

# Synthesis of the C9–C23 (C9'–C23') Fragment of the Dimeric Natural Product Rhizopodin

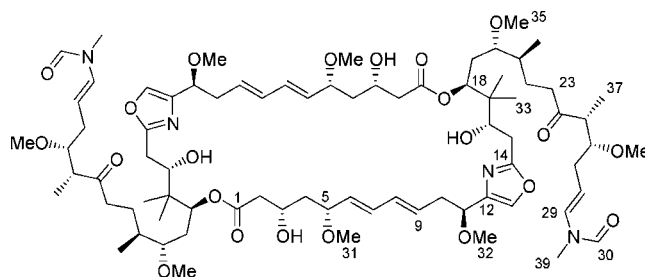
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## ABSTRACT



A stereoselective assembly of the C9–C23 (C9'–C23') fragment of rhizopodin, a 38-membered bis-lactone natural product, has been developed. A highly efficient approach to this fragment assembles >50% of the carbon skeleton and the stereochemical elements present in the natural product.

Rhizopodin is a structurally unique polyketide that was isolated from the myxobacterium *Myxococcus stipitatus* in 1993.<sup>1</sup> Being originally considered as a monomeric lactone, its structure and absolute stereochemistry were recently revised as shown in Figure 1.<sup>2–4</sup> The planar structure of rhizopodin is distinguished by a C<sub>2</sub>-symmetric, 38-membered dilactone exhibiting 18 stereogenic centers, two conjugated diene systems in combination with two disubstituted oxazoles, and two enamide side chains.<sup>2–4</sup> Rhizopodin displays impressive biological properties including potent cytostatic activity against a range of tumor cell lines in the low

nanomolar range.<sup>1,5</sup> It bears two enamide side chains, each of which binds a single G-actin molecule, resulting in a ternary rhizopodin/G-actin complex.<sup>2</sup> The ability of rhizopodin to interfere with actin cytoskeleton dynamics has allowed it to play important roles as a probe molecule for chemical biology. The low supply of rhizopodin, together with its interesting biological activity and intriguing structure, makes it an attractive target for total synthesis. As part of our research program directed toward the total synthesis,<sup>6</sup> stereochemical and structural studies,<sup>7</sup> and biological evaluation of natural products,<sup>8</sup> we have embarked on the synthesis

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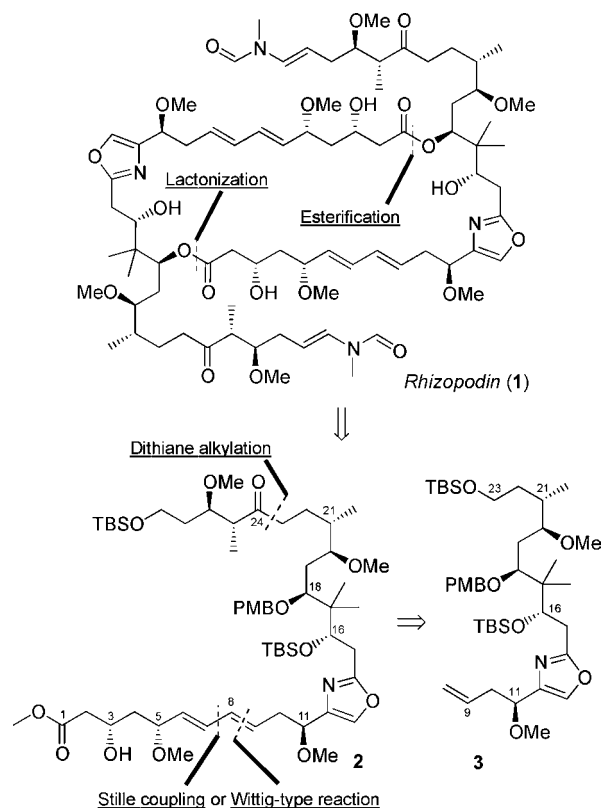
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of rhizopodin. Herein we report a highly stereocontrolled synthesis of fragment **3**, corresponding to the C9–C23 (C9'–C23') fragment of the natural product.



