely unreliable and we were only able to perform this coupling reaction in high yield on one occasion, despite considerable efforts (Scheme 32). Indeed, the use of freshly prepared Cy_2BCl,[89] performing the reaction over CaH_2 as a drying reagent, co-evaporating the reactants with dry toluene under an argon atmosphere to remove trace amounts of water, and employing completely fresh chemicals did not render this transformation more reliable and, typically, only trace amounts of the desired bis-aldol product (**123**) could be detected by ESI-HRMS. It should be mentioned, that Paterson et al. described the successful implementation of this aldol-coupling strategy with the same side-chain compound (**4**) on a very similar macrocyclic bis-aldehyde that only differed in the nature of the silyl-protecting groups. However, the same aldol reaction was also unreliable in our model system (**119**, Scheme 31). After examining several different model systems, we assumed that the *N*-vinyl-formamide moiety was responsible for the inconstant outcome in the boron-mediated aldol-coupling reactions. By applying the previously developed conditions with the Li-enolate of compound **4**, we obtained the desired bis-aldol product (**123**) in 25% yield, together with the respective mono-aldol product, which only had one side chain attached (50% yield). Owing to the high polarity of these compounds, their separation was difficult, but could be achieved by preparative TLC. The α-methyl aldehyde moiety of compound **3** and the respective mono-aldol product were prone to racemization at the C21-methyl stereocenter within about 24 h, thus impeding the recovery of these compounds and their reuse in another lithium-aldol reaction. However, despite these difficulties, we were eventually capable of obtaining useful amounts of material to investigate the envisaged β-hydroxy elimination at the C22 position to form the respective bis-enone (**124**).

In our model study (Scheme 31), this transformation had been effected in very good yields with several reagents. However, much to our disappointment, we were unable to successfully apply the dehydration conditions that we developed for compound **120** in a reliable fashion to compound **123**. The two-step procedure (Ac_2O then DBU), Burgess′ reagent, and Martin's sulfurane all failed to give rise to compound **124**. The Paterson group has reported a successful application of this strategy to a very similar substrate (the C16/C16′-bis-TES analogue).[101] After considerable efforts, compound **123** had to be considered as a dead end, which prompted us to revise our endgame strategy.

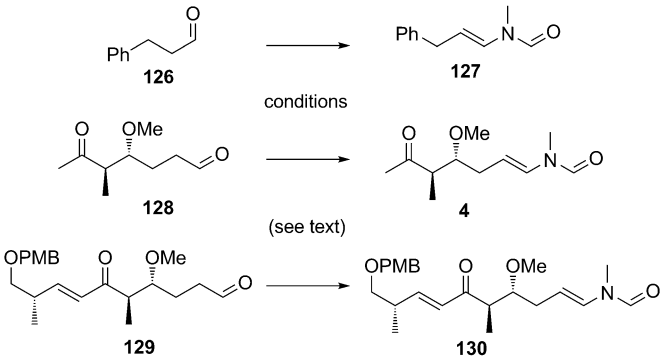
HWE strategy and completion of the total synthesis: Thus, we turned our attention to an alternative HWE reaction, which utilized side-chain fragment **5** (Figure 2). This route required the introduction of the labile *N*-methyl-vinyl-formamide moiety at a late stage in the entire synthesis. Gratifyingly, the double-HWE reaction could be successfully implemented by treating dimethyl phosphonate **5** under anhydrous conditions with BaO and the subsequent addition of bis-aldehyde **3** in an THF/H_2O mixture (40:1, Scheme 33).[102] The obtained bis-enone was subsequently re-



Scheme 33. HWE strategy to attach the side chain and further elaboration to afford diol **125**.

duced in quantitative yield by using Stryker's reagent, as previously evaluated with model compound **120** (Scheme 31). Treatment of the respective bis-TES ether with catalytic amounts of CSA in MeOH furnished diol **125** in very good yield (67%, 3 steps).

