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Synthesis of the Macrocyclic Core of Rhizopodin

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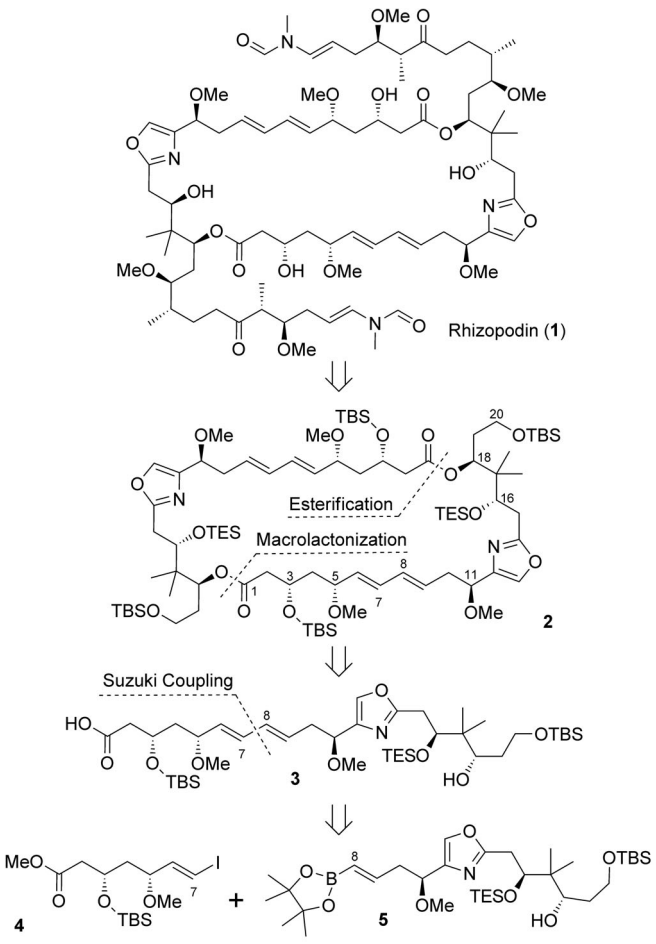
Rhizopodin (**1**) is a recently discovered marine natural product with impressive biological properties, including potent cytostatic activity against a range of tumor cell lines in the low nanomolar range.[1] The mechanism of action is known to involve interference with actin dynamics. Originally isolated from the myxobacterium *Myxococcus stipitatus* in 1993 and recently revised as shown in Scheme 1,[2] this compound possesses a novel molecular architecture, the central domain of which consists of a 38-membered dilactone containing two disubstituted oxazoles and two conjugated diene systems. Our laboratory is engaged in a program devoted to marine natural products[3] and view their synthesis as a key route to structural modification and subsequent activity control. Because of its important biological activity and novel molecular features, rhizopodin (**1**) was selected as a prime target for our synthetic studies.[3j] Not surprisingly, rhizopodin has also attracted considerable attention from other synthetic chemists. Over the past few years, several synthetic approaches to fragments and advanced intermediates of rhizopodin have been reported;[4] these approaches include Nicolaou's synthesis of mono-rhizopodin and 16-*epi*-mono-rhizopodin,[5] and Menche's effects culminated in a completed total synthesis.[6] While this manuscript was in preparation, Paterson and co-workers reported an elegant total synthesis of rhizopodin[7] that employs a conceptually similar route towards the formation of the macrocyclic core. This disclosure prompted us to present our own progress toward the synthesis of rhizopodin. Herein, we describe our independent synthesis of **2**, which corresponds to the fully functionalized macrocyclic core of rhizopodin.



Scheme 1. Retrosynthetic analysis.

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As outlined in our retrosynthetic analysis, rhizopodin could be simplified by using the 38-membered macrodilactone (**2**) as the advanced precursor with the side chains being installed at a later stage in the total synthesis. It was envisaged that **2** could be constructed by macrolactonization of the corresponding precursor derived from intermediate **3**, which was envisaged to be assembled from fragments **4** and **5** (Scheme 1). This strategy would reduce the number of protecting group manipulations and oxidation state adjustments.