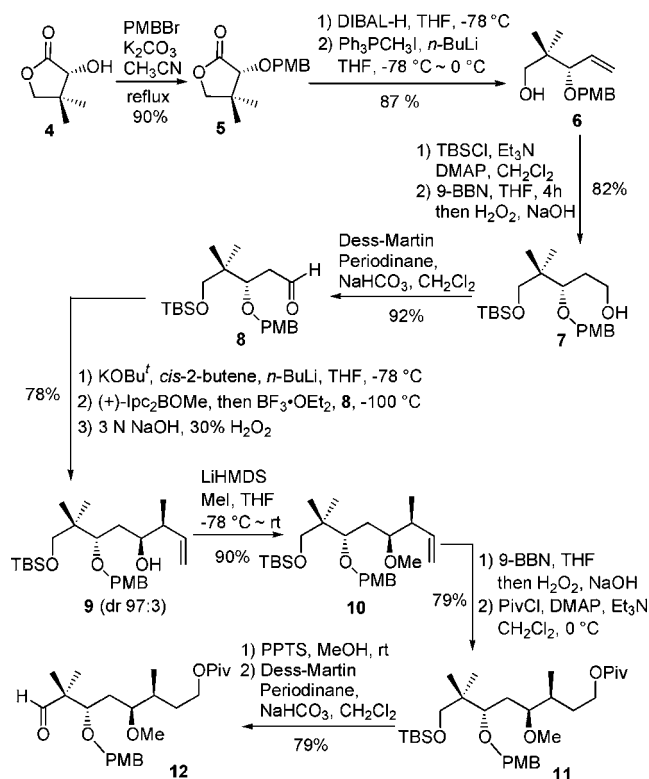
**Figure 1.** Synthetic strategy for the synthesis of rhizopodin.

Our synthetic approach, which is shown in Figure 1, would exploit the dimeric nature of **1**. The acid-labile *N*-methyl-*N*-vinylformamide moiety at the terminus was designed to be introduced at the final stage of the synthesis and the macrocyclic ring was envisioned to be constructed through a sequential esterification/lactonization from the monomeric subunit **2**. The required monomer ultimately would be derived from the C9–C23 (C9'–C23') fragment **3** via a sequence of reactions involving dithiane alkylation and Stille reaction<sup>9</sup> (or a Wittig-type reaction<sup>10</sup>).

A stereocontrolled synthesis of fragment **3** commenced with the protection of *D*-Pantolactone as its *p*-methoxybenzyl ether **5** (Scheme 1). DIBAL-H reduction of **5** in THF at  $-78^{\circ}\text{C}$  afforded the corresponding lactol that was homologated

under standard Wittig conditions with methylenetriphenylphosphorane to provide terminal alkene **6** in 87% yield. Protection of the primary alcohol in **6** by using *tert*-butyldimethylsilyl chloride, followed by alkene hydroboration/oxidation<sup>11</sup> with 9-borabicyclo[3.3.1]nonane (9-BBN) and alkaline hydrogen peroxide furnished the corresponding alcohol **7** in 82% yield (over the two steps).

**Scheme 1.** Synthesis of the C16–C23 Fragment



Treatment of alcohol **7** with the Dess–Martin reagent<sup>12</sup> provided the aldehyde **8** in 92% yield, which was subsequently reacted with Brown's (*Z*)-crotyldiisopinocampheylborane<sup>13</sup> prepared from (+)-diisopinocampheyl(methoxy)borane, and yielded the *syn* homoallylic alcohol **9** in 78% yield, with distereomeric ratio higher than 97:3. *O*-Methylation of homoallylic alcohol **9** with iodomethane in the presence of LiHMDS afforded **10** in 90% yield. Hydroboration/oxidation<sup>11</sup> of the terminal alkene with 9-BBN and  $\text{H}_2\text{O}_2$  provided the corresponding alcohol, which was then protected as its pivaloate **11** in 79% yield over the two steps. Selective cleavage of the *tert*-butyldimethylsilyl (TBS) ether from **11** with pyridinium *p*-toluenesulfonate (PPTS) in methanol, followed by oxidation of the resulting primary hydroxyl with the Dess–Martin periodinane gave aldehyde **12**.<sup>12</sup> With aldehyde **12** in hand, efforts were focused on the

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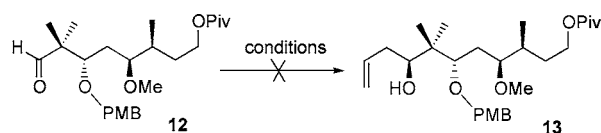
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**Scheme 2.** Allylation of Aldehyde **12**