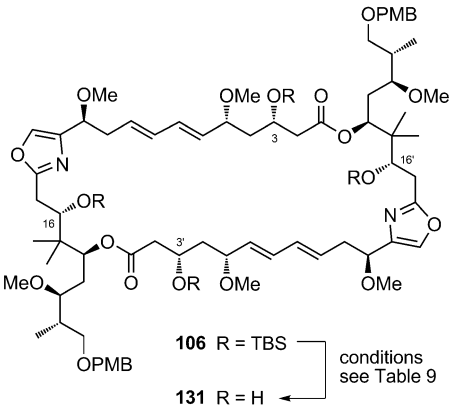
Next, our strategy relied on first introducing the *N*-vinyl-formamide motifs and then removing the TBS groups. During the preparation of side-chain building block **4**, which contained the *N*-vinyl-formamide unit, we became aware of the difficulties in preparing this structural motif in acceptable reproducible yields. With the rationale of not squandering any material of diol **125**, we used several model systems to further investigate this transformation (**126**, **128**, and **129**; Scheme 34). The commonly described literature procedure



Scheme 34. Model systems to investigate the formation of the *N*-vinyl formamide.

for this reaction requires heating a mixture of the aldehyde and *N*-methyl formamide (NMF) in the presence of catalytic amounts of Brønsted acids, such as PPTS or *p*-toluenesulfonic acid (PTSA). An important issue was the efficient removal of the water that was generated within this condensation process, either by using molecular sieves or by azeotropic distillation.[103] However, on applying these procedures to our model systems, we obtained varying results. Even in the case of simple aldehyde **126**, only low yields or even no conversion were observed. Whereas the results with compounds **128** and **129** were somewhat more promising, small-scale reactions remained problematic. Furthermore, we were concerned about the stability of the macrocycle under these rather harsh and acidic conditions. In contrast, another procedure that used phosphorus(V) oxide as a dehydrating agent and a large excess of NMF[104] gave reliable yields of 50–70% of the respective desired *N*-vinyl formamides, accompanied by undefined byproducts that were derived from the P_2O_5/NMF mixture.

In a likewise manner, we decided to first carry out a model study to establish successful conditions for the removal of the four TBS groups; however, this transformation was found to be extremely challenging. Thus, we chose PMB-protected macrocycle **106** as a model substrate for evaluating the promising reagents (Scheme 35).



Scheme 35. Model study to evaluate various conditions for global deprotection.

As shown in Table 9, a variety of reagents were investigated and the products were analyzed by crude NMR spectroscopy and by ESI-HRMS. However, these reactions mostly

Table 9. Deprotection of the TBS groups in macrocycle **106**.[a]

