Cross-Metathesis Approach for Stereocontrolled Synthesis of the C1–C15 Fragment of Rhizopodin

Honggang Gui,[a] Junyang Liu,[a,b] Liankai Song,[a] Chunngai Hui,[b] Junmin Feng,[a] Zhengshuang Xu,*[a] Tao Ye*[b]

[a] Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, University Town of Shenzhen, Xili, Nanshan District, Shenzhen, 518055, P. R. of China

[b] Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, P. R. of China
Fax +852(2)2641912; E-mail: tao.ye@polyu.edu.hk; E-mail: xuzs@pkusz.edu.cn

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Abstract: The C1–C15 fragment of rhizopodin was synthesized through either Suzuki coupling reaction of vinyl iodide and vinyl boronate or cross-metathesis of a terminal olefin and a diene adduct in the presence of Hoveyda–Grubbs II catalyst.

Key words: cross-metathesis, cross-coupling, stereocontrolled synthesis, conjugated diene, rhizopodin

Rhizopodin was isolated by Höfle and Reichenbach from the myxobacterium *Myxococcus stipitatus* and was assigned as a monomeric lactone in 1993.[1] Its structure and absolute stereochemistry were recently revised as shown in Scheme 1.[2,3] Rhizopodin exhibits significant biological properties including potent cytostatic activity in the low nanomolar range against a range of tumor cell lines.[1–3] The distinctive structural features and biological activities, together with our interest in macrocyclic marine natural products[4] prompted us to undertake studies on the synthesis of rhizopodin. Recently, various synthetic approaches toward the synthesis of rhizopodin have been reported.[5] The syntheses of monorhizopodin and 16-*epi*-monorhizopodin were achieved by Nicolaou and coworkers in 2011[5e] and, since then, two total syntheses of rhizopodin have been reported.[5g,j]

So far, total syntheses of the macrocycle of rhizopodin have employed either intramolecular Suzuki coupling reaction or macrolactonization.[5g–j] An alternative approach to the macrocyclizations was sought and we opted to close the macrocyclic core by ene-diene cross-metathesis[6] as shown in our retrosynthetic plan (Scheme 1). To test the feasibility of the key ene-diene cross-metathesis step of our designed strategy toward rhizopodin, a model study based on the construction of the C1–C15 fragment (**1**) of rhizopodin was undertaken. Herein we detail two synthetic approaches to fragment **1**.

Retrosynthetic analysis of **1** led us to disconnect between positions C8 and C9, which imposed the construction of the conjugated diene through cross-metathesis of fragments **2** and **3**. Alternatively, a Suzuki cross-coupling of vinyl boronate **4** with vinyl iodide **5** was envisioned to deliver diene **1** (Scheme 1). Oxazole-containing fragments **2** and **4** were planned to originate from the common precursor **10**, which, in turn, would be prepared from the known methyl-2-(chloromethyl)oxazole-4-carboxylate (**7**; Scheme 2).

The synthesis of fragments **2** and **4** is outlined in Scheme 2. Oxazole **7** was obtained from commercially available 2,2-dichloronitrile (**6**) by using a known sequence.[7] Reaction of **7** with sodium acetate in the presence of acetic acid and acetic anhydride and treatment of the resultant acetate derivative with potassium carbonate and methanol afforded the corresponding alcohol **8** in 61% yield over two steps. After protection of the primary alcohol as its TBS ether, the methyl ester was reduced with DIBAL-H in THF to give alcohol **9** in 84% yield. This route is operationally convenient and proceeds well on large scale (>35 g of **9** was obtained). It should be mentioned that alcohol **9** could be obtained by a reported procedure;[8] however, in our hands, we were unable to reproduce the reaction on large scales. Swern oxidation[9] of the primary alcohol of **9**, followed by Keck allylation[10] of the resulting aldehyde, provided homoallylic alcohol **10** in 72% yield with >97% enantiomeric excess, as measured on its Mosher ester.[11] The absolute stereochemistry at the newly created stereogenic center was also assigned at this point by synthesis and comparison of the ^{1}H NMR spectra of its Mosher derivatives.[12] Thus, homoallylic alcohol **10** was reacted with both (*S*)- and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid to generate diastereomeric (*S*)- or (*R*)-Mosher esters **12** and **13**, respectively (Table 1). Subtraction of the chemical shifts of the protons of (*R*)-Mosher ester **13** from those of (*S*)-Mosher ester **12** in the vicinity of the ester-bearing stereocenter then provides differences ($\Delta\delta$), the signs of which are used to assign the configuration of the stereocenter. The signs of the $\Delta\delta$ are shown in Table 1, and the absolute stereochemistry at C11 was elucidated to be the (*S*)-configuration.

