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Formal Synthesis of Actin Binding Macrolide Rhizopodin

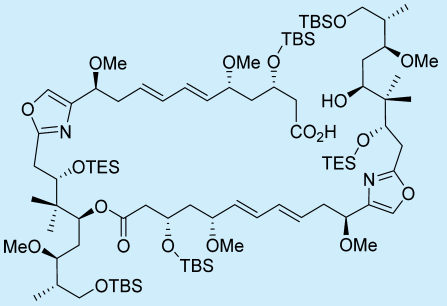
Kiran Kumar Pulukuri[†] and Tushar Kanti Chakraborty*[,†,‡]

[†]CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031, India

[‡]Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

Supporting Information

ABSTRACT: Formal synthesis of an actin binding macrolide rhizopodin was achieved in 19 longest linear steps. The key features of the synthesis include a stereoselective Mukaiyama aldol reaction, dual role of a Nagao auxiliary (first, as a chiral auxiliary of choice for installing hydroxy centers and, later, as an acylating agent to form an amide bond with an amino alcohol), late stage oxazole formation, and Stille coupling reactions.



Actin, one of the major components of cytoskeleton in eukaryotic cells and responsible for many important cellular functions such as cell shape, cell division, motility, and adhesion, is found to be an attractive target for the development of drugs for various diseases.[1] Small natural products that disrupt the dynamics of actin cytoskeleton serve as valuable molecular probes for understanding the complex mechanisms associated with its function.[2] Cytochalasins B, D and latrunculins A, B are some of the earliest actin binding molecules that have been studied extensively.[1] Rhizopodin (**1**, Figure 1) is another such novel actin binding polyketide isolated from the culture broth of the *Myxococcus stipitatus*.[3] Based on extensive NMR studies and the crystal structure of its complex with rabbit G-actin, the structure was found to be 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.[4] Rhizopodin displays potent antiproliferative activity against various cancer cell lines in low nanomolar concentration and also displays activity against certain fungi.[5] Most importantly,

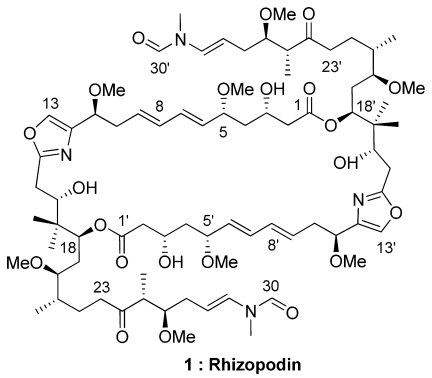
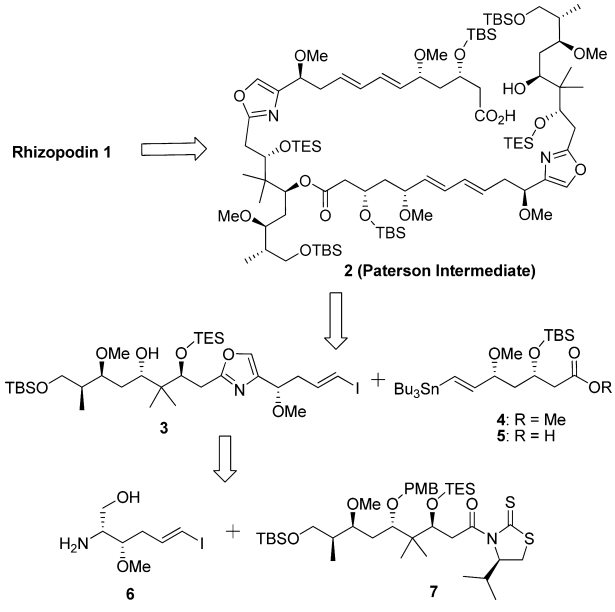


Figure 1. Structure of rhizopodin **1**.

Scheme 1. Retrosynthesis of Rhizopodin 1



rhizopodin displays irreversible effects on actin cytoskeleton by binding with a few critical sites of actin. Its impressive biological activity and complex architecture make it a challenging target for the synthetic community.