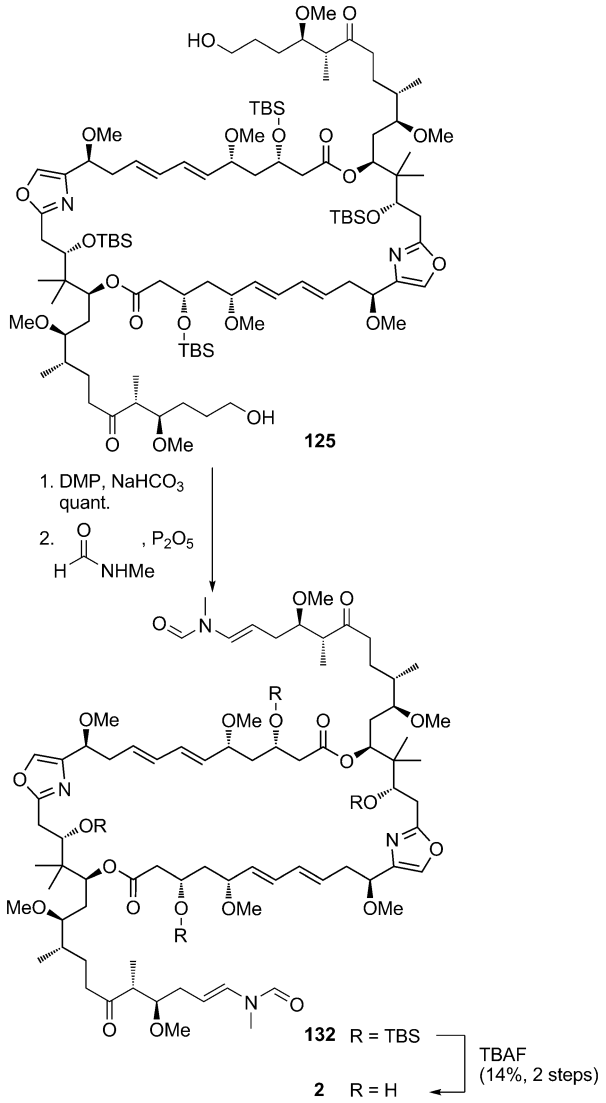
Entry	Reagent ([equiv])	Solvent	*T* [°C]	*t* [h]	Result
1	HCl/MeOH	THF	0	1	dec.
2	HF-pyridine	THF	RT	72	n.c.
3	HF	MeCN	0	4	dec.
4	H_2SiF_6	MeCN	RT	14	dec.
5	CsF, MeOH	MeCN	60	14	n.c.
6	$Bu_4N(SiF_2O_3)$	MeCN	RT	72	dec.
7	TBAF, AcOH	THF	RT	24	n.c.
8	TBAF(*t*BuOH)$_4$	THF	70	2	dec.
9	TBAF, SiO_2	THF	RT	60	n.c.
10	TBAF	THF	RT	20	**131** (−4 TBS)
11	TAS-F (25)	DMF	RT	72	−2 TBS, trace amounts of **131**
12	TAS-F (100)	DMF	RT	72	dec.
13	dry TAS-F (20)	THF	RT	24	−1/−2 TBS
14	dry TAS-F (20)	MeCN	RT	72	−2 TBS

[a] n.c. = no conversion; dec. = no defined compound(s) of reasonable molecular weight could be detected. TBAF = tetrabutylammonium fluoride, AcOH = acetic acid, TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

resulted in either no conversion (Table 9, entries 2, 5, 7, and 9) or decomposition without any distinct product formation (Table 9, entries 1, 3, 4, 6, 8, and 12). When TAS-F was employed (Table 9, entry 11), trace amounts of the desired fully deprotected macrocycle could be detected; however, the main product was a compound that lacked two TBS groups. We assumed that the product was a C3/C3′-TBS-deprotected compound, in which the sterically hindered C16/C16′-TBS-ethers had essentially remained untouched. Modification of the reaction conditions in terms of the solvent and the number of equivalents of TAS-F remained fruitless. Eventually, we found that TBAF was suitable for liberating all of the OH groups, with the formation of the fully TBS-deprotected macrocycle (**131**; Table 9, entry 10).[105,106]

The results from these model studies prompted us to tackle the remaining steps of the total synthesis. Thus, first,

we oxidized diol **125** (Scheme 36) by using DMP into the corresponding bis-aldehyde in quantitative yield, which was highly unstable and, hence, was directly used without further



Scheme 36. Introduction of the *N*-vinyl formamide units and final deprotection.

characterization. The oxidizing reagent had to be freshly prepared to obtain good results. Treatment with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO), Parikh–Doering conditions, or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)/$PhI(OAc)_2$ were much less effective.

Only decomposition was observed when the macrocyclic bis-aldehyde that was derived from compound **125** was heated in the presence of *N*-methyl formamide and PPTS, presumably owing to the instability of the diene moiety under these conditions. These conditions had been successfully applied by Nicolaou et al. in their synthesis of monorhizopodin.[15]

Much to our delight, application of the aforementioned procedure (P_2O_5 in neat NMF) to the bis-aldehyde that was derived from compound **125** reliably furnished the desired bis-*N*-vinyl formamide (**132**, Scheme 36) in acceptable conversion, as judged by crude NMR spectroscopic analysis, as well as undefined products that were derived from P_2O_5/NMF. However, compound **132** showed some "tailing" during TLC analysis, thereby impeding its clean purification without the considerable loss of material. However, it was possible to isolate small quantities of pure compound **132** for its characterization by ^{1}H NMR spectroscopy and ESI-HRMS. To not squander any of the obtained material, we decided to employ the crude mixture that was obtained from the condensation reaction with NMF/P_2O_5 in the final global deprotection step.