O-Methylation of the homoallylic alcohol **10** by using iodomethane and sodium hydride in THF provided **2** in 84% yield. Olefin cross-metathesis between **2** and vinyl pinacol boronate **11** under the influence of the Hoveyda–

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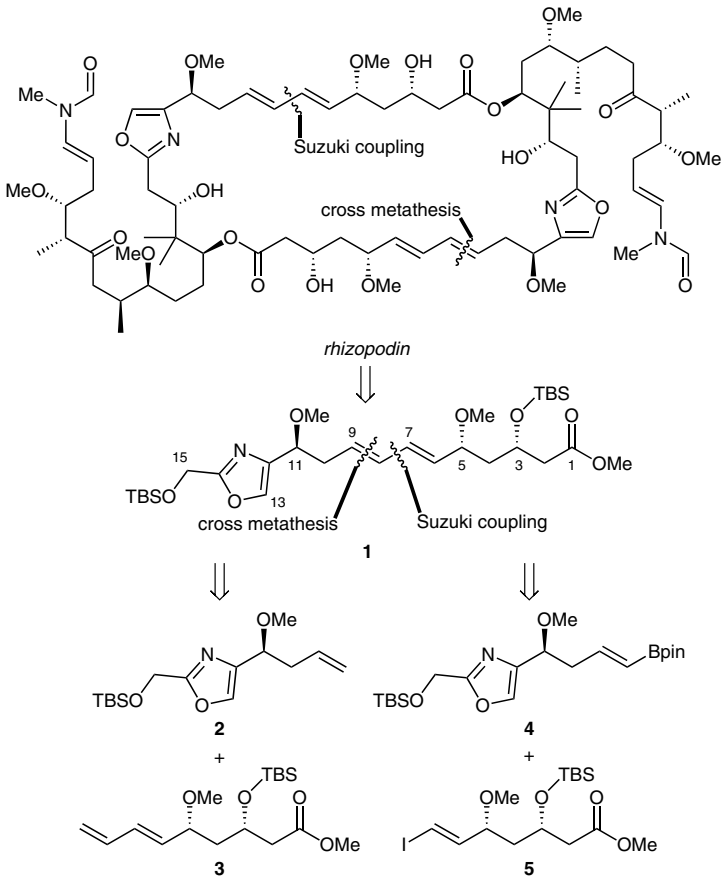
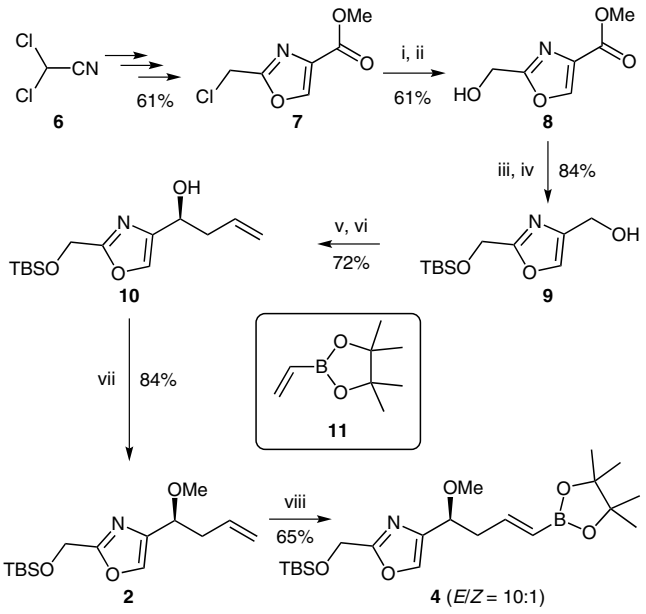


