Natural Product Synthesis

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Total Synthesis and Biological Evaluation of Monorhizopodin and 16-*epi*-Monorhizopodin**

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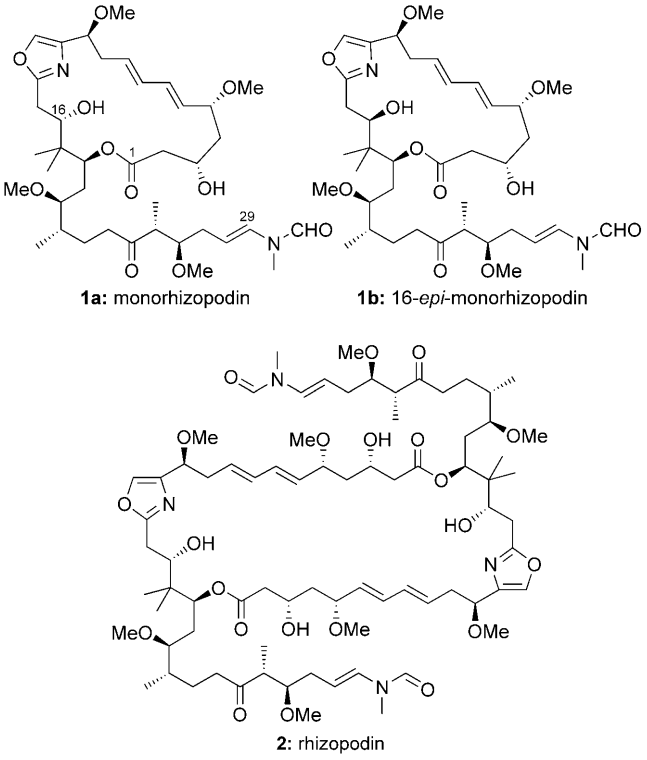
For many years, polyketide natural products have provided the scientific community with a rich source of novel molecular architectures, many of which have become important therapeutics for clinical use.[1] In 1993, the polyketide rhizopodin was isolated from the myxobacterium *Myxococcus stipitatus*.[2] It was shown to display an interesting array of biological properties, including potent antitumor activity against a range of cancer cell lines in the low nanomolar range and the ability to inhibit the polymerization of actin.[2,3] Despite its original structural assignment as the 19-membered monomeric lactone **1a** (monorhizopodin), recent studies revealed dimeric structure **2** to be the correct architecture of rhizopodin (Scheme 1).[4] These molecules have started to attract attention from the synthetic community, although no total syntheses have been reported to date.[5]

We were intrigued as to whether the originally proposed structure for monorhizopodin (**1a**) might exhibit comparable biological properties to its parent dimer (**2**), as these molecules contain several common structural elements, including an enamide side chain that is crucial for biological activity. X-ray crystallographic analysis of a rhizopodin–actin complex indicated that the binding of **2** to actin was largely a result of favorable van der Waals interactions between the enamide side chain and certain hydrophobic residues in the binding cleft.[6] Thus, the construction of **1a** might shed light on the effect of the macrocycle itself upon the binding affinity of these compounds. Herein, we describe a highly convergent and enantioselective total synthesis of monorhizopodin (**1a**) and its C16 epimer (**1b**), as well as preliminary biological evaluation of these compounds.



Scheme 1. Structures of monorhizopodin (**1a**), 16-*epi*-monorhizopodin (**1b**), and rhizopodin (**2**).

Scheme 2 depicts, in retrosynthetic format, the outline of the synthetic strategy employed for the construction of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**). Thus, rupture of the macrolactone and the C22–C23 and C29–N bonds led, after functional group adjustments, to hydroxy carboxylic acid **3** and ketophosphonate **4** as potential precursors to the target molecules. Disassembly of **3** at the indicated bond (C15–C16) through a SmI_2-mediated Barbier reaction revealed iodoester **5** and aldehyde **6** as the required building blocks for its construction. Finally, disconnection of the diene system of **5** through a Stille coupling traced the origins of this compound to vinyl iodide **7** and oxazole-containing vinyl stannane **8**. The choice for the SmI_2-mediated Barbier coupling over the more conventional Grignard reaction was based on the remarkably mild nature of the former reagent.[7] This characteristic was thought to be essential for the survival of the resulting secondary alcohol,