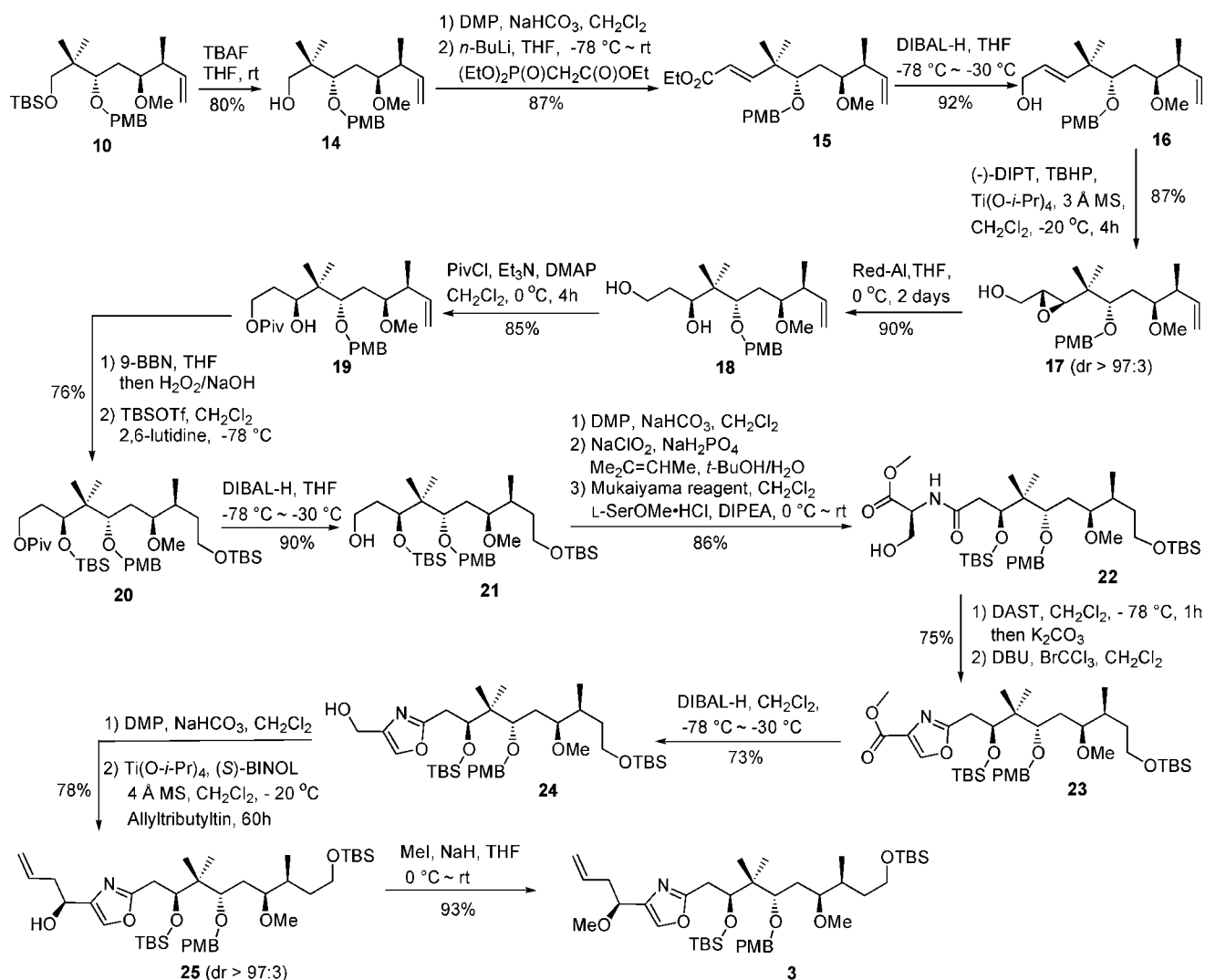
- (1) allyltri(*n*-butyl)tin, (*S*)-BINOL, Ti(*O*-*i*-Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 2 days
- (2) allyltri(*n*-butyl)tin, BF<sub>3</sub>•OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C ~ -45 °C, 4 h
- (3) allyltri(*n*-butyl)tin, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 4 h
- (4) allyltrimethylsilane, TiF<sub>4</sub>, (*S*)-BINOL, CH<sub>2</sub>Cl<sub>2</sub>:CH<sub>3</sub>CN (97:3), -20 °C, 2 days
- (5) allyltrimethylsilane, BF<sub>3</sub>•OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -20 °C, 4 h
- (6) allyltrimethylsilane, SnCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 6 h

introduction of the homoallylic alcohol functionality that would serve as a precursor for the construction of the oxazole unit. Unfortunately, all attempts to effect allylation of aldehyde **12** under the influence of various Lewis acids did not succeed (Scheme 2).<sup>14,15</sup> In most cases, the reactions

led only to decomposition of the starting material. We believe the problem here is steric in origin.