Scheme 1 Retrosynthetic analysis

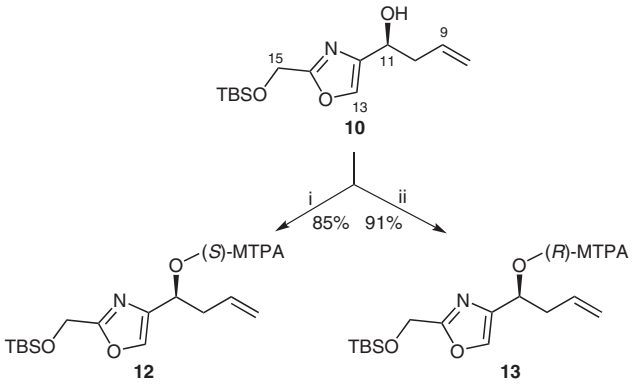


Scheme 2 Preparation of intermediates **2** and **4**. *Reagents and conditions*: (i) NaOAc, HOAc-Ac_2O; (ii) K_2CO_3, MeOH; (iii) TBSCl, imidazole, CH_2Cl_2; (iv) DIBAL-H, THF; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (vi) (*S*)-BINOL, Ti(O*i*-Pr)$_4$, allyltributylstannane, CH_2Cl_2, –20 °C, 72 h; (vii) NaH, MeI, THF; (viii) **11**, Hoveyda–Grubbs II catalyst, toluene, 80 °C.

Grubbs II catalyst furnished vinyl boronate **4** in 65% yield (*E*/*Z* = 10:1; Scheme 2).[13]

The preparation of coupling partners **3** and **5** commenced from methyl ester **14**, which was prepared according to conditions described by Paterson[14] (Scheme 3). Methyl ester **14** was reduced to aldehyde **15** in 94% yield by using DIBAL-H in dichloromethane. Subsequent treatment of **15** with *β*-(+)-allyldiisopinocampheylborane according to Brown et al.[15] provided a 10:1 mixture of *syn*- and *anti*-monomethylated diols, favoring the desired isomer, which was protected as its TBS ether **16** (55% yield over two steps). Oxidative cleavage of the terminal olefin by using the Sharpless protocol,[16] and esterification of the resultant acid with trimethylsilyldiazomethane[17] provided methyl ester **17** in 63% yield over two steps. Selective removal of the primary TBS group in the presence of the secondary TBS group under mild acidic conditions provided alcohol **18** in 88% yield. Oxidation of the primary alcohol in **18** by using the Dess–Martin periodinane reagent[18] buffered with sodium bicarbonate afforded the corresponding aldehyde, which served as the precursor leading to both **3** and **5**. Thus, a Horner–Wadsworth–Emmons olefination between the diethyl allylphosphonate and the aldehyde derived from **18** successfully led to the required diene **3** in 53% yield and good *E*/*Z* selectivity (15:1). In parallel, treatment of the aldehyde with iodo-

Table 1 Stereochemical Assignment of **10**[a]



Hydrogen	δ_S (*S*-MTPA ester)	δ_R (*R*-MTPA ester)	δ_S–δ_R
TBS(*t*-Bu)	0.910	0.901	+0.009
TBS(Me)	0.104	0.088	+0.016
15	4.742	4.701	+0.042
13	7.574	7.409	+0.165
11	6.050	6.077	–
10	2.745	2.790	–0.045
9	5.634	5.759	–0.125
8	5.082 5.030	5.171 5.133	–0.089 –0.103