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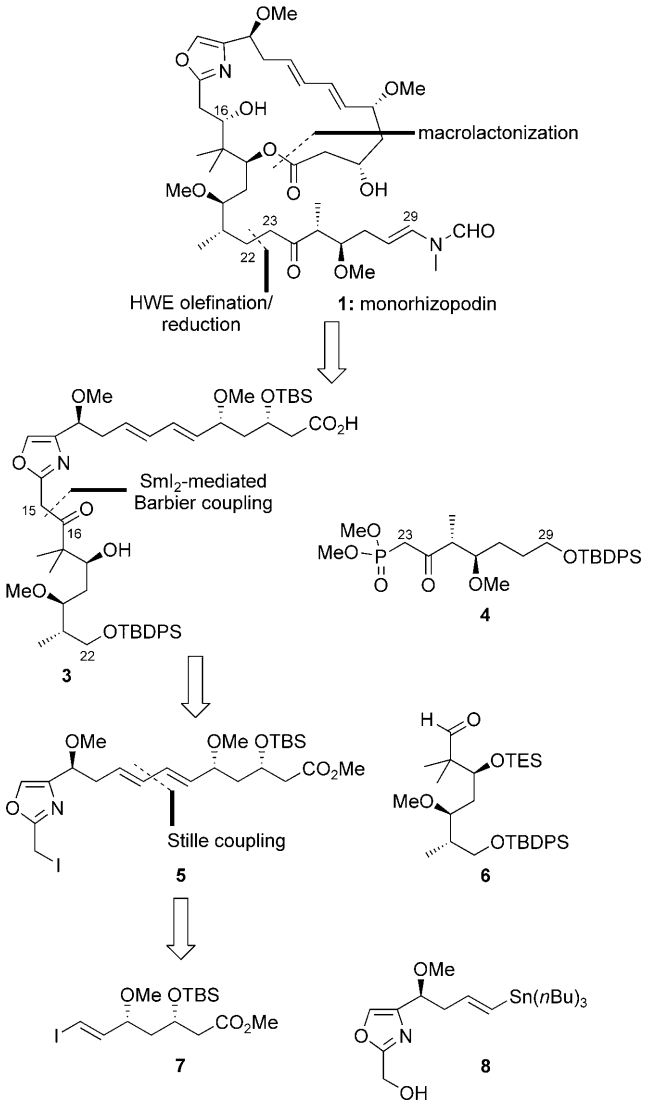
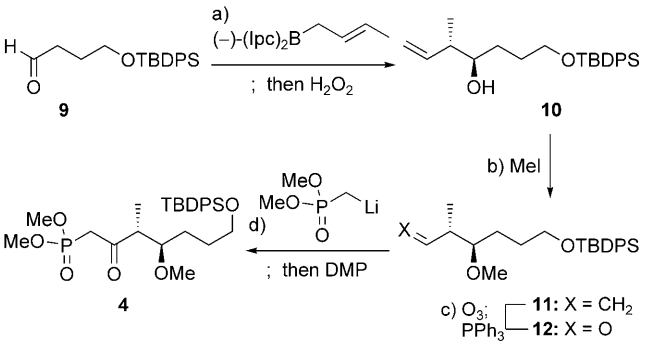


Scheme 2. Retrosynthetic analysis of monorhizopodin (**1**). HWE = Horner–Wadsworth–Emmons, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.