The silyl-deprotection conditions that were developed in our model study with macrocyclic compound **106** had shown that TBAF could be employed to liberate all of the TBS protecting groups and, gratifyingly, as shown in Scheme 36, the treatment of crude compound **132** with TBAF in THF at room temperature allowed the isolation of rhizopodin (**2**) after HPLC purification in 14% yield over the final two steps.[101,107] The cleavage of the extremely hindered C16/C16′-OTBS groups was definitely the most challenging transformation within these final steps and was accompanied by partial decomposition. However, the obtained characterization data (^{1}H and ^{13}C NMR spectroscopy and ESI-HRMS) of the isolated synthetic material were in excellent accordance with the reported data for natural rhizopodin. Furthermore, the optical rotation value was also in full agreement with the literature data. Therefore, the structural assignment of the natural product was fully confirmed.

Conclusion

In summary, a highly convergent synthesis of the polyketide macrolide rhizopodin has been accomplished in a longest linear sequence of 29 steps with an overall yield of 0.25%, which has unequivocally established its absolute and relative configurations. Along the way, we have developed two independent routes for the synthesis of the challenging central C8–C22 fragment and an efficient synthesis of the C1–C7 building block. These fragments could be successfully used to forge the macrocyclic core of rhizopodin through Heck or Suzuki macrocyclization reactions, as well as through a Yamaguchi macrolactonization reaction. Two different C23–C29 side chains were synthesized, which could be introduced by using either aldol or HWE coupling approaches. The HWE strategy was found to be superior and the resulting material could be successfully elaborated into the authentic natural product by the late-stage introduction of labile *N*-vinyl formamide motifs. The outlined modular synthesis of rhizopodin should be instructive and amenable towards the development of potent analogues of this actin-polymerization inhibitor. Studies concerning the design and synthesis

of such analogues are currently under investigation in our laboratories.

