

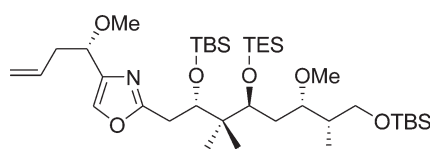
Stereocontrolled Synthesis of the
C8–C22 Fragment of RhizopodinManuel Kretschmer[†] and Dirk Menche^{*‡}

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ABSTRACT



A convergent synthesis of the central C8–C22 core of the potent macrolide antibiotic rhizopodin is reported. Notable features of the stereocontrolled approach include an asymmetric reverse prenylation of an alcohol using a method of Krische, a thiazolium catalyzed transformation of an epoxyaldehyde as described by Bode, and a late-stage oxazole formation from advanced intermediates. This route demonstrates the applicability of these methodologies in complex natural product synthesis.

In 1993, the Höfle group reported the structure of rhizopodin (**1**, Scheme 1) from the myxobacterium *Myxococcus stipitatus*.¹ This macrolide displays impressive biological properties including antifungal and antiproliferative activities at low nanomolar concentrations. This potency has been attributed to its ability to specifically bind to globular actin (G-actin) and thus impede its polymerization to filamentous actin (F-actin).^{1b} Rhizopodin has also been shown to hamper the phagocytic efficiency of yeast cells.²

While originally reported as a monomeric compound,¹ its structure was revised in 2008 to a C₂-symmetric dimer during studies aimed at determining its absolute configuration.³ Based on extensive NMR analyses, in combination with derivatization and molecular modeling experiments, a complete stereochemical assignment was made by our group,⁴ which was independently confirmed by

Schubert and co-workers through an X-ray structure of rabbit-actin bound rhizopodin.⁵

The unique structure of rhizopodin which consists of a total of 18 stereogenic centers within a 38-membered macrolide ring incorporates two oxazole rings and two diene systems. The macrocyclic core bears two side chains with labile *N*-vinyl-formamide motifs, which are believed to be critical parts of the pharmacophore unit.⁵ The combination of remarkable structure and potent bioactivity, together with its low availability from natural sources, make rhizopodin an attractive target, and several fragment syntheses have been reported.^{6–8} However, despite these efforts, an efficient and, in particular, concise and stereoselective route to the central C8–C22 fragment (**2**, Scheme 1) has not been achieved. This central fragment is characterized by five stereogenic centers, a highly hindered stereotetrad centered around the quaternary carbon at C17 in combination with the oxazole core. Retrosynthetically, we anticipated this central building block arising from amine **3** and acid **4** with assembly of the oxazole unit via a cyclodehydration strategy.

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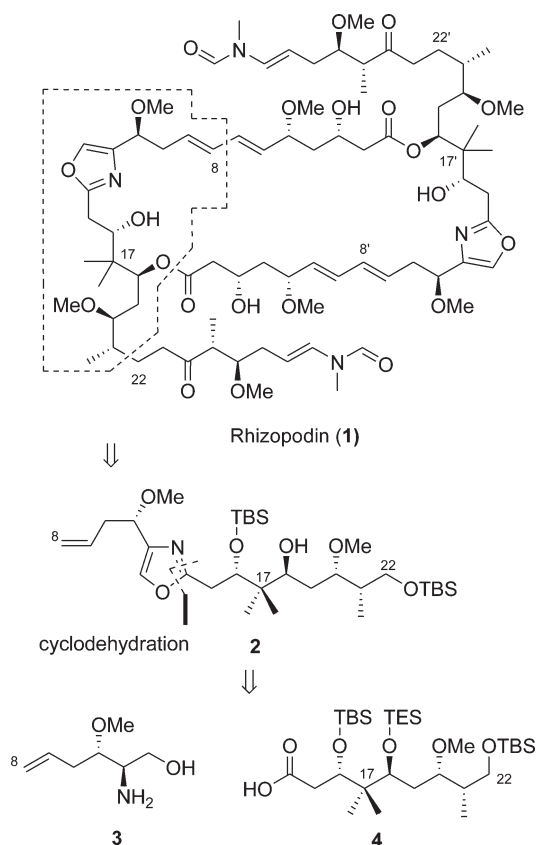
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Scheme 1. Synthetic Approach to the Central Fragment **2** of Rhizopodin (**1**)