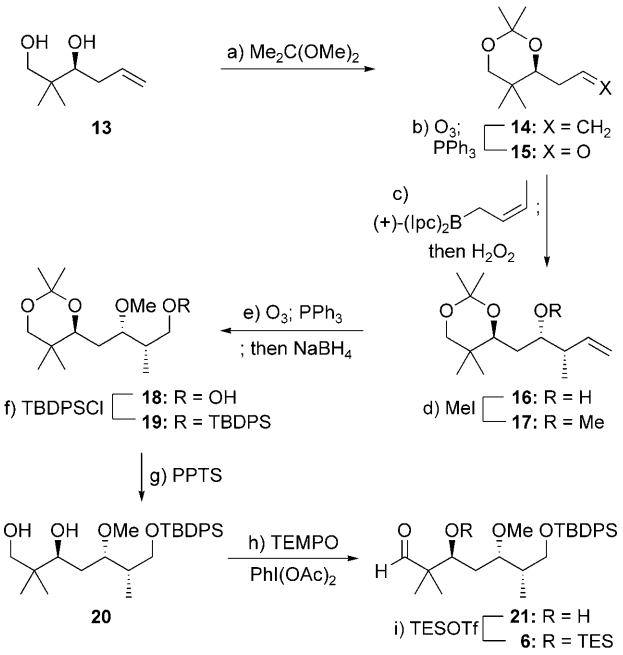
Scheme 3. Construction of ketophosphonate **4**. Reagents and conditions: a) (−)-(Ipc)$_2$-*trans*-crotyl borane (1.2 equiv), $BF_3{\cdot}OEt_2$ (1.2 equiv), THF, −78 °C, 1 h; 3 N NaOH (aq), H_2O_2, Et_2O, 25 °C, 10 h, 91 %, d.r. > 10:1; b) NaH (1.5 equiv), MeI (1.5 equiv), THF, 0 to 25 °C, 1 h, 76 %; c) O_3, CH_2Cl_2, −78 °C; then PPh_3 (1.5 equiv), 25 °C, 1 h, 84 %; d) MeP(O)(OMe)$_2$ (5.5 equiv), *n*BuLi (5.5 equiv), THF, −78 °C, 1 h; **12** (1.0 equiv), −78 °C, 2.5 h; DMP (1.4 equiv), CH_2Cl_2, 25 °C, 10 min, 98 % for two steps. DMP = Dess–Martin periodinane, Ipc = isopinocampheyl, THF = tetrahydrofuran.

whose facile elimination toward the oxazole moiety was considered to be potentially problematic.

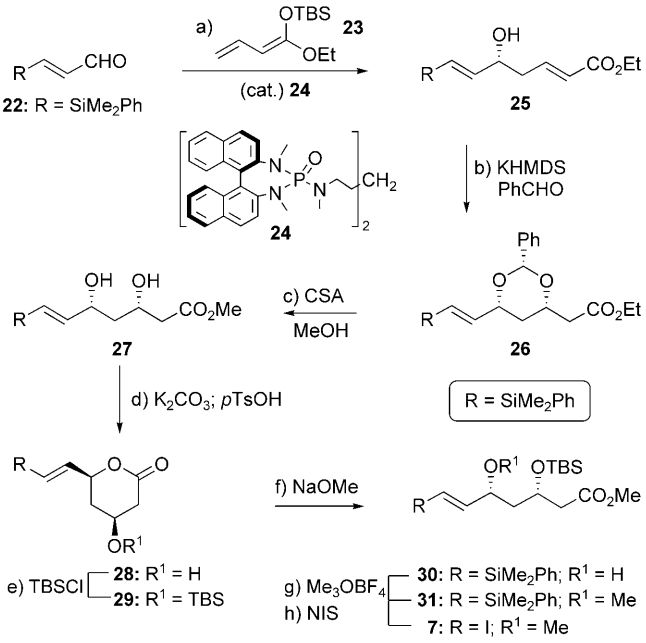
The synthesis of monorhizopodin (**1a**) and its 16-*epi*-diastereoisomer (**1b**) commenced with the construction of the requisite building blocks in their enantiomerically pure forms, starting with ketophosphonate **4**. Thus, as shown in Scheme 3, enantioselective crotylation of aldehyde **9**[8] with (−)-(Ipc)$_2$-*trans*-crotyl borane by employing Brown's protocol afforded alcohol **10** in 91 % yield as a > 10:1 mixture of diastereomers and > 95 % *ee*. Methylation (NaH, MeI, 76 % yield) and cleavage of the terminal olefin by ozonolysis (O_3; Ph_3P, 84 % yield) of the latter compound led to aldehyde **12** through intermediate **11**. Reaction of aldehyde **12** with the lithium species derived from dimethyl methylphosphonate and *n*BuLi, and subsequent DMP oxidation of the resulting mixture of diastereomeric alcohols, furnished ketophosphonate **4** in 98 % overall yield.

