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Stereoselective Synthesis of the Monomeric Unit of Actin Binding Macrolide Rhizopodin

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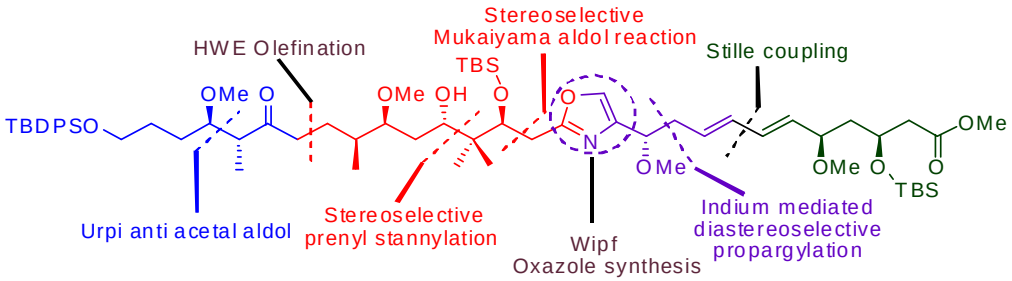


Abstract

An efficient, scalable and stereocontrolled synthesis of the entire carbon framework of an actin binding dimeric macrolide rhizopodin has been accomplished in its protected form. The key features of our synthesis include a titanium catalyzed anti acetal aldol reaction, substrate controlled diastereoslelective prenyl stannylation, Mukaiyama aldol reaction, an indium mediated diastereoselective propargylation and an advanced stage Stille coupling reaction.

Keyword: Stereoselective Synthesis; Macrolide Rhizopodin

Introduction

Myxobacteria were found to be a rich source of novel secondary metabolites, which includes several biologically active cytotoxic compounds such as epothilone, chondramide, tubulysin A, etc.[1] Rhizopodin (**1**) (Figure 1) is another such novel and unique polyketide isolated in 1993 from the culture broth of the M*yxococcus stipitatus*.[2] Initially, the structure of **1** was found to be a 19-membered macrolide, which was later revised as a C_2-symmetric 38-membered dilactone exhibiting 18 stereogenic centers, two conjugated diene systems in combination with two disubstituted oxazoles, and two enamide side chains.[3] Importantly, **1** shows potent cytotoxic activity against various cancer cell lines in low nanomolar concentration and also displays activity against certain fungi.[4] The cytotoxic activity of **1** results from its ability to bind, thereby inhibiting the polymerization of G-actin. The effects of **1** resemble those of lantrunculin but are elicited at a 10-fold lower concentration. In contrast to lantrunculin, the effects of **1** are irreversible on the cytoskeleton of actin and take a little longer to appear. The scarcity of **l** together with its intriguing biological activity and

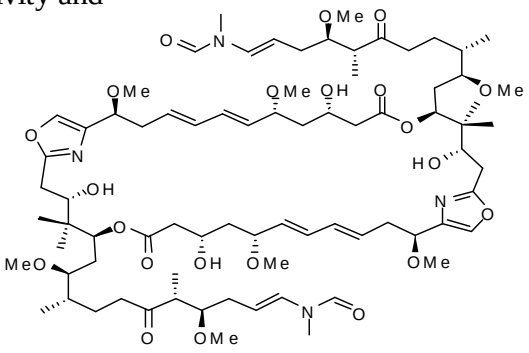
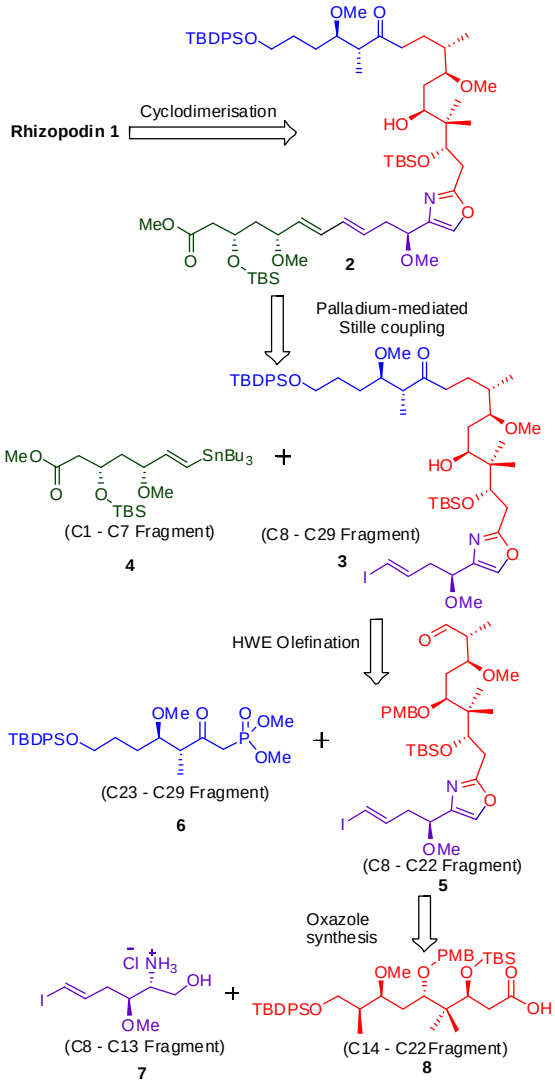