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[1] a) H. Reichenbach, *J. Ind. Microbiol. Biotechnol.* **2001**, *27*, 149–156; b) S. C. Wenzel, R. Müller, *Nat. Prod. Rep.* **2007**, *24*, 1211–1224; c) G. Rückert, *Z. Pflanzenernaehr. Bodenk.* **1979**, *142*, 330–343.
[2] K. Weissman, R. Müller, *Nat. Prod. Rep.* **2010**, *27*, 1276–1295.
[3] F. Sasse, H. Steinmetz, G. Höfle, H. Reichenbach, *J. Antibiot.* **1993**, *46*, 741–748.
[4] T. M. A. Gronewold, F. Sasse, H. Lünsdorf, H. Reichenbach, *Cell Tissue Res.* **1999**, *295*, 121–129.
[5] a) J. S. Allingham, V. A. Klenchin, I. Rayment, *Cell. Mol. Life Sci.* **2006**, *63*, 2119–2134; b) K.-S. Yeung, I. Paterson, *Angew. Chem.* **2002**, *114*, 4826–4847; *Angew. Chem. Int. Ed.* **2002**, *41*, 4632–4653.
[6] a) J. Rao, N. Li, *Curr. Cancer Drug Targets* **2004**, *4*, 345–354; b) M. A. Jordan, L. Wilson, *Curr. Opin. Cell Biol.* **1998**, *10*, 123–130.
[7] N. Klippel, U. Bilitewski, *Anal. Lett.* **2007**, *40*, 1400–1411.
[8] R. Jansen, H. Steinmetz, F. Sasse, W.-D. Schubert, G. Hagelüken, S. C. Albrecht, R. Müller, *Tetrahedron Lett.* **2008**, *49*, 5796–5799.
[9] N. Horstmann, D. Menche, *Chem. Commun.* **2008**, 5173–5175.
[10] G. Hagelueken, S. C. Albrecht, H. Steinmetz, R. Jansen, D. W. Heinz, M. Kalesse, W.-D. Schubert, *Angew. Chem.* **2009**, *121*, 603–606; *Angew. Chem. Int. Ed.* **2009**, *48*, 595–598.
[11] D. Pistorius, R. Müller, *ChemBioChem* **2012**, *13*, 416–426.
[12] J. Piel, *Nat. Prod. Rep.* **2010**, *27*, 996–1047.
[13] a) R. Reid, M. Piagentini, E. Rodriguez, G. Ashley, N. Viswanathan, J. Carney, D. V. Santi, R. Hutchinson, R. McDaniel, *Biochemistry* **2003**, *42*, 72–79; b) P. Caffrey, *ChemBioChem* **2003**, *4*, 654–657.
[14] a) Z. Cheng, L. Song, Z. Xu, T. Ye, *Org. Lett.* **2010**, *12*, 2036–2039; b) T. Chakraborty, K. K. Pulukuri, M. Sreekanth, *Tetrahedron Lett.* **2010**, *51*, 6444–6446; c) T. K. Chakraborty, M. Sreekanth, K. K. Pulukuri, *Tetrahedron Lett.* **2011**, *52*, 59–61; d) K. K. Pulukuri, T. K. Chakraborty, *Org. Lett.* **2012**, *14*, 2858–2861.
[15] K. C. Nicolaou, X. Jiang, P. J. Lindsay-Scott, A. Corbu, S. Yamashiro, A. Bacconi, V. M. Fowler, *Angew. Chem.* **2011**, *123*, 1171–1176; *Angew. Chem. Int. Ed.* **2011**, *50*, 1139–1144.
[16] M. Dieckmann, M. Kretschmer, P. Li, S. Rudolph, D. Herkommer, D. Menche, *Angew. Chem.* **2012**, *124*, 5765–5768; *Angew. Chem. Int. Ed.* **2012**, *51*, 5667–5670.
[17] S. M. Dalby, J. Goodwin-Tindall, I. Paterson, *Angew. Chem.* **2012**, *125*, 6645–6649; *Angew. Chem. Int. Ed.* **2013**, *52*, 6517–6521.
[18] Part of these results have been communicated previously, see ref. [16] and: a) M. Kretschmer, D. Menche, *Org. Lett.* **2012**, *14*, 382–385; b) M. Dieckmann, S. Rudolph, S. Dreisigacker, D. Menche, *J. Org. Chem.* **2012**, *77*, 10782–10788.
[19] a) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, J. Stafford, *Angew. Chem.* **2007**, *119*, 6279–6283; *Angew. Chem. Int. Ed.* **2007**, *46*, 6167–6171; b) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, H. Knust, J. Stafford, *Chem. Asian J.* **2008**, *3*, 367–387.
[20] Because examples of similar dimerization strategies were scarce, we did not consider such an approach to be promising and, hence, relied on a stepwise and more flexible strategy for the construction of compound **2**.