The synthesis of fragment **5** involves elongation of diol **6** in two directions into the corresponding α,β-unsaturated

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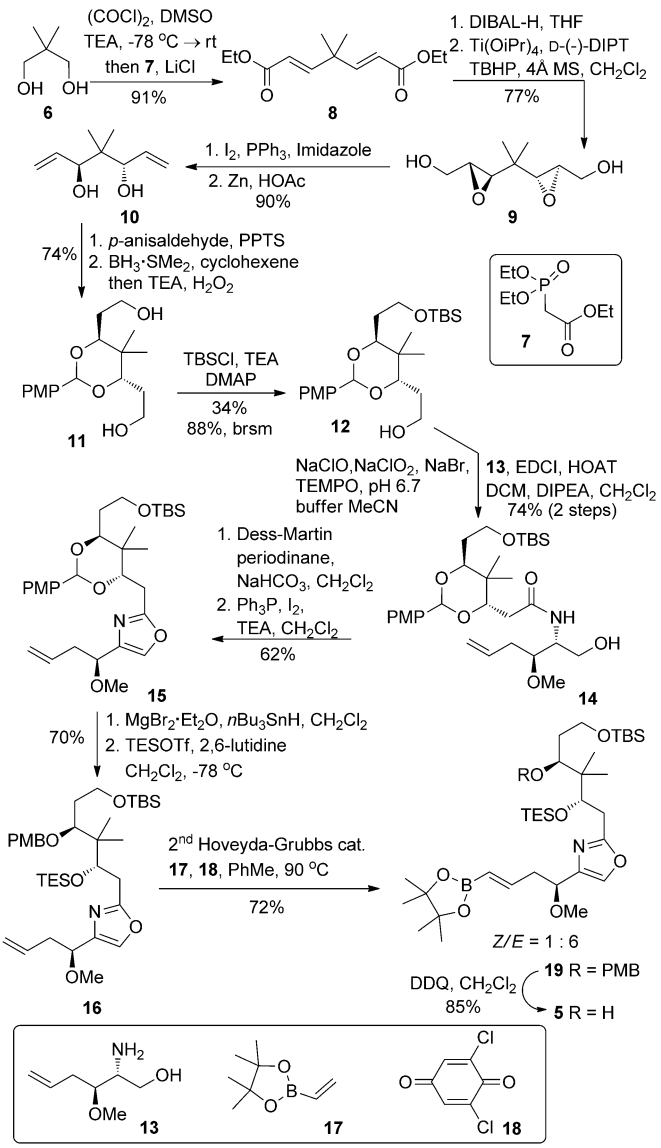

Scheme 2. Synthesis of intermediate **5**. DMSO = dimethylsulfoxide, TEA = triethylamine, DIBAL-H = diisobutylaluminium hydride, DIPT = diisopropyl tartrate, TBHP = *tert*-butyl hydroperoxide, MS = molecular sieves, PPTS = pyridinium *p*-toluenesulfonate, PMP = *p*-methoxyphenyl, TBS = *tert*-butyldimethylsilane, DMPA = 4-dimethylaminopyridine, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbo-diimide, HOAT = 1-hydroxy-7-azabenzotriazole, DIPEA = diisopropylethylamine, TES = triethylsilyl, Tf = trifluoromethanesulfonate, PMB = p-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

diester **8** (Scheme 2). Thus, Swern oxidation of diol **6** afforded the corresponding dialdehyde, which was subjected to Horner–Wadsworth–Emmons olefination with phosphonate **7** to give **8** in 91% yield over the two steps. Reduction of **8** with DIBAL-H produced the corresponding allylic alcohol, which was then subjected to a Sharpless asymmetric epoxidation, using D-(−)-DIPT, to afford the diepoxy alcohol **9** in very good yield (77%). The primary hydroxy groups of **9** were converted into the corresponding iodo groups with iodine, triphenylphosphine, and imidazole in THF and subsequent reductive elimination of the iodo groups with activated Zn dust in EtOH[8] provided the allylic alcohol **10** in 90% yield over two steps. Conversion of **10** into alcohol **12** was achieved by employing three straightforward transformations: (i) protection of the 1,3-diol moiety of **10** to the corresponding PMP acetal, (ii) double hydroboration of two terminal alkenes followed by an oxidative workup to give rise to diol **11**, and (iii) desymmetrization of diol **11** by mono-*tert*-butyldimethyl-silylation. Oxidation of the primary hydroxy group of **12** by the sequential action of TEMPO/NaClO and $NaClO_2$ gave the corresponding acid,[9] which was then condensed with amino alcohol **13**[10] to give rise to **14** in 74% yield. Dess–Martin oxidation of hydroxy amide **14** followed by one-pot cyclodehydration of the resulting aldehyde under Wipf conditions[11] afforded the oxazole **15** in 62% yield. Further elaboration to the doubly protected diol **16** was then effected by an oxazole-directed acetal cleavage using $MgBr_2{\cdot}Et_2O$ and nBu_3SnH[12] and protection of the resulting C16 alcohol as its TES ether. The structure and regiochemistry of the acetal-cleavage adduct were confirmed by ^1H and ^{13}C NMR spectroscopic experiments employing COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence), and HMBC (heteronuclear multiple bond correlation) correlations (see the Supporting Information). Olefin cross-metathesis of **16** with **17** in the presence of additive **18**[13] afforded vinyl boronate ester **19** in 72% yield with an *E*/*Z* ratio of 6:1. Building on the experience gained in our previous approach towards rhizopodin,[3j] we elected to remove the PMB ether in **19** with DDQ to give rise to alcohol **5**, which would alleviate later chemoselectivity complications arising from oxidative conditions.