Figure 1: Structure of Rhizopodin **1**

1) Reichenbach, H. *J. Ind. Microbiol. Biotech*. **2001**, *27*, 149.
2) Sasse, F.; Steinmetz, H.; Höfle, G.; Reichenbach, H. *J. Antibiot*. **1993**, *46*, 741.
3) (a) Hagelueken, G.; Albrecht, S. C.; Steinmetz, H.; Jansen, R.; Heinz, D. W.; Kalesse, M.; Schubert, W. D. *Angew. Chem., Int. Ed*. **2009**, *48*, 595. (b) Horstmann, N.; Menche, D. *Chem. Commun*. **2008**, *41*, 5173. (c) Jansen, R.; Steinmetz, H.; Sasse, F.; Schubert, W. D.; Hagelueken, G.; Muller, R. *Tetrahedron Lett*. **2008**, *49*, 5796.
4) Gronewold, T. M.; Sasse, F.; Lunsdorf, H.; Reichenbach, H. *Cell Tissue Res*. **1999**, *295*, 121.

challenging architecture make it an attractive target for total synthesis. As part of our continuous interest in the development of C_2-symmetric peptidomimetics, and total synthesis of biologically active C_2-symmetric diolides,[5] we embarked on the total synthesis of rhizopodin **1**. The first total synthesis of **1** has just appeared.[6] Earlier Nicolaou *et al*. reported the synthesis of mono rhizopodin,[7] while others described fragment synthesis.[8] We also reported the synthesis of C1-C15 and C16-C28 fragments of the molecule.[9] Herein, we describe an efficient, stereoselective and highly convergent synthesis of the entire monomeric unit of rhizopodin **1**.

Scheme 1: Retrosynthesis of Rhizopodin **1**



5) (a) Chakraborty, T. K.; Roy, S.; Koley, D.; Dutta, S. K.; Kunwar, A. C. *J. Org. Chem*. **2006**, *71*, 6240. (b) Chakraborty, T. K.; Ghosh, S.; Rao, M. H. V. R.; Kunwar, A. C. *Arkivoc* **2005**, *xi*, 89. (c) Chakraborty, T. K.; Srinivasu, P.; Kumar, S. K.; Kunwar, A. C. *J. Org. Chem*. **2002**, *67*, 2093. (d) Chakraborty, T. K.; Reddy, V. R. *Tetrahedron Lett*. **2006**, *47*, 2099. (e) Chakraborty, T. K.; Reddy, V. R.; Chattopadhyay, A. K. *Tetrahedron Lett*. **2006**, *47*, 7435. (f) Chakraborty, T. K.; Reddy, V. R.; Gajula, P. K. *Tetrahedron* **2008**, *64*, 5162.

6) Dieckmann, M.; Kretschmer, M.; Li, P.; Rudolph, S.; Menche, D. *Angew. Chem., Int. Ed*. DOI: 10.1002/anie.201201946.