[21] A. F. Salit, C. Meyer, J. Cossy, B. Delouvrie, L. Hennequin, *Tetrahedron* **2008**, *64*, 6684–6697.
[22] a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739; b) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.
[23] a) V. I. Tararov, G. König, A. Börner, *Adv. Synth. Catal.* **2006**, *348*, 2633–2644; b) A. Fürstner, M. Albert, J. Mlynarski, M. Matheu, E. DeClercq, *J. Am. Chem. Soc.* **2003**, *125*, 13132–13142.
[24] a) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1993**, *71*, 1–7; b) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **1991**, *32*, 4163–4166.
[25] M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, *J. Org. Chem.* **2005**, *70*, 1227–1236.
[26] Only a few examples of the formation of related side-products have been reported; see: ref. [22].
[27] J. Einhorn, C. Einhorn, F. Ratajczak, J. L. Pierre, *J. Org. Chem.* **1996**, *61*, 7452–7454.
[28] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
[29] a) N. Hashimoto, T. Aoyama, T. Shioiri, *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478; b) E. Kühnel, D. D. P. Laffan, G. C. Lloyd-Jones, T. Martínez del Campo, I. R. Shepperson, J. L. Slaughter, *Angew. Chem.* **2007**, *119*, 7205–7208; *Angew. Chem. Int. Ed.* **2007**, *46*, 7075–7078.
[30] For a comprehensive review, see: J. Li, D. Menche, *Synthesis* **2009**, 2293–2315.
[31] A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587; b) T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250–5256; c) A. Abiko, J.-F. Liu, *J. Org. Chem.* **1996**, *61*, 2590–2591.
[32] J. Li, D. Menche, *Synlett* **2009**, 2417–2420.
[33] C. G. Knudsen, H. Rapoport, *J. Org. Chem.* **1983**, *48*, 2260–2266.
[34] M. Toumi, F. Couty, G. Evano, *Angew. Chem.* **2007**, *119*, 578–581; *Angew. Chem. Int. Ed.* **2007**, *46*, 572–575.
[35] M. C. Hillier, A. T. Price, A. I. Meyers, *J. Org. Chem.* **2001**, *66*, 6037–6045.
[36] S. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo, M. Nakano, *J. Org. Chem.* **1991**, *56*, 2276–2278.
[37] K. Mikami, S. Matsumoto, A. Ishida, S. Takamuku, T. Suenobu, S. Fukuzumi, *J. Am. Chem. Soc.* **1995**, *117*, 11134–11141.
[38] M. C. Hillier, A. I. Meyers, *Tetrahedron Lett.* **2001**, *42*, 5145–5147.
[39] a) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; b) R. M. Hanson, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 1922–1925; c) Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
[40] M. Miyashita, T. Suzuki, M. Hoshino, A. Yoshikoshi, *Tetrahedron* **1997**, *53*, 12469–12486.
[41] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
[42] a) M. A. Tius, A. H. Fauq, *J. Org. Chem.* **1983**, *48*, 4131–4132; b) M. R. Johnson, T. Nakata, Y. Kishi, *Tetrahedron Lett.* **1979**, *20*, 4343–4346.
[43] M. Sasaki, K. Tanino, M. Miyashita, *Org. Lett.* **2001**, *3*, 1765–1767.
[44] K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126–8127.
[45] a) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; b) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
[46] a) M. T. Crimmins, B. W. King, E. A. Tabet, K. Chaudhary, *J. Org. Chem.* **2001**, *66*, 894–902; b) M. T. Crimmins, J. She, *Synlett* **2004**, 1371–1374.
[47] K. Soai, A. Ookawa, *J. Org. Chem.* **1986**, *51*, 4000–4005.
[48] M. Körner, M. Hiersemann, *Org. Lett.* **2007**, *9*, 4979–4982.
[49] a) D. B. Grotjahn, D. A. Lev, *J. Am. Chem. Soc.* **2004**, *126*, 12232–12234; b) A. Labonne, T. Kribber, L. Hintermann, *Org. Lett.* **2006**, *8*, 5853–5856.