Aldehyde **6** was synthesized from known diol **13**[9] as summarized in Scheme 4. Thus, acetonide formation from **13** ($Me_2C(OMe)_2$, (±)-CSA (cat.), 96 % yield) and subsequent ozonolysis of the resulting olefin (**14**, O_3; Ph_3P, 83 % yield) led to aldehyde **15**, which was subjected to reagent-controlled crotylation under Brown's conditions ((+)-(Ipc)$_2$-*cis*-crotyl borane) to afford secondary alcohol **16** in 75 % yield as a single diastereomer. Methylation of **16** (NaH, MeI) and subsequent ozonolysis (O_3; Ph_3P) and reduction with $NaBH_4$ gave primary alcohol **18**, whose silylation (TBDPSCl, imidazole, DMAP (cat.)) led to acetonide TBDPS ether **19**, via intermediates **17** and **18**, in 75 % overall yield for the four steps. Liberation of the 1,3-diol system of **19** required mild acid conditions (PPTS) and recycling (3×) to avoid significant degradation of the TBDPS ether and resulted in 56 % yield of diol **20** (plus 33 % recovered starting material). Selective oxidation of the primary hydroxy group of **20** ($PhI(OAc)_2$, TEMPO (cat.)), and subsequent TES protection (TESOTf, 2,6-lutidine), furnished, via intermediate **21**, the required aldehyde **6** (75 % overall yield for the 2 steps).

Scheme 5 summarizes the construction of vinyl iodide **7**. By following a procedure developed by Denmark et al., α,β-unsaturated aldehyde **22**[10] was treated with silyl ketene acetal **23**[11] in the presence of catalyst **24** and $SiCl_4$[12] to afford secondary alcohol **25** in 69 % yield and > 90 % *ee*. Exposure of **25** to KHMDS and benzaldehyde afforded benzylidene acetal **26** (71 % yield), whose configuration was confirmed by nOe interactions. Subsequent treatment of **26** with (±)-CSA in MeOH revealed dihydroxy methyl ester **27** through cleavage of the acetal group and transesterification (54 % yield plus 44 % recovered starting material). Selective protection of the hydroxy group proximal to the ester moiety was achieved through δ-lactone formation within **27** (K_2CO_3; *p*TsOH, 96 % overall yield) and silylation (TBSCl, DMAP, 84 % yield), thus leading to TBS ether **29** via hydroxy compound **28**. Subsequent opening of the δ-lactone moiety of **29** (NaOMe, 86 % yield), and subsequent methylation (Me_3OBF_4, 2,6-di-*tert*-



Scheme 4. Construction of aldehyde **6**. Reagents and conditions: a) (±)-CSA (0.010 equiv), $Me_2C(OMe)_2$, DMF, 25 °C, 2 h, 96%; b) O_3, CH_2Cl_2, −78 °C; then PPh_3 (2.0 equiv), 25 °C, 1 h, 83%; c) (+)-$(Ipc)_2$-*cis*-crotyl borane (1.2 equiv), $BF_3{\cdot}OEt_2$ (1.2 equiv), THF, −78 °C, 1 h; 3 N NaOH (aq), H_2O_2, Et_2O, 25 °C, 10 h, 75%; d) NaH (1.3 equiv), MeI (2.0 equiv), THF, 0 to 25 °C, 1 h, 89%; e) O_3, CH_2Cl_2, −78 °C; then PPh_3 (2.0 equiv), 25 °C, 1 h; $NaBH_4$ (1.1 equiv), MeOH, 0 °C, 30 min, 86% for two steps; f) TBDPSCl (1.1 equiv), imidazole (1.3 equiv), DMAP (0.10 equiv), CH_2Cl_2, 0 to 25 °C, 1 h, 98%; g) PPTS (1.0 equiv), CH_2Cl_2, MeOH, 25 °C, 16 h, 56% (33% recovered **19**); h) TEMPO (0.30 equiv), $PhI(OAc)_2$ (3.0 equiv), CH_2Cl_2, 25 °C, 12 h, 85%; i) TESOTf (1.2 equiv), 2,6-lutidine (2.4 equiv), CH_2Cl_2, −78 °C, 30 min, 88%. DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *para*-toluenesulfonate, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