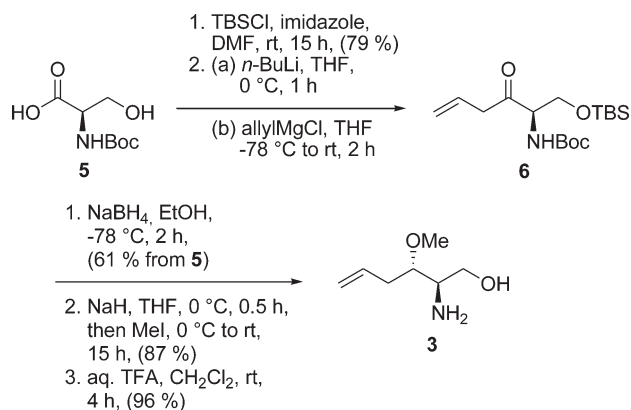


The synthesis of amine **3**, illustrated in Scheme 2, started from commercially available *N*-Boc-D-serine (**5**). *O*-Protection as a TBS-ether (79%) followed by treatment of the respective lithium carboxylate with allyl magnesium chloride afforded a configurationally unstable homoallylic ketone **6**⁹ which was directly exposed to NaBH₄. At –78 °C, a high level of stereoselectivity (11:1) was obtained, presumably through substrate chelation control.¹⁰ After removal of the undesired isomer by column chromatography, the aminoalcohol (not shown) was obtained diastereomerically pure in 61% yield over three steps. The elaboration into **3** was straightforward. Selective *O*-methylation was achieved using carefully controlled amounts of NaH and methyl iodine in THF, followed by subsequent deprotection of the carbamate and the TBS-ether using aqueous TFA in 96% yield.

With a scalable route toward **3** in hand, an entry to acid **4** was required. Our final and successful strategy, as outlined in Scheme 3, commenced with an asymmetric reverse prenylation following a method developed by the group of Krische.¹¹ In detail, exposure of known PMB-protected

alcohol **7**¹² to 1,1-dimethyl allene (**8**) in the presence of propionaldehyde and catalytic amounts of iridium complex **9** smoothly delivered **10** in quantitative yield in an enantiomeric excess of 82%.^{13–15} Notably, in contrast to previous routes to this fragment, our approach enables a stereoselective construction of both stereogenic centers adjacent to C17 by employing chiral catalysts.

Scheme 2. Synthesis of Amine Building Block **3**



After protection of the alcohol as silyl ether **11** (TBS triflate, lutidine, 96%), the olefin was cleaved oxidatively (O₃, dimethyl sulfide) to afford aldehyde **12**. A likewise tested alternative effort to transform **12** more directly into **17** by an asymmetric allylation and subsequent oxidative cleavage resulted in only low yields and/or stereoselectivities in the allylation step, in agreement with previous results,⁶ presumably due to steric hindrance of the carbonyl group of **12**. We therefore decided to pursue a different strategy.¹⁶

To this end, **12** was treated with methyl diethyl phosphonoacetate/NaHMDS to give the corresponding unsaturated ester in 84% yield over both steps. Reduction of the product ester (86%) with di-*iso*-butyl aluminum hydride (DiBAIH) furnished an allylic alcohol that was subjected to Sharpless' asymmetric epoxidation.¹⁷ Epoxide **13** was isolated in good yield in a diastereomeric ratio of 7.5:1 in

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(13) The *ee* and the configuration of the new stereogenic center were determined using Mosher's ester analysis. See the Supporting Information for full details.

(14) After completion of the synthesis of **4**, Krische and co-workers reported an improved procedure for the purification of structurally related catalysts: Gao, X.; Townsend, I. A.; Krische, M. J. *J. Org. Chem.* **2011**, 76, 2350.

(15) In principle, the central core of fragment **4** may also be accessible by Krische's method of a double enantioselective allylation. However, such an approach may have resulted in ensuing difficulties in selective differentiation of the resulting two hydroxyls and alkenes. Therefore, it was not pursued: Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, 48, 5018.

(16) Related sequences have been previously employed, see e.g.: (a) Hillier, M. C.; Price, A. T.; Meyers, A. I. *J. Org. Chem.* **2001**, 66, 6037. (b) Reference 6.