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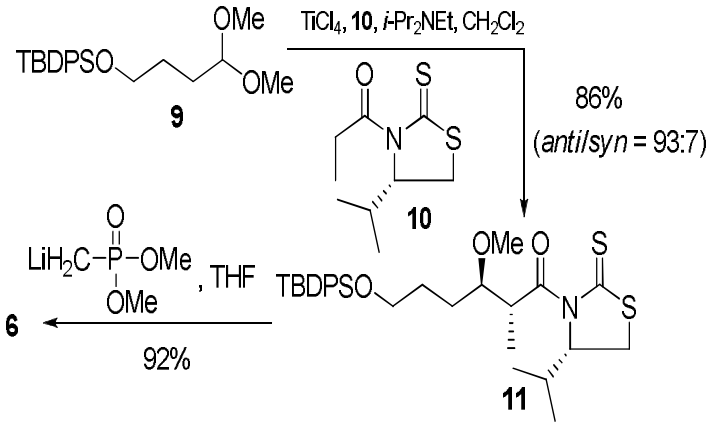
8) (a) Cheng, Z.; Song, L.; Xu, Z.; Ye, T. *Org. Lett*. **2010**, *12*, 2036. (b) Kretschmer, M.; Menche, D. *Org. Lett*. **2012**, *14*, 382.

9) (a) Chakraborty, T. K.; Pulukuri, K. K.; Sreekanth, M. *Tetrahedron Lett*. **2010**, *51*, 6444. (b) Chakraborty, T. K.; Sreekanth, M.; Pulukuri, K. K. *Tetrahedron Lett*. **2011**, *52*, 59.

Our retrosynthetic analysis of **1** is depicted in Scheme 1. With our previous experience in the synthesis of C_2-symmetric diolides, we envisaged that the 38-membered dilactone could be synthesized from cyclodimerisation of suitably protected monomer **2**, which could be obtained from a palladium catalysed C-C bond formation between vinyl iodide **3** and vinyl stannane **4**. We previously reported the synthesis of vinyl stannane **4** via an iterative acetate aldol reaction.[9a] Vinyl iodide **3** would arise from the Horner-Wadsworth–Emmons (HWE) olefination with keto phosphonate **6** and aldehyde **5** containing oxazole and vinyl iodide. Aldehyde **5**, in turn, would be obtained from oxazole assembly of amino alcohol **7** and carboxylic acid **8** via an amide bond formation, oxidation and cyclodehydration strategy.

Scheme 2: Synthesis of ketophosphonate fragment **6**



Our synthetic endeavor began from the synthesis of keto phosphonate **6** (Scheme 2) which started with the direct installation of *anti* β-methoxy-α-methyl stereocenters in a single operation by utilizing the Urpi diastereoselective *anti* acetal aldol reaction.[10] Treatment of dimethyl acetal **9**[11] with the titanium enolate generated from (*S*)-valine derived *N*-propionylthiozolidine thione **10** provided the desired aldol product in 86% yield (*anti*:*syn* = 93:7, dr). Optically pure *anti* isomer **11** was isolated in 79% yield by simple column chromatography. Treatment of **11** with lithiated methyl dimethylphosphonate (generated using *n*-BuLi) directly furnished the β-keto phosphonate **6** in 92% yield.[12]

Next, the synthesis of amino alcohol **7** started from the (*R*)-Garner aldehyde **12** (Scheme 3) which was prepared from D-serine following a reported procedure.[13] An asymmetric indium mediated propargylation of aldehyde **12**, using (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol **13** as a chiral auxiliary developed by Singaram *et. al*,[14] produced the homo propargyl alocohol **14** in 83% yield with a good diastereoselectivity (10:1 dr, HPLC).[15] Selective methylation of the secondary hydroxyl group followed by one pot hydrozirconation – iodination using a Schwartz reagent (generated *in situ* from Cp_2ZrCl_2 and DIBAL-H), following Negishi's protocol,[16] provided exclusively *E*-vinyl iodide **15** in 78% yield in two steps. Treatment of **15** with 4M HCl in dioxane furnished the desired amino alcohol **7**.[17] Due to high sensitivity of **7** for work-up as well as chromatography, the product was confirmed by ^{1}H NMR of crude reaction mixture after removal of reaction volatiles and was used as such for the next reaction.

10) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615. (b) Galvez, E.; Parello, R. ; Romea, P.; Urpí, F. *Synlett* **2008**, 2951.

11) Okada, H.; Mori, T.; Saikawa, Y.; Nakata, M. *Tetrahedron Lett.* **2009**, *50*, 1276.