The synthesis of vinyl iodide **4** commenced from the known ester **20**.[14,6] Methyl ester **20** was subjected to successive reduction with DIBAL-H and oxidation with Dess–Martin periodinane to afford the corresponding aldehyde. The reaction of this aldehyde with Nagao's *N*-acetylthiazolidine-2-thione (**21**)[15] in the presence of tin triflate[16] and *N*-ethylpiperidine proceeded in high diastereoselectivity (d.r. = 10:1) to yield the corresponding β-hydroxy adduct **22** as the major diastereomer. Protection of the resulting secondary hydroxy group of **22** as its TBS ether, followed by displacement of the thiazolidinethione auxiliary with methanol in the presence of DMAP afforded **23** in 69% yield. Acidic cleavage of primary TBS ether afforded alcohol **24** in 75% yield. Oxidation of alcohol **24** with Dess–Martin periodinane afforded the corresponding aldehyde, which was homologated using the Takai protocol[17] to furnish vinyl iodide **4** in 68% yield over two steps (Scheme 3).

With the key intermediates **4** and **5** in hand, we next turned our attention to their coupling reaction (Scheme 4). In the event, intermolecular coupling of vinyl iodide **4** and vinyl boronate ester **5** proceeded smoothly in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium and silver oxide[18] to provide the diene **25** in 84% yield. Saponification of the methyl ester in the presence of a number of sensitive functionalities was achieved by heat-

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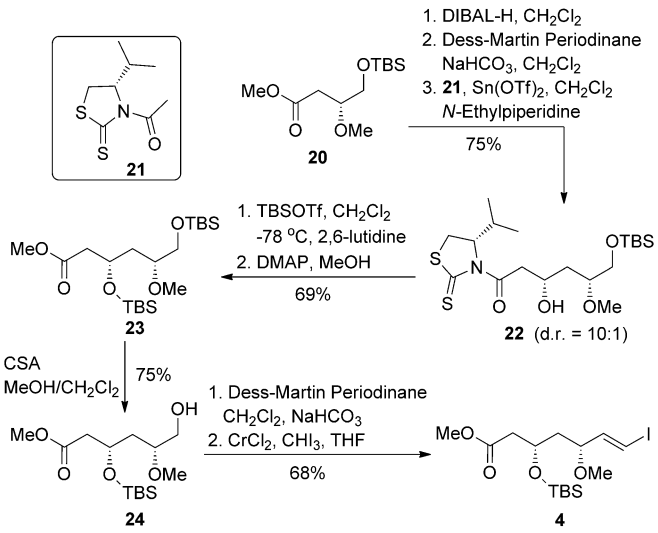
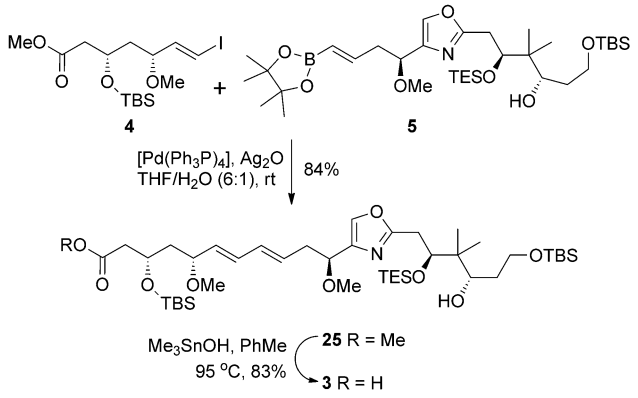
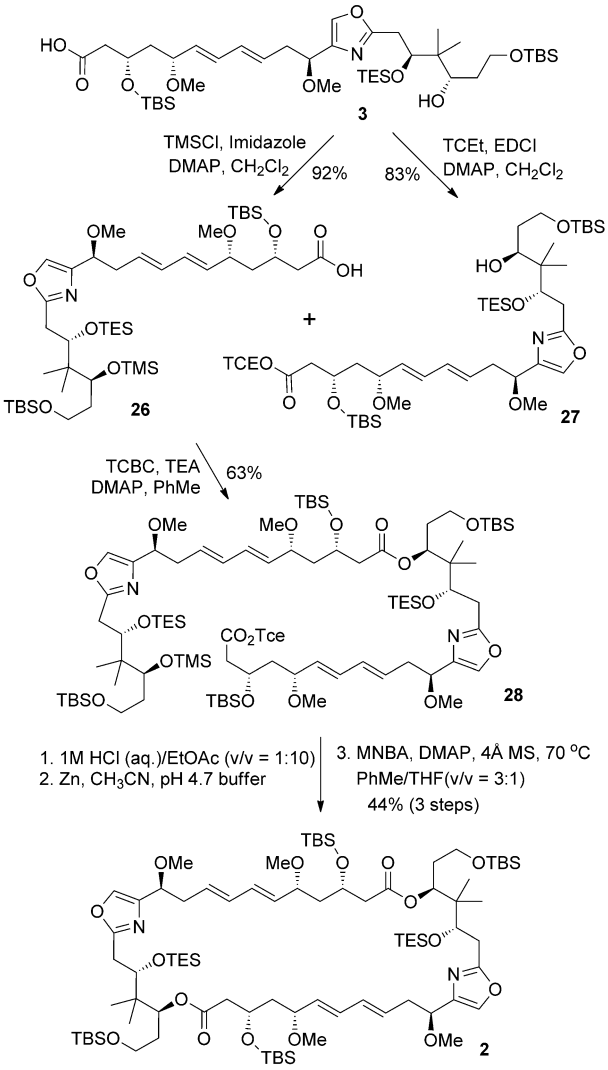