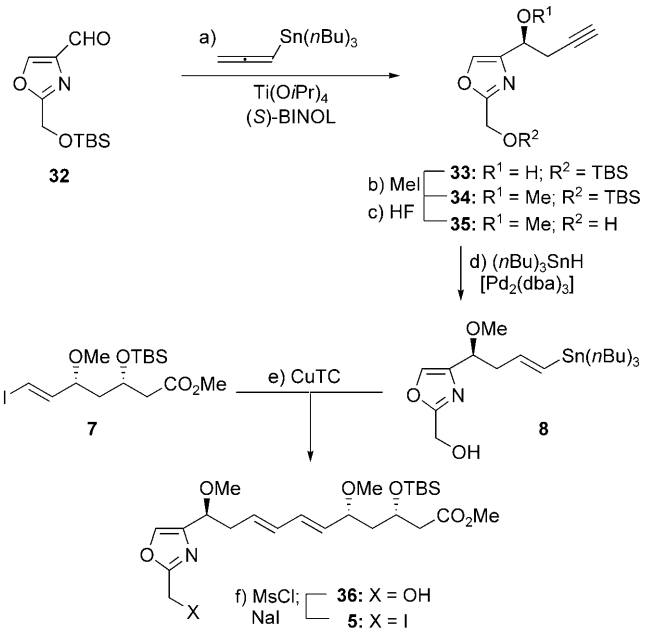


Scheme 5. Construction of vinyl iodide **7**. Reagents and conditions: a) **23** (1.2 equiv), cat. (*R*,*R*)-**24** (0.015 equiv), $SiCl_4$ (1.1 equiv), iPr_2NEt (0.20 equiv), CH_2Cl_2, −78 °C, 2 h, 69%; b) PhCHO (3.3 equiv), KHMDS (0.30 equiv), THF, 0 °C, 1 h, 71%; c) (±)-CSA (0.30 equiv), MeOH, 25 °C, 20 h, 54% (44% recovered **26**); d) K_2CO_3 (2.0 equiv), MeOH, H_2O, 25 °C, 15 min; *p*TsOH (1.0 equiv), THF, 25 °C, 1 h, 96% for two steps; e) TBSCl (2.4 equiv), DMAP (3.9 equiv), CH_2Cl_2, 25 °C, 2 h, 84%; f) NaOMe (2.0 equiv), MeOH, 0 °C, 1 h, 86%; g) Me_3OBF_4 (4.0 equiv), 2,6-di-*tert*-butyl-4-methyl pyridine (5.0 equiv), CH_2Cl_2, 25 °C, 12 h, 80%; h) NIS (3.0 equiv), MeCN, 60 °C, 10 h, 96%. CSA = camphorsulfonic acid, KHMDS = potassium hexamethyldisilazide, NIS = *N*-iodosuccinimide, *p*TsOH = *para*-toluenesulfonic acid.

butyl-4-methyl pyridine, 80% yield) and iodination (NIS, 96% yield), furnished vinyl iodide **7** via intermediates **30** and **31**.