12) Crimmins, M. T.; Siliphaivanh, P. *Org. Lett.* **2003**, *5*, 4641.

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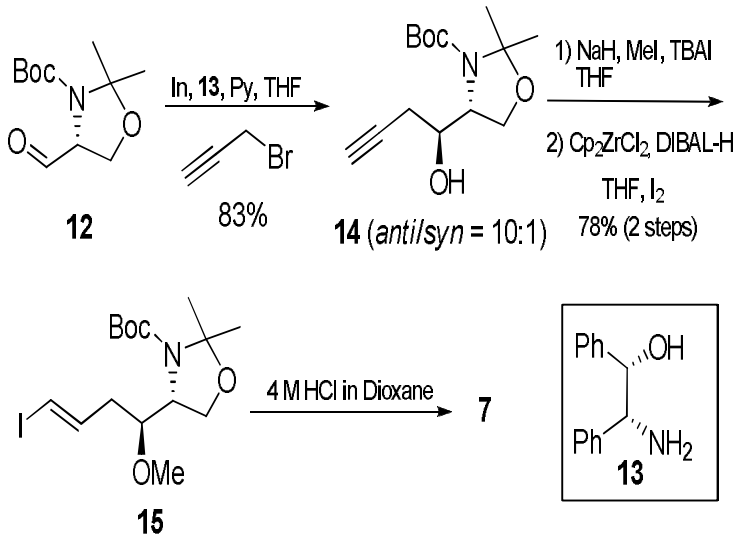
15) (a) Stereochemistry of the product was confirmed by comparing with reported data. See: Koviach, J. L.; Chappell, M. D.; Halcomb, R. L. *J. Org. Chem.* **2001**, *66*, 2318. (b) The diastereomeric ratio was determined by HPLC of the benzoate prepared by treatment with benzoyl chloride, NEt_3 and DMAP.

16) Huang, Z.; Negishi, E.-I. *Org. Lett.* **2006**, *8*, 3675.

17) Han, G.; Tamaki, M.; Hruby, V. J. *J. Peptide Res.* **2001**, *58*, 338.

Scheme 3: Synthesis of amino alcohol fragment **7**



On the other hand, carboxylic acid **8** was synthesized (Scheme 4) in a stereocontrolled manner starting from protected compound **17**, which was prepared in four steps from PMB protected aldehyde **16** following a literature procedure.[9b] Oxidative removal of the PMB group in **17** using DDQ gave the primary alcohol **18** in 94% yield. Dess-Martin periodinane oxidation[18] of the resultant primary alcohol yielded the corresponding aldehyde, which was then subjected to methoxy directed[19] chelation controlled prenyl stannylation using $TiCl_4$ to obtain the alcohol in 86% yield with a 9:1 ratio (determined by the ^1H NMR integration) of separable diastereomers in favor of the desired *anti* isomer **20**. Lower selectivities were observed with other Lewis acids such as $MgBr_2.Et_2O$, $ZnBr_2$ and $BF_3.Et_2O$. This transformation establishes the C17 geminal dimethyl and C18 stereocenter with a good level of 1,3-*anti* stereoinduction. The C18 hydroxyl group was protected as *p*-methoxybenzyl ether to obtain **21** using $PMBOC(=NH)CCl_3$ and $La(OTf)_3$.[20] Dihydroxylation of olefin followed by oxidative cleavage of resulting diol provided the corresponding aldehyde in good yield. To install the β-hydroxy ester, a Lewis acid mediated Mukaiyama aldol reaction[21] between the aldehyde and commercially available silyl enol ether **22** was investigated. After screening various Lewis acids and conditions, the monodentate Lewis acid $BF_3.Et_2O$ was identified to promote the desired aldol addition in toluene to give the required β-hydroxyl ester **23** in 82% yield (3 steps) with 3.4:1 diastereoselectivity in favor of the desired *anti* isomer.[22] Noteworthy is that the use of bidentate Lewis acid $TiCl_4$ provided the aldol product in reversal of diastereoselectivity (1:1.7, dr).[23] Since the resultant diastereomers were not separable at this stage we continued further as such for the silyl protection of hydroxyl group followed by saponification of methyl ester to obtain the acid **8** in 90% yield (*anti*/*syn* = 3.4:1).