Scheme 3. Synthesis of intermediate **4**. CSA = camphorsulfonic acid.



Scheme 4. Synthesis of intermediate **3**. THF = tetrahydrofuran.



Scheme 5. Synthesis of macrocyclic core **2**. TCEt = trichloroethanol, TCE = trichloroethyl, TMS = trimethylsilyl, TCBC = 2,4,6-trichlorobenzyl chloride, MNBA = 2-methyl-6-nitrobenzoic anhydride.

ing **25** with 5 equivalents of Me_3SnOH[19] in toluene at 95 °C for 36 h. Acid **3** was obtained in 83 % yield and this moiety was readily converted into compounds **26** and **27** for further elaboration into macrodilactone **2**.

As shown in Scheme 5, **26** was obtained in 92 % yield by treatment of **3** with trimethylsilyl chloride and imidazole, whereas **27** was produced by converting **3** into the corresponding trichloroethyl ester in 83 % yield through an EDC-mediated esterification. Esterification between acid **26** and alcohol **27** was achieved by using a modification of the Yamaguchi protocol,[20] reported by Yonemitsu[21]; this afforded **28** in 63 % yield. The secondary alcohol-bound TMS group was selectively removed with a mixture of HCl (1 M, aq)/ethyl acetate (1:10) at ambient temperature and the trichloroethyl ester was then reductively cleaved in a mixture held at pH 4.7 using a buffer,[22] and this provided the required *seco*-acid, in preparation for the key macrolactonization step. For our substrate, we found that the Shiina macrolactonization[23] was the most effective. A solution of the *seco*-acid intermediate was slowly added to a solution of DMAP and 2-methyl-6-nitrobenzoic anhydride (MNBA) containing powdered molecular sieves to give rise to macrodilactone (**2**) in 44 % yield.

In summary, the macrocyclic skeleton of the marine natural product rhizopodin has been prepared through a convergent route that employed Sharpless epoxidation, Robinson–Gabriel oxazole synthesis, olefin cross-metathesis, Suzuki coupling, a Yamaguchi esterification, and Shiina macrolactonization as the key steps. The elaboration of macrodilactone **2** and alternative synthetic strategies to natural rhizopodin are ongoing in our laboratories and will be reported in due course.