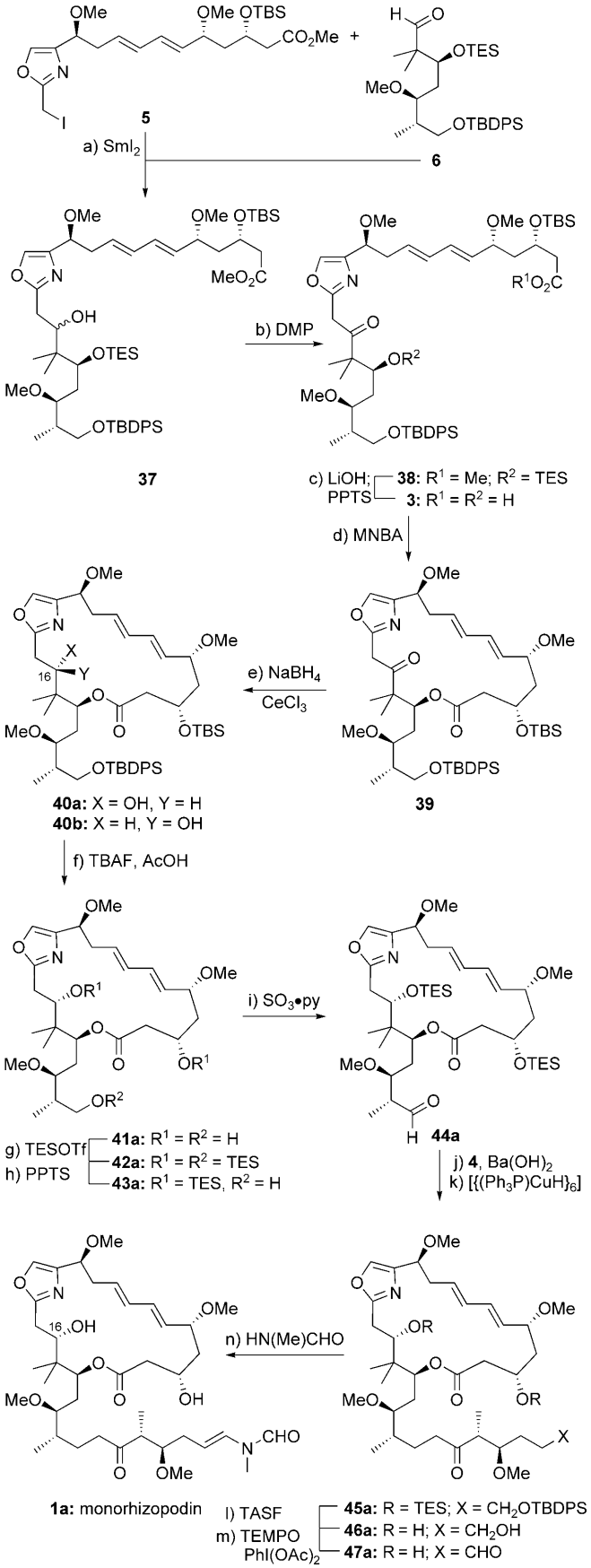
Vinyl stannane **8** was constructed from known oxazole aldehyde **32**[13] and converted into advanced iodide **5** as summarized in Scheme 6. Thus, treatment of **32** with allenyltri-*n*-butylstannane in the presence of $Ti(OiPr)_4$ and (*S*)-BINOL afforded alcohol **33** in 60% yield (plus 24% recovered starting material) and >95% *ee*.[14] Methylation of **33** (NaH, MeI, 93% yield) and subsequent desilylation (aqueous HF, 86% yield) led to primary alcohol **35** via intermediate **34**. Regio- and stereoselective addition of tri-*n*-butyltin hydride to the terminal acetylene unit of **35** was achieved through palladium catalysis ($[Pd_2(dba)_3]$, $Cy_3P{\cdot}HBF_4$, iPr_2NEt, $(nBu)_3SnH$, 67% yield) and afforded vinyl stannane **8**. Coupling of this stannane with vinyl iodide **7** in the presence of CuTC[15] led to alcohol **36** (75% yield), which was converted into the desired advanced iodide **5** by sodium iodide through its mesylate derivative (MsCl, Et_3N; NaI, 96% overall yield).

With fragments **4**–**6** now available, the stage was set for their coupling and elaboration to the targeted molecules monorhizopodin (**1a**) and its 16-*epi*-diastereoisomer (**1b**). As shown in Scheme 7, a mixture of **5** (1.0 equiv) and **6** (1.5 equiv) was exposed to the action of SmI_2 in THF and afforded a 1:1 diastereomeric mixture of alcohols **37** at C16 (56% yield). Given the complexity of these substrates, the performance of SmI_2 in this coupling reaction is remarkable and provides further testament for the power of this reagent in organic synthesis.[7] Having achieved coupling of the key fragments, the resulting mixture of alcohols **37** was oxidized through the action of DMP and afforded ketone **38** in 95% yield. Saponification of the methyl ester of **38** (LiOH, 60 °C) and subsequent removal of the TES group (PPTS) then led to hydroxy acid **3** (62% overall yield), which was now primed for macrolactonization. After screening several reaction conditions we found that optimal results could be obtained by employing the protocol developed by Shiina et al.[16] Thus, slow addition of hydroxy acid **3** to solution of MNBA in toluene and DMAP at 60 °C afforded keto macrolactone **39** in good yield. Owing to its tailing TLC properties, this ketone was difficult to purify and, therefore, was reduced with $NaBH_4$ in the presence of $CeCl_3$ in MeOH at −20 °C to give hydroxy compounds **40a** and **40b** as a chromatographically separable mixture of diastereomers (ca. 2:1 in favor of **40a**; under the high dilution conditions employed in the macrolactonization process, no dimeric material was observed).