To date, two total syntheses of rhizopodin have been reported. Menche's group achieved the first total synthesis and confirmed the absolute configuration of rhizopodin.[6] This was followed by the elegant synthesis by the Paterson group[7] and synthesis of several fragments, including monorhizopodin and

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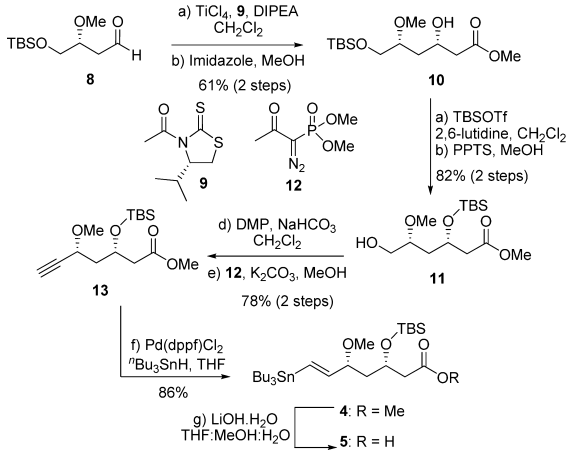
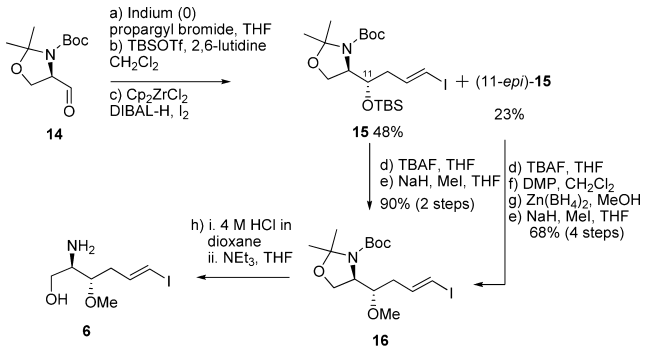
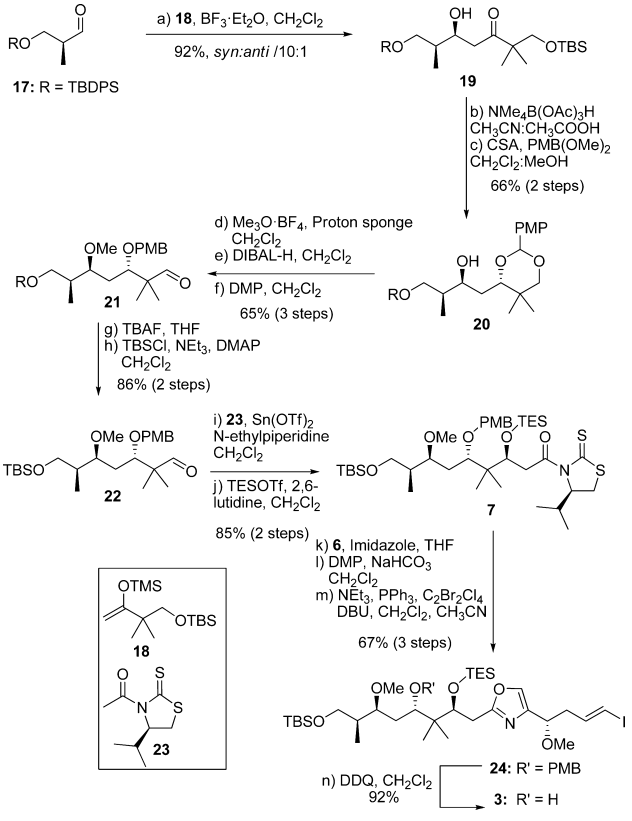
Scheme 2. Preparation of C1−C7 Fragments 4 and 5