Scheme 4: Synthesis of carboxylic acid fragment **8**

18) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

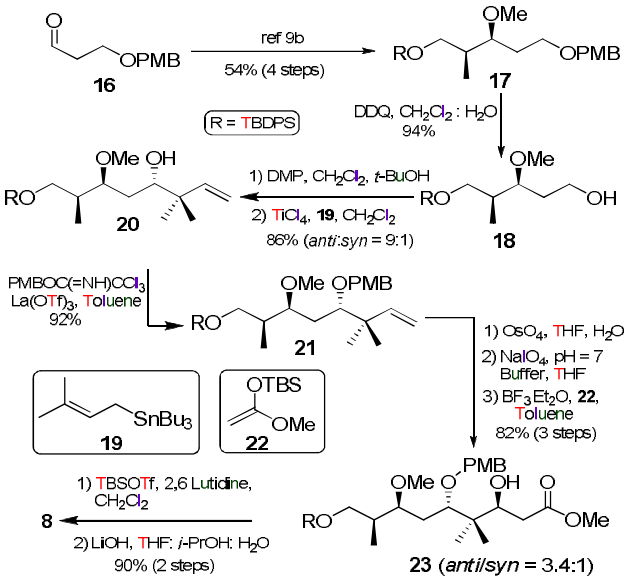
19) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem*. **1986**, *51*, 5478. b) Keck, G. E.; Castellino, S. *J. Am.Chem. Soc*. **1986**, *108*, 3847. c) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett*. **1984**, *25*, 1883. For methoxy directed allylation see: Paterson, I.; Coster, M. J.; Chen, D. Y.-K.; Gibson, K. R.; Wallace, D. J. *Org. Biomol. Chem*. **2005**, *3*, 2410.

20) Rai, A. N.; Basu, A. *Tetrahedron Lett*. **2003**, *44*, 2267.

21) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503. (b) Paterson, I.; Smith, J. D. *J. Org. Chem*. **1992**, *57*, 3261.(c) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (d) Mutou, T.; Suenaga, K.; Fujita, T.; Itoh, T.; Takada, N.; Hayamizu, K.;Kigoshi, H.; Yamada, K. *Synlett* **1997**, 199. (e) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc*. **1996**, *118*, 4322. f) Evans, D. A.; Allison, B. D.; Yang, M.G. *Tetrahedron Lett*. **1999**, *40*, 4457.

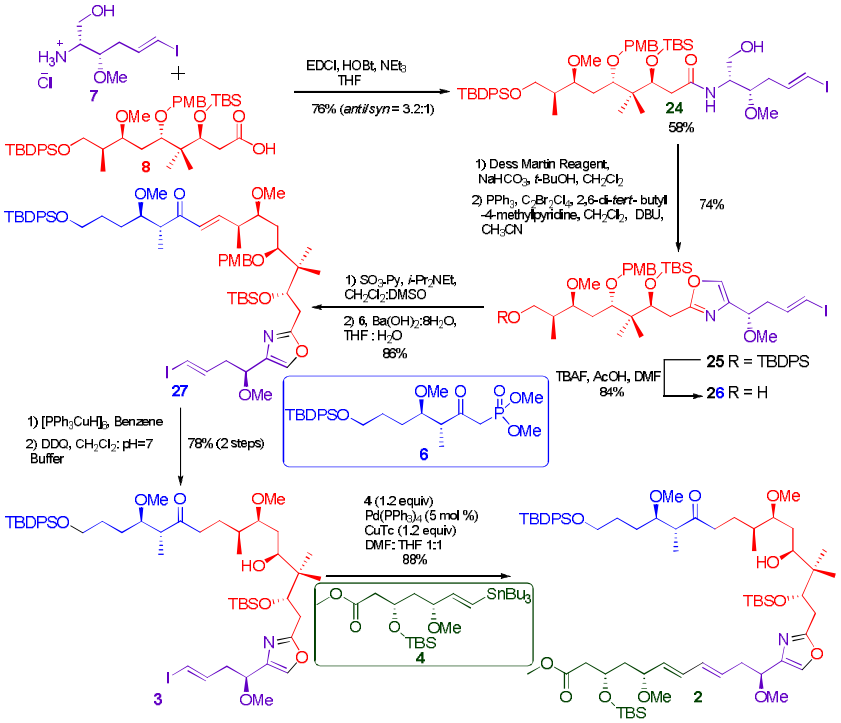
22) (a) The absolute configuration of the major C16 stereogenic center was determined as (16*S*) by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters. See: Supporting Information for details. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.