[50] R. Takeuchi, S. Nitta, D. Watanabe, *J. Org. Chem.* **1996**, *61*, 3045–3051.
[51] For a review on the scope of this transformation, see: a) G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599–7662; b) K. Tamao, M. Kumada, *Tetrahedron Lett.* **1984**, *25*, 321–324; c) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694–1696.
[52] a) S. B. Han, I. S. Kim, H. Han, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 6916–6917; b) for a correction, see:S. B. Han, I. S. Kim, H. Han, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 12517.
[53] S. Shibahara, M. Fujino, Y. Tashiro, N. Okamoto, T. Esumi, T. Takahashi, J. Ishihara, S. Hatakeyama, *Synthesis* **2009**, 2935–2953.
[54] X. Gao, I. A. Townsend, M. J. Krische, *J. Org. Chem.* **2011**, *76*, 2350–2354.
[55] W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217–3219.
[56] H. Li, X. Jiang, Y. Ye, C. Fan, T. Romoff, M. Goodman, *Org. Lett.* **1999**, *1*, 91–93.
[57] a) P. Wipf, C. P. Miller, *J. Org. Chem.* **1993**, *58*, 3604–3606; b) M. C. Bagley, K. E. Bashford, C. L. Hesketh, C. J. Moody, *J. Am. Chem. Soc.* **2000**, *122*, 3301–3313.
[58] Further examination of this transformation revealed that compound **89** was a special case, because the treatment of similar compounds (e.g., compound **76**) under identical conditions only resulted in recovery of the starting materials (>95%).
[59] U. Klar, B. Röhr, F. Kuczynski, W. Schwede, M. Berger, W. Skuballa, B. Buchmann, *Synthesis* **2005**, 301–305.
[60] F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.
[61] a) R. I. Storer, T. Takemoto, P. S. Jackson, S. V. Ley, *Angew. Chem.* **2003**, *115*, 2625–2629; *Angew. Chem. Int. Ed.* **2003**, *42*, 2521–2525; b) R. I. Storer, T. Takemoto, P. S. Jackson, D. S. Brown, S. V. Ley, *Chem. Eur. J.* **2004**, *10*, 2529–2547.
[62] B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier, C. S. Brindle, *J. Am. Chem. Soc.* **2007**, *129*, 2206–2207.
[63] J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001–3003.
[64] A. Hassan, Y. Lu, M. J. Krische, *Org. Lett.* **2009**, *11*, 3112–3115.
[65] J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. Nylund-Kolz, B. W. Phillips, *J. Org. Chem.* **2002**, *67*, 7750–7760.
[66] V. Kumar, S. Dev, *Tetrahedron Lett.* **1983**, *24*, 1289–1292.
[67] For a review of the application of this reaction in the synthesis of natural products, see: M. Yus, C. Nájera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147–6212.
[68] A. B. Smith, G. K. Friestad, J. Barbosa, E. Bertounesque, K. G. Hull, M. Iwashima, Y. Qiu, B. A. Salvatore, P. G. Spoors, J. J.-W. Duan, *J. Am. Chem. Soc.* **1999**, *121*, 10468–10477.
[69] For a kinetic study, see: a) E. L. Eliel, A. H. Hartmann, A. G. Abatjoglou, *J. Am. Chem. Soc.* **1974**, *96*, 1807–1816; evidence for the exclusive formation of a single anionic conformation was obtained from an X-ray structural analysis, see: b) R. Amstutz, D. Seebach, P. Seiler, B. Schweizer, J. D. Dunitz, *Angew. Chem.* **1980**, *92*, 59–60; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 53–54.
[70] D. Seebach, J. Gabriel, R. Hässig, *Helv. Chim. Acta* **1984**, *67*, 1083–1099.
[71] J. M. Lehn, G. Wipff, *J. Am. Chem. Soc.* **1976**, *98*, 7498–7505.
[72] M. Dieckmann, S. Rudolph, C. Lang, W. Ahlbrecht, D. Menche, *Synthesis* **2013**, *45*, 2305–2315.
[73] a) B. M. Kim, S. F. Williams, S. Masamune, in *Comprehensive Organic Synthesis Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcook), Pergamon, Oxford, **1991**, p. 229; b) K.-S. Yeung, I. Paterson, *Chem. Rev.* **2005**, *105*, 4237–4313; c) B. Schetter, R. Mahrwald, *Angew. Chem.* **2006**, *118*, 7668–7687; *Angew. Chem. Int. Ed.* **2006**, *45*, 7506–7525.
[74] M. Dieckmann, D. Menche, *Org. Lett.* **2013**, *15*, 228–231.
[75] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
[76] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
[77] I. Paterson, M. Donghi, K. Gerlach, *Angew. Chem.* **2000**, *112*, 3453–3457; *Angew. Chem. Int. Ed.* **2000**, *39*, 3315–3319.
[78] S. F. Martin, J. A. Dodge, *Tetrahedron Lett.* **1991**, *32*, 3017–3020.
[79] E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012.
[80] C. Morril, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031–6034.
[81] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[82] a) D. Menche, J. Hassfeld, J. Li, S. Rudolph, *J. Am. Chem. Soc.* **2007**, *129*, 6100–6101; b) D. Menche, J. Hassfeld, J. Li, K. Mayer, S. Rudolph, *J. Org. Chem.* **2009**, *74*, 7220–7229.
[83] F. E. Ziegler, U. R. Chakraborty, R. B. Weisenfeld, *Tetrahedron* **1981**, *37*, 4035–4040.