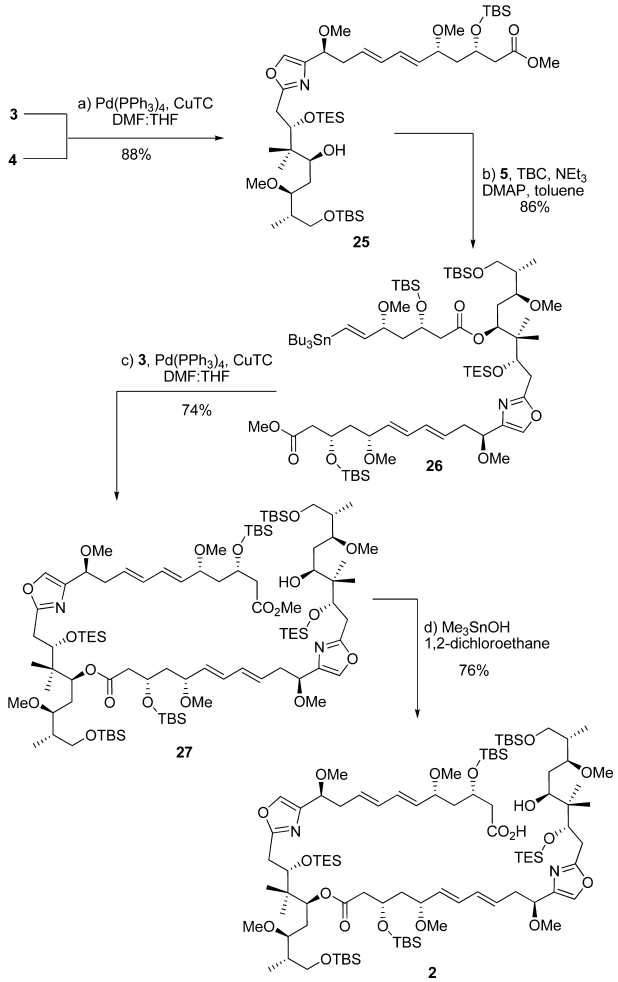
Scheme 3. Preparation of C8−C13 Fragment 6



Scheme 4. Preparation of C8−C22 Fragment 4



Scheme 5. Synthesis of Seco Acid 2



the macrocyclic core of rhizopodin by others.[8] We have also reported the syntheses of C1−C15, C16−C27 fragments and later the entire monomeric unit of rhizopodin in its protected form.[9] In continuation of our efforts toward the synthesis of rhizopodin, we now report a new approach to the synthesis of C1−C7, C8−C14, and C16−C23 fragments and an advanced intermediate **2** in Paterson's total synthesis of rhizopodin.

Our retrosynthetic plan involves a highly convergent route to the seco acid **2**, as shown in Scheme 1. We envisaged that the seco acid **2** could be prepared from vinyl iodide **3** and vinyl stannane **4** and **5** by a sequential cross-coupling, esterification, and cross-coupling reactions. Vinyl iodide **3** could be prepared by an oxazole formation, which involves a direct amide bond formation between amino alcohol **6** and the thiozolidine auxiliary **7**, followed by oxidation and cyclodehydration.

Synthesis of vinylstannane **5** started with an acetate aldol reaction of known aldehyde **8**,[8f] with a titanium enolate derived from chiral auxiliary **9**[10] (Scheme 2). The resulting aldol adduct was immediately converted to methyl ester **10** using imidazole in methanol to get the chromatographically separable mixture of diastereomers in a 5:1 ratio. Diastereomerically pure product **10** was isolated in 61% yield. Protection of the secondary alcohol as its TBS ether, followed by selective primary silyl deprotection using PPTS in methanol, gave the hydroxy compound **11** in 82% yield.

Oxidation of **11** followed by treatment of the resultant aldehyde with Bestmann−Ohira reagent[11] **12** gave the alkyne

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13 in 78% yield. Hydrostannylation of alkyne with $Pd(dppf)Cl_2$ and $^nBu_3SnH$ afforded the vinylstannane **4** in 86% yield with a 95:5 (*E*/gem) ratio. Methyl ester hydrolysis of **4** gave the carboxylic acid **5** in good yield.

Previously, we reported[9c] the synthesis of the amino alcohol fragment using an asymmetric indium mediated homopropargylation of Garner aldehyde **14**,[12] which proved to be less viable on a multigram scale. An alternative route (Scheme 3) to this fragment was undertaken. An indium mediated Barbier type addition of propargyl bromide to aldehyde **14** gave an inseparable mixture of homopropargyl alcohols which were subjected to silyl protection followed by one-pot hydrozirconation and iodination[13] to gain vinyl iodide **15** as a separable mixture of C11 epimers in 71% yield (2:1 dr). Silyl deprotection followed by *O*-methylation of pure C11 hydroxy gave the methyl ether **16** in 90% yield. The C11 epimer was also converted to methyl ether **16**, by a sequence of reactions as shown in Scheme 3, in 68% yield. Treatment of **16** with 4 M HCl in dioxane gave the desired amino alcohol fragment **6**.