Since the allylation-based route was operationally jeopardized by the steric hindrance of the aldehyde, we turned to the use of an epoxide-opening-based approach<sup>16</sup> so as to generate the required precursor for the synthesis of the oxazole fragment (Scheme 3). Thus, treatment of TBS ether **10** with TBAF afforded primary alcohol **14** in 80% yield. Alcohol **14** was oxidized with Dess–Martin periodinane<sup>12</sup> to provide the corresponding aldehyde, which was subjected to a Horner–Wadsworth–Emmons olefination<sup>17</sup> with ethyl diethylphosphonoacetate to afford (*E*)- $\alpha,\beta$ -unsaturated ethyl ester **15** in 87% yield over the two steps. DIBAL-H reduction of ester **15** afforded allylic alcohol **16**, which was subjected to a Sharpless asymmetric epoxidation<sup>18</sup> with use of (–)-diisopropyl tartrate to obtain the epoxy alcohol **17** in 87% yield with 94% diastereomeric excess. As expected, hydroxyl-directed reductive opening of epoxide **17** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) at 0 °C in THF produced alcohol **18** in 90% yield.<sup>19</sup> Selective protection of the primary hydroxyl

**Scheme 3.** Assembly of the C9–C23 Fragment **3**



group in **18** with pivaloyl chloride in the presence of DMAP furnished the corresponding pivaloate **19** in 85% yield. The terminal alkene in **19** was converted into the corresponding primary alcohol via a hydroboration/oxidation process;<sup>11</sup> this was then protected as its TBS ether **20** in 76% yield over the two steps. Selective removal of the pivaloate functionality in **20** by DIBAL-H reduction afforded the free alcohol **21** in 90% yield. Sequential Dess–Martin<sup>12</sup> and Pinnick<sup>20</sup> oxidations of primary alcohol **21** afforded the corresponding carboxylic acid, which was then activated by Mukaiyama reagent<sup>21</sup> and coupled with L-serine methyl ester to give dipeptide **22** in 86% yield over the three steps. Activation of hydroxy amide **22** with diethylaminosulfur trifluoride (DAST) in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C afforded the oxazoline,<sup>22</sup> which was then treated with bromo-

trichloromethane (BTCM) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)<sup>23</sup> at 0 °C to produce oxazole **23** in 75% yield. DIBAL-H reduction of the ester group in **23** furnished the corresponding alcohol **24** in 73% yield. Dess–Martin oxidation<sup>12</sup> of alcohol **24** afforded an aldehyde, which was subjected to Keck allylation<sup>14</sup> to produce the homoallylic alcohol **25** with >94% diastereoselectivity and 65% yield over the two steps (78% yield based on recovered starting material). Finally, *O*-methylation of homoallylic alcohol **25** with iodomethane in the presence of sodium hydride afforded **3** in 93% yield.

In summary, we have accomplished an efficient and highly stereoselective synthesis of **3** corresponding to the C9–C23 fragment of rhizopodin (28 steps, 4.1% overall yield). Key transformations in the sequence include installation of the C(20) and C(21) stereogenic centers via asymmetric crotylboration and hydroxyl-directed reductive opening of an epoxide, construction of the oxazole via Williams' oxazoline dehydrogenation protocol, and introduction of the C(11) stereogenic center via an asymmetric Keck allylation. Progress toward the development of an efficient total synthesis of rhizopodin will be reported in due course.

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**Supporting Information Available:** Full details for experimental procedures for compounds **3**, **5**, **5a**, **6**, **6a**, **7–10**, **10a**, **11**, **11a**, **12**, **14–19**, **19a**, **20–22**, **22a**, and **23–25**, and <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **3**, **5**, **5a**, **6**, **6a**, **7**, **9–10**, **10a**, **11**, **11a**, **12**, **14–19**, **19a**, **20–22**, **22a**, and **23–25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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