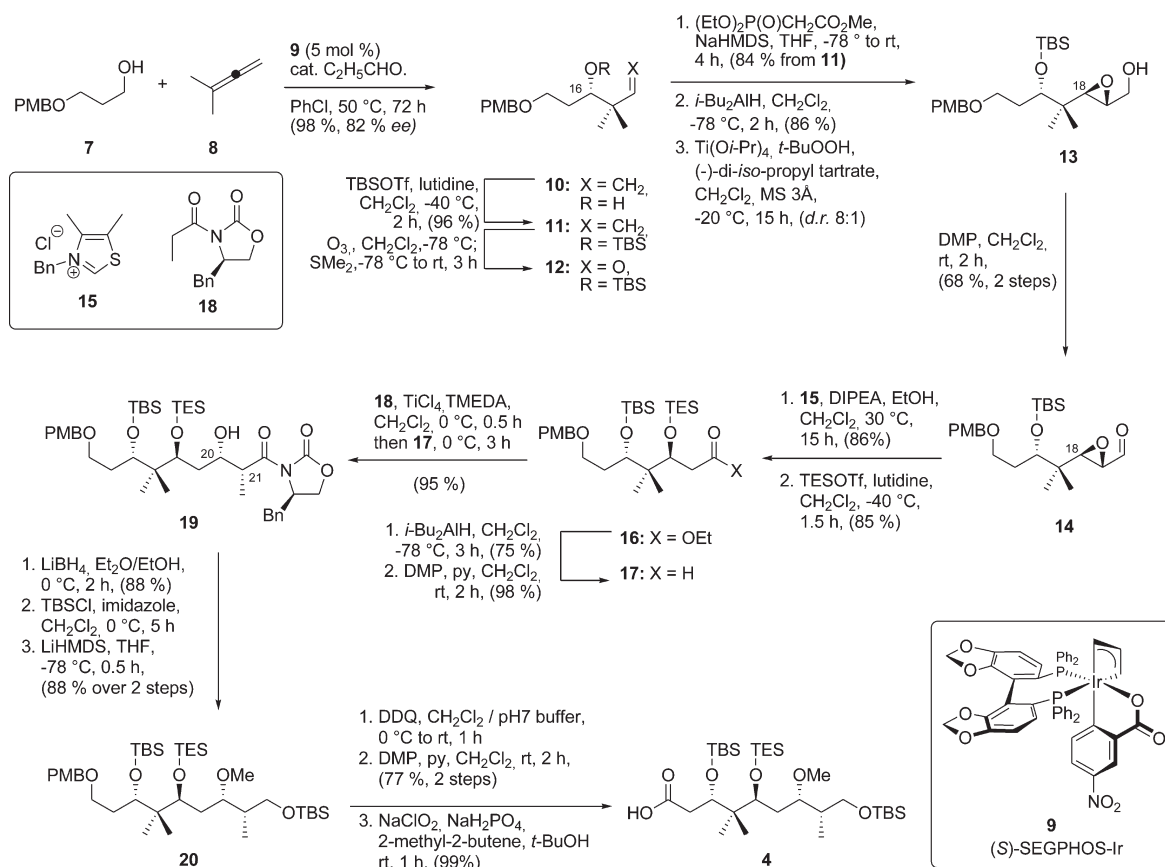
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Scheme 3. Successful Strategy for the Construction of **4**



favor of the isomer with the desired configuration at C18, as judged from ^1H NMR.

With epoxide **13** in hand, various conditions to reductively open this compound with different hydride sources (RedAl, DIBALH , LiAlH_4 , AlH_3 among others) were tested, but all met with failure giving product mixtures. These resulted mainly from silyl migration which occurred under the basic reaction conditions or the formation of regioisomeric diols with only traces of the desired 1,3-diol. In contrast, exposure to $\text{NaBSePh}(\text{OEt})_3$ ¹⁸ gave a β -hydroxyaldehyde in excellent yield, which could not be protected orthogonally. All attempts to install an acetate, benzoate, or TES group led to decomposition of the labile compound.

We thus turned our attention to alternative possibilities to transform **13** into a synthetically useful intermediate and took note of a method introduced by the group of Bode¹⁹ which allows the conversion of enantioenriched 2,3-epoxy-aldehydes to chiral β -hydroxyesters.