Scheme 6. Synthesis of vinyl stannane **8** and advanced iodide **5**. Reagents and conditions: a) $Ti(OiPr)_4$ (1.0 equiv), (*S*)-BINOL (1.0 equiv), M.S. (4 Å), CH_2Cl_2, 40 °C, 1 h; **32** (1.0 equiv), allenyl-tri-*n*-butylstannane (1.2 equiv), −24 °C, 72 h, 60% (24% recovered **32**); b) NaH (2.0 equiv), MeI (2.0 equiv), THF, 0 to 25 °C, 1 h, 93%; c) 48% aq HF (2.0 equiv), MeCN, 25 °C, 3 h, 86%; d) $[Pd_2(dba)_3]$ (0.0050 equiv), $Cy_3P{\cdot}HBF_4$ (0.020 equiv), iPr_2NEt (0.040 equiv), $(nBu)_3SnH$ (1.2 equiv), CH_2Cl_2, 25 °C, 10 min, 67%; e) **7** (1.0 equiv), **8** (1.0 equiv), CuTC (10.0 equiv), NMP, 0 °C, 30 min, 75%; f) MsCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, −78 °C, 30 min; NaI (5.0 equiv), acetone, 25 °C, 1 h, 96% for two steps. BINOL = 1,1′-bi(2-naphthol), CuTC = copper(I) thiophene-2-carboxylate, Cy = cyclohexyl, dba = *trans*,*trans*-dibenzylideneacetone, Ms = methanesulfonyl, M.S. = molecular seives, NMP = *N*-methyl-2-pyrrolidinone.

Interestingly, reduction of ketone **39** with $NaBH_4$ alone delivered alcohol **40b** exclusively. Other reducing agents led to unsatisfactory results. The configurations of diastereomers **40a** and **40b** were determined by the ^{13}C NMR method



Scheme 7. Fragment coupling and completion of the total synthesis of monorhizopodin (**1a**). Reagents and conditions: a) **5** (1.0 equiv), **6** (1.5 equiv), SmI_2 (3.0 equiv), THF, 25 °C, 5 min, 56%; b) DMP (3.0 equiv), CH_2Cl_2, 25 °C, 15 min, 95%; c) $LiOH{\cdot}H_2O$ (6.0 equiv), $(CH_3)_2CHOH/THF/H_2O$ (4:1:1), 60 °C, 1 h; PPTS (1.0 equiv), CH_2Cl_2, MeOH, 25 °C, 12 h, 62% for two steps; d) **3** (1.0 equiv in THF/toluene (1:1), slow addition by syringe pump), MNBA (2.0 equiv), DMAP (6.0 equiv), M.S. (4 Å), toluene, 60 °C, 20 h; $NaBH_4$ (3.0 equiv), $CeCl_3{\cdot}7H_2O$ (10.0 equiv), MeOH, −20 °C, 30 min, 70% for two steps, d.r. = 2:1; e) TBAF (10.0 equiv), AcOH (10.0 equiv), DMF, 25 °C, 12 h, 89%; f) TESOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, −78 °C, 30 min, 66%; g) PPTS (0.10 equiv), CH_2Cl_2, MeOH, 25 °C, 30 min, 89%; h) $SO_3{\cdot}py$ (2.0 equiv), iPr_2NEt (6.0 equiv), CH_2Cl_2, DMSO, 25 °C, 30 min, 81%; i) **4** (2.0 equiv), $Ba(OH)_2$ (0.5 equiv), THF, H_2O, 25 °C, 2 h, 65%; j) $[\{CuH(PPh_3)\}_6]$ (1.0 equiv), benzene, 25 °C, 8 h, 87%; k) TASF (5.0 equiv), DMF, 25 °C, 8 h, 70%; l) TEMPO (0.10 equiv), $PhI(OAc)_2$ (2.0 equiv), CH_2Cl_2, 25 °C, 4 h, 74%; m) HN(Me)CHO (20 equiv), PPTS (0.14 equiv), M.S. (4 Å), C_6H_6, 80 °C, 8 h, 78%. DMSO = dimethylsulfoxide, MNBA = 2-methyl-6-nitrobenzoic anhydride, py = pyridine, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBAF = tetra-*n*-butylammonium fluoride.