[84] G. C. Fu, A. F. Littke, *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
[85] T. Jeffery, *Tetrahedron* **1996**, *52*, 10113–10130.
[86] The reaction was performed at a concentration of 0.005 M.
[87] The yield and outcome of this reaction strongly depended on the batch of $Pd(OAc)_2$ that was used; a reason for this observation could not be determined.
[88] M. Penner, V. Ranniyar, L. T. Kaspar, D. G. Hall, *J. Am. Chem. Soc.* **2009**, *131*, 14216–14217.
[89] S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
[90] a) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis* 4th ed., Wiley, Stuttgart, **2006**; b) P. J. Kocieński, *Protecting Groups*, 3rd ed, Thieme, New York, **2005**.
[91] The reaction was performed at a concentration of 0.009 M.
[92] C. J. Salomon, E. G. Mata, O. A. Mascaretti, *J. Org. Chem.* **1994**, *59*, 7259–7266.
[93] The reaction was performed at a concentration of 0.017 M.
[94] Following an empirical model, we assumed that the configuration at the C22 position arose from inherent substrate control. In this case, both 1,4-*syn* and 1,5-*anti* induction would lead to the product as shown, see: C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1–200.
[95] a) E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26–31; for the preparation of the reagent see: b) G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.
[96] J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 2339–2341.
[97] W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291–293.
[98] K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436–6437.
[99] B. Zhu, J. S. Panek, *Eur. J. Org. Chem.* **2001**, 1701–1704.
[100] R. K. Boeckman, P. Shao, J. J. Mullins, *Org. Synth.* **2004**, *10*, 696–698.
[101] The Paterson group did not comment on the reproducibility of this sequence. We had previously reported our difficulties in accessing compound **124** by using this route (see ref. [17]).
[102] I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774–776.
[103] K. Suenaga, T. Kimura, T. Kuroda, K. Marsui, S. Miya, S. Kuribayashi, A. Sakagura, H. Kigoshi, *Tetrahedron* **2006**, *62*, 8278–8290.
[104] a) I. Paterson, C. Watson, K.-S. Yeung, P. A. Wallace, R. A. Ward, *J. Org. Chem.* **1997**, *62*, 452–453; b) I. Paterson, C. Cowden, C. Watson, *Synlett* **1996**, 209–211.
[105] The Paterson group reported that, under similar conditions, structurally related macrocyclic halves of rhizopodin that contained OTBS groups at the C3 and C16 positions, an OTES group at the C18 position, and an OTIPS group at the C22 position could be deprotected in useful yields (52%), whereas, for a macrocyclic analogue with the attached side chain with O-TBS groups at the C16 and C16′ positions and O-TES groups at the C3 and C3′ positions, an elimination product was observed in approximately 20% yield. The yield of this transformation could only be approximated based on the experimental data given, because the final product was only obtained as a mixture with TBAF in a ratio of approximately 1:10. Because TBAF was not removed during the reaction workup, but rather was carried through the complete isolation procedure (in-

cluding evaporation of the solvents, etc.), it was not clear when the elimination has occurred. A higher yield for the final deprotection step was reported by the Paterson group in the global deprotection of rhizopodin that contained OTES groups at the C16 and C16′ positions but OTBS groups at both the C3 and C3′ positions (67% yield).

[106] It should be stressed that no products that resulted from elimination of the C16/C16′-OTBS groups were found, as reported by Paterson and co-workers (see ref. [17]) for a structurally related compound with the complete side chains but containing OTES groups at the C3 and C3′ positions, neither by NMR spectroscopy nor by HRMS (also see ref. [101]). Because TBAF was not removed during the reaction workup, but rather was carried through the complete isolation procedure (including evaporation of solvents, etc.), it was not clear when the elimination has occurred.

[107] This reaction was independently performed five times by two different persons in our group; in all cases, rhizopodin was obtained, albeit in low yields, thus demonstrating the feasibility of this approach in principal. A HPLC trace of the crude product is provided in the Supporting Information. A more efficient protecting-group strategy was reported by the Paterson group; see ref. [101].

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