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Experimental Section

HCl (1.2 mL, 1 M in water) was added to a solution of **28** (18.6 mg, 10 μmol) in ethyl acetate (3 mL) at room temperature. The reaction was stirred and monitored by TLC until the starting material was consumed (approx. 1.5 h). The reaction mixture was diluted with ethyl acetate (80 mL), washed with brine (10 mL), and dried over Na_2SO_4. The solution was concentrated in vacuo to afford the desired alcohol, which was employed in next step without further purification. The above alcohol was dissolved in MeCN/KH_2PO_4 (1 M, 6 mL, v/v = 1:1) at room temperature. After zinc dust (100 mg) was added, the reaction mixture was stirred vigorously for 10 h. The reaction mixture was diluted with ethyl acetate (100 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel chromatography (ethyl acetate/*n*-hexane = 1:4 to 1:2) to give the *seco*-acid (14.0 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (s, 1H), 7.49 (s, 1H), 6.22–6.05 (m, 4H), 5.82–5.58 (m, 2H), 5.46–5.34 (m, 2H), 5.13–5.04 (m, 1H), 4.34–4.25 (m, 2H), 4.25–4.15 (m, 4H), 3.92–3.79 (m, 3H), 3.81–3.71 (m, 2H), 3.65–3.58 (m, 1H), 3.57–3.49 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H), 3.08 (dd, J = 15.3, 3.2 Hz, 1H), 3.05–2.84 (m, 3H), 2.72–2.47 (m, 8H), 1.98–1.82 (m, 3H), 1.79–1.66 (m, 3H), 1.6–1.54 (m, 2H), 0.96–0.85 (m, 66H), 0.58–0.34 (m, 12H), 0.12 (s, 6H), 0.10 (s, 3H), 0.10 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.02 ppm (s, 3H). HRMS (ESI): *m/z* calc. for $C_{84}H_{161}N_2O_{17}Si_6^+$: $[M+H]^+$: 1638.0405, found 1638.0394.

MNBA (12.2 mg, 34 μmol), DMAP (10.3 mg, 82 μmol), and powdered 4 Å molecular sieves (30.0 mg) were stirred in toluene (2.5 mL). After the mixture was brought to 70 °C, a solution of the above *seco*-acid (14.0 mg, 8.5 μmol) in THF/toluene (2 mL, v/v = 1:1) was added dropwise with a syringe pump over 3 h. The reaction mixture was stirred at 70 °C for an additional 12 h prior to being cooled to room temperature and quenched by saturated aqueous solution of NH_4Cl (1.0 mL). The mixture was diluted with ethyl acetate (200 mL) and the organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel chromatography (ethyl acetate/*n*-hexane = 1:8 to 1:5) to give **2** (7.1 mg, 44 %) as a colorless oil. $[\alpha]_D^{20} = -13\ cm^3\ g^{-1}\ dm^{-1}$ (c = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (s, 2H), 6.18–6.03 (m, 4H), 5.66 (dt, J = 14.3, 7.1 Hz, 2H), 5.36 (dd, J = 14.5, 8.1 Hz, 2H), 5.07–4.99 (m, 2H), 4.20 (t, J = 6.0 Hz, 2H), 4.18–4.07 (m, 4H), 3.76–3.63 (m, 2H), 3.64–3.52 (m, 2H), 3.55–3.43 (m, 2H), 3.33 (s, 6H), 3.20 (s, 6H), 3.04 (dd, J = 15.4, 2.8 Hz, 2H), 2.89 (dd, J = 15.3, 9.0 Hz, 2H), 2.62 (t, J = 6.7 Hz, 4H), 0.94–0.76 (m, 66H), 0.49–0.29 (m, 12H), 0.05 (s, 12H), −0.00 ppm (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.6, 163.6, 140.6, 135.0, 133.1, 131.9, 131.8, 129.9, 79.2, 76.3, 76.0, 74.6, 66.4, 60.3, 56.8, 55.9, 43.0, 42.4, 37.7, 33.8, 32.8, 29.7, 25.9, 25.9, 20.8, 19.9, 18.2, 18.0, 7.0, 5.0, −4.4, −4.6, −5.4, −5.4 ppm. HRMS (ESI): *m/z* calc. for $C_{84}H_{159}N_2O_{16}Si_6^+$: $[M+H]^+$: 1620.0300, found 1620.0382.

Acknowledgements

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Natural Products

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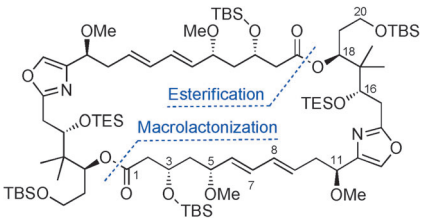

Rhizing star: A stereoselective synthesis of the fully functionalized macrocyclic core of rhizopodin, a cytotoxic 38-membered macrolide, has been disclosed. The key steps involve Sharpless epoxidation, Robinson–Gabriel oxazole synthesis, olefin cross-metathesis, Suzuki coupling, Yamaguchi esterificationn, and Shiina macrolactonization.

Synthesis of the Macrocyclic Core of Rhizopodin

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