developed by Rychnovsky et al.[17] Thus, the acetonides obtained from **40a** and **40b** upon reductive macrolactone opening, selective protection of the primary alcohol with a TBDPS group, and acetonide formation were employed (**40a** gave *anti*-acetonide **40a′** (^{13}C NMR ($CDCl_3$): $\delta =$ 101.61 ppm), while **40b** gave *syn*-acetonide **40b′** (^{13}C NMR ($CDCl_3$): $\delta = 99.04$ ppm); see the Supporting Information). In preparation for the side chain attachment, the silyl protecting groups of diastereomer **40a** (corresponding to the C16 rhizopodin configuration) were removed (TBAF, AcOH) and afforded triol **41a** in 89% yield. The latter compound was then converted into its *tris*-TES derivative **42a** (TESOTf, 2,6-lutidine, 66% yield), which underwent selective monodesilylation (PPTS, 89% yield) and oxidation (SO_3·py, 81% yield) and afforded aldehyde **44a** through primary alcohol **43a**. This aldehyde was then treated with ketophosphonate **4** in the presence of $Ba(OH)_2$ and afforded the corresponding α,β-unsaturated ketone (65% yield), which was reduced with Stryker's reagent and led to its saturated counterpart (**45a**) in 87% yield. At this juncture, all that remained to complete the synthesis of monorhizopodin (**1a**) was global deprotection and installation of the enamide moiety. To this end, *tris*-silylated ketone **45a** was first exposed to TASF (to produce triol **46a**, 70% yield) and then to $PhI(OAc)_2$/TEMPO (cat.) to furnish, through selective oxidation of the primary alcohol, dihydroxy aldehyde **47a** (74% yield). The latter was condensed with *N*-methyl formamide (PPTS, M.S. (4 Å), 80 °C) and afforded monorhizopodin (**1a**) in 78% yield as a mixture of *E*/*Z* geometrical isomers (ca. 2:1 in favor of the *E* isomer). By following the same sequence, 16-*epi*-monorhizopodin (**1b**) was also synthesized from diastereoisomer **40b** (see the Supporting Information). The ^{1}H and ^{13}C NMR and IR spectroscopic data of **1a** and **1b** were similar to those reported for rhizopodin (**2**).[4] The monomeric structures of these compounds were confirmed by mass spectrometry.

With synthetic samples of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**) available to us, we were in a position to evaluate their biological properties in actin polymerization and cytotoxicity assays. As shown in Figure 1, monorhizopodin (**1a**) exhibited potent inhibitory activity of actin polymerization, as expected from its enamide side chain structural motif. This activity, which is mimicked by monorhizopodin's 16-*epi*-isomer (**1b**), albeit with somewhat lower potency, is comparable to that of latrunculin A (see Figure 1), which was used as a standard in this assay. However, neither monorhizopodin (**1a**) nor 16-*epi*-monorhizopodin (**1b**) exhibited cytotoxicity against MDA-MB-231 breast cancer cells (up to 100 μM concentrations), thus presenting an interesting dichotomy and a puzzle regarding their divergence from rhizopodin (**2**). Although further investigations are needed to explain this phenomenon, we hypothesize that either these compounds are unable to displace G-actin binding proteins, such as profilin,[18] within cells, or that they fail to penetrate the cell membrane to reach their target.

In conclusion, a highly convergent total synthesis of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**) has been developed, rendering these monomeric homologues of the powerful antitumor agent rhizopodin (**2**) available for biological investigations. Preliminary studies showed these compounds to be endowed with actin-binding properties but devoid of any associated cytotoxicity, thus posing interesting questions regarding the role of the dimeric nature of rhizopodin (**2**) in its mode of action. Further studies directed toward the elucidation of the mechanism of action and the differences of rhizopodin (**2**) and its monomeric homologues, (**1a**) and (**1b**), as well as the total synthesis of the former are in progress.

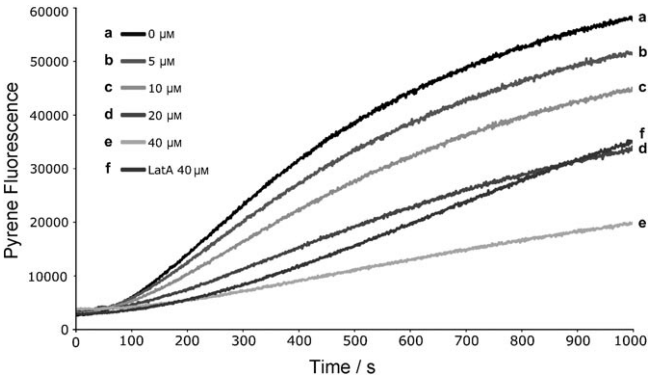


Figure 1. Inhibition of actin polymerization by monorhizopodin (**1a**). The concentration of actin was 5 μM, that of monorhizopodin (**1a**) was as indicated. For the corresponding graphs obtained with 16-*epi*-monorhizopodin (**1b**) and further details of the assay, see the Supporting Information. LatA = latrunculin A.

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