23) Other lewis acids $TiCl_2(O\text{-}iPr)_2$, $MgBr_2.Et_2O$, $ZnBr_2$ and $LiClO_4$ were also investigated, but turned out to be less effective. In these conditions either no reaction or decomposition of aldehyde was observed.



With both amino alcohol **7** and carboxylic acid **8** in hand, we endeavored to combine them through an oxazole synthesis (Scheme 5). Firstly, an amide coupling between amino alcohol **7** and carboxylic acid **8** using EDCI, HOBt and NEt_3[24] afforded a mixture of hydroxyl amide (*anti*/*syn* = 3.2:1) in 76% yield. At this stage both C16 epimers were separated by column chromatography and optically pure *anti* isomer **24** was isolated in 58% yield. Dess-Martin periodinane mediated oxidation of hydroxyl amide **24** followed by one pot cyclodehydration of resultant aldehyde and subsequent elimination of HBr from bromooxazoline intermediate following Wipf conditions[25] afforded the oxazole **25** in 74% yield. Selective primary silyl deprotection using acetic acid buffered TBAF[26] furnished the primary alcohol **26** in 84% yield. Parikh Doering oxidation[27] of primary alcohol **26** furnished the corresponding aldehyde

Scheme 5: Assembly of fragments **7**, **8**, **6** and **4** to complete the synthesis of **2**



24) Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem*. **1961**, *26*, 2525.
25) Wipf, P.; Miller, C. P. *J. Org. Chem*. **1993**, *58*, 3604. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc*. **1995**, *117*, 558.
26) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306.
27) Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc*. **1967**, *89*, 5505.

which was subjected to HWE olefination with keto phosphonate **6** in the presence of $Ba(OH)_2$[28] to achieve the enone **27** in 86% yield. Selective 1,4-reduction of enone using Stryker's reagent[29] followed by oxidative cleavage of PMB ether gave the alcohol **3** (C8-C29 fragment) in 78 % yield.

With key fragment **3** in hand, the stage was now set to couple with vinyl stannane **4** through C7-C8 bond formation using the Stille reaction.[30] Initial attempts to accomplish the Stille coupling of vinyl iodide **3** and vinyl stannane **4** with standard Stille conditions using 10 mol% of Pd (0, II) catalysts were less effective and gave the desired diene only in 30% yield, along with by product resulted from the homo coupling of vinyl iodide **3**. After examining several conditions by using various combinations of palladium catalysts ($Pd(PPh_3)_4$, $PdCl_2(CH_3CN)_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$), transmetallation ligands ($As(PPh_3)_3$, TFP), transmetallation catalysts (CuCl, CuI, CuTc) and solvents (NMP, DMF, THF), it was found, to our delight, that use of 5 mol% $Pd(PPh_3)_4$ and stoichiometric amount of copper thiophene-2-carboxylate (CuTc) in DMF:THF (1:1) mixture[31] gave the coupled product **2** in 88% yield.

In summary, a concise and scalable synthesis of the protected monomeric unit **2** of rhizopodin, suitable for subsequent steps and a late-stage introduction of the enamide side chains, was achieved in a highly convergent way in 21 steps (longest linear sequence) starting from **16**. Notable features of our synthesis include a diastereoselective *anti* acetal aldol reaction, highly diastereoselective propargylation of Garner aldehyde, substrate controlled *anti* stereoselective prenyl stannylation, a Mukaiyama aldol reaction, an advanced oxazole synthesis and Stille coupling. Further work towards the total synthesis of rhizopodin **1** and its simplified structural analogs is in progress.

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Supporting Information Available: Experimental procedures, spectral data, ^1H and ^{13}C spectral data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

28) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

29) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am.Chem. Soc*. **1988**, *110*, 291. (b) Terminal olefin resulting from the reduction of vinyl iodide appeared as a side product in 5-10% yield.

30) Stille, J. K.; Groh, B.L. *J Am. Chem. Soc*. **1987**, *109*, 813. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748. (c) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun*. **2008**, 2873.

31) Both Pd and CuTc are required for this coupling.