Synthesis of key C8−C22 fragment **3** started with the Mukaiyama aldol reaction[14] between TBDPS protected (*S*)-Roche aldehyde **17**[15] and silyl ketene acetal **18**,[16] as shown in Scheme 4. Previously, similar aldol reactions of aldehyde **17** with boron and lithium enolates derived from methyl ketone were reported, but gave the aldol products in lower selectivities.[17] We anticipated that the geminal dimethyl group in ketene acetal **18** would induce better Felkin−Anh selectivity. As expected, treatment of the aldehyde **17** with silyl enol ether **18** in the presence of $BF_3{\cdot}Et_2O$ gave the desired β-hydroxyl ketone **19** in 92% yield with very good diastereoselectivity (dr 10:1).[18] The selection of protecting groups was critical for the stereoselectivity of the aldol reaction.[19] A stereoselective reduction of **19** using $Me_4NB(OAc)_3H$[20] gave the *anti* 1,3-diol in very good yield with excellent diastereoselectivity, which was subjected to one-pot selective deprotection of TBS ether and regioselective protection of the resultant triol as PMP acetal to obtain the compound **20** in 66% yield. PMP acetal **20** was converted to aldehyde **21** in 65% yield in three steps, which involved methylation, regioselective opening of PMP acetal, and oxidation of the resultant alcohol. Selective removal of TBDPS ether at a later stage of synthesis was found to be problematic; hence, it was changed to TBS ether in a two-step sequence to give rise to TBS protected aldehyde **22** in 86% yield. Next, compound **22** was subjected to an acetate aldol reaction with tin enolate, generated from thiazolidinethione auxiliary **23**,[21] which gave the desired aldol product with excellent diastereoselectivity (dr 12:1), which was further transformed into the triethylsilyl ether **7** in 85% yield (two steps). With gram quantities of **6** and **7** in hand, their coupling was carried out by an oxazole formation. First, direct displacement of the thiazolidinethione auxiliary in **7** by the amino alcohol **6** was carried out to get the hydroxyl amide, which was subjected to oxidation, subsequent cyclodehydration, and elimination using modified Wipf conditions[22] to obtain the desired oxazole **24** in 67% yield. Oxidative removal of C18 PMB ether gave the C8−C22 fragment **3** in 92% yield. This key C8−C22 fragment was synthesized in 13 linear steps, with an overall yield of 17%.

With the key fragment **3** in hand, Stille coupling[23] between vinyl iodide **3** and vinyl stannane **4** was easily executed using our previously optimized conditions[9c] to give the diene in 88% yield (Scheme 5). Next, esterification of hydroxy diene with carboxylic acid **5** was carried out following Yamaguchi conditions[24] to gain the vinyl stannane **26** in 86% yield, which was subjected to another Stille coupling with the vinyl iodide **12** to give the bis-diene methyl ester **27** in 74% yield. Unfortunately, basic hydrolysis of methyl ester using various bases, such as LiOH, $Ba(OH)_2$, etc., was quite problematic, as under these conditions deprotection of TES ethers at C16, C16′ was observed prior to the hydrolysis of the methyl ester. After a brief survey of various conditions, treatment of methyl ester with Me_3SnOH[25] in dichloroethane enabled a clean saponification to give the carboxylic acid **2** in 76% yield.[26]

In conclusion, we have completed the formal synthesis of actin binding macrolide rhizopodin in 19 longest linear steps in a highly convergent manner. The notable features of our synthesis include a stereoselective Mukaiyama aldol reaction, dual role of a Nagao auxiliary, first as a chiral auxiliary for installing hydroxy centers on complex substrates and, later, as an acid activating agent to form an amide bond with an amino alcohol, late stage oxazole formation, and Stille coupling reactions. Further studies are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details as well as characterization data and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tushar@orgchem.iisc.ernet.in.

Notes

The authors declare no competing financial interest.

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(18) The stereochemistry of the aldol product was confirmed by comparison with the previous literature data; see ref 17a, b and comparison with the known data after a few steps.

(19) Bulky TBDPS protection was necessary to obtain good Felkin−Anh selectivity and regioselectivity in the opening of PMB acetal. For detailed studies on the directing effects exerted by the stereogenic centers during C18−C20 aldol couplings of rhizopodin, see: Dieckmann, M.; Rudolph, S.; Lang, C.; Ahlbrecht, W.; Dirk Menche, D. *Synthesis* **2013**, *45*, 2305.

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(26) The spectral and optical rotation data of synthetic compound **2** were matching with the reported data (ref 7; also see Supporting Information).

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