Consequently, **13** was oxidized to the corresponding epoxy-aldehyde **14** by means of the Dess-Martin-periodinane (DMP)²⁰ (68%) and directly treated with thiazolium salt

15 in the presence of Hünig's base to afford a β -hydroxyester in high yield (86%) which, in turn, was transformed into the TES-congener **16** (TES triflate, lutidine, 85%).

After routine oxidation state manipulations, which enhanced the diastereomeric purity of the material (12:1) following careful chromatography of the intermediates, the stage was set for an aldol reaction between aldehyde **17** and oxazolidinone **18**. After variable results with boron enolates,²¹ exposure of **17** to the titanium enolate of **18** according to Crimmins' conditions²² afforded the desired C20/C21-*syn*-isomer **19** exclusively in reproducibly high yields (95%). Reductive removal of the auxiliary under Soai's conditions (88%),²³ followed by selective silylation of the primary alcohol and subsequent methylation, provided **20** incorporating the complete C16–C21-stereotetrad in 88% yield over two steps.

Next, the PMB-ether was selectively cleaved by means of DDQ in a buffered aqueous media, and the liberated intermediary alcohol was sequentially oxidized using DMP and $\text{NaClO}_2/\text{NaH}_2\text{PO}_4$ to furnish **4** in good yields (76% over three steps).

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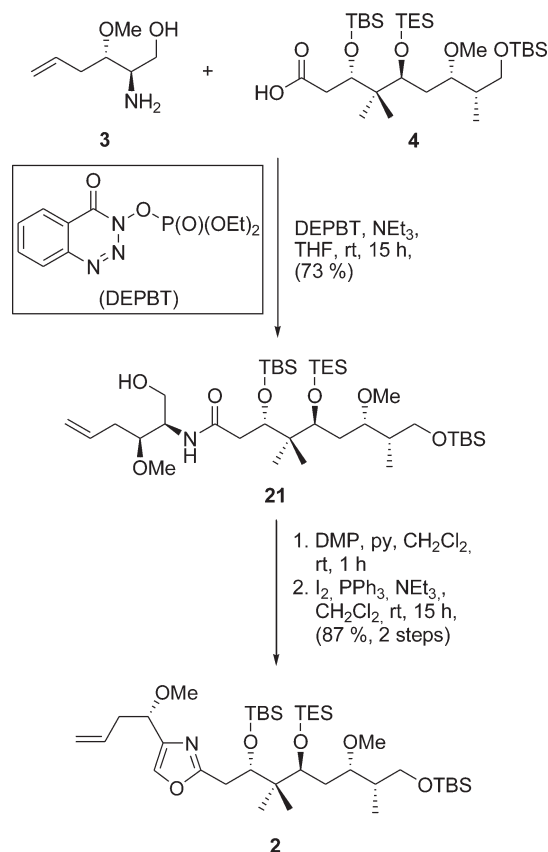
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Scheme 4. Completion of the Synthesis of Fragment 2



With sufficient amounts of **3** and **4** now prepared, we proceeded with their assembly en route to **2** (Scheme 4).

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(25) This reaction may be regarded as a modified Robinson–Gabriel reaction. See: Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604.

To this end, building blocks **3** and **4** were coupled in the presence of 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT),²⁴ giving rise to β -hydroxy amide **21** in good yield (73%) without the requirement for additional protection/deprotection steps. For the conversion into the desired oxazole motif, **21** was first oxidized with DMP to an intermediary aldehyde which was directly exposed to iodine and triphenylphosphine.²⁵ Gratifyingly, ring closure and elimination took place, as expected, and finally enabled access to the complete fragment **2** in 87% yield.

In summary, we have achieved a stereoselective synthesis of the C8–C22 fragment of rhizopodin in an overall yield of 8.1% based on a convergent approach which compares favorably to previous routes with respect to the number of steps and/or stereoselectivity. Notable features of the present route are the creation of the stereogenic center at C16 via the Krische asymmetric reverse prenylation from an alcohol precursor and the organocatalytic conversion of a derived epoxyaldehyde into a synthetically useful β -hydroxyester using a method of Bode, together with a late-stage oxazole formation from advanced and elaborated intermediates. This route demonstrates the true applicability of these strategies in complex natural product synthesis and may be useful in devising a scalable synthetic route toward rhizopodin.

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Supporting Information Available. Experimental details, spectral data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.