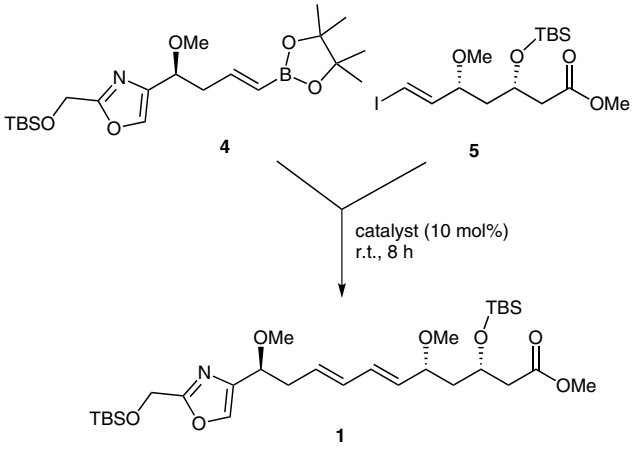
[a] Reaction conditions: (i) oxallyl chloride, DMF, CH_2Cl_2, (*S*)-MTPA; then Et_3N, DMAP, CH_2Cl_2, **10**, 85%; (ii) oxallyl chloride, DMF, CH_2Cl_2, (*R*)-MTPA; then Et_3N, DMAP, CH_2Cl_2, **10**, 91%.

form and chromous chloride in THF[19] gave vinyl iodide **5** in 63% overall yield with greater than 10:1 *E*/*Z* selectivity.

With the four requisite fragments **2**–**5** in hand, the stage was set to test the palladium-catalyzed cross-coupling reaction (Table 2) and ene-diene cross-metathesis (Table 3). First, we explored the Suzuki coupling reaction[20] of vinyl boronate **4** and vinyl iodide **5** under various conditions. Initially the widely used protocol was employed using $[Pd(Ph_3P)_4]$-Ph_3As and Cs_2CO_3 in THF. Unfortunately, the desired product **1** was obtained in only 35% isolated yield (Table 2, entry 1). When the catalyst was switched to $[Pd(dppf)_2Cl_2]$, diene **1** was isolated in a much improved yield (52%; entry 2). Further optimization of the catalytic systems led to the identification of a remarkably simple protocol, in which vinyl boronate **4** and vinyl iodide **5** were exposed to $[Pd(Ph_3P)_4]$ and TlOEt in THF–H_2O (v/v 4:1) to furnish **1** in 73% isolated yield (entry 3).[21]

We then examined the key ene-diene cross-metathesis reaction under several conditions by varying the solvent, catalyst, and temperature. As shown in Table 3, initial cross-metathesis of alkene **2** and diene **3** at 80 °C in toluene with Grubbs I catalyst provided no conversion (entry 1). Furthermore, attempts to mediate the cross-metathesis

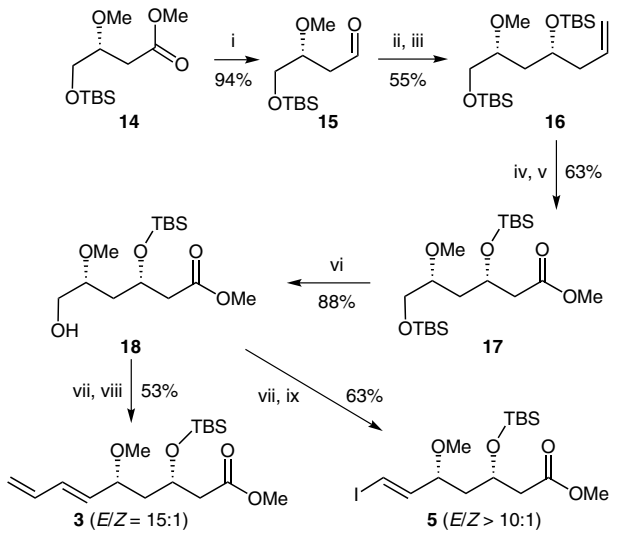
Table 2 Suzuki Coupling for the Synthesis of Diene **1**[a]



Entry	Ratio **4**/**5**	Catalyst/ligand	Solvent	Base	Yield (%)
1	1.3:1.0	$[Pd(Ph_3P)_4]/Ph_3As$	THF	Cs_2CO_3	35
2	1.3:1.0	$[Pd(dppf)_2Cl_2]/Ph_3As$	THF	Cs_2CO_3	52
3	1.3:1.0	$[Pd(Ph_3P)_4]$	THF–H_2O	TlOEt	73

[a] Reaction conditions: See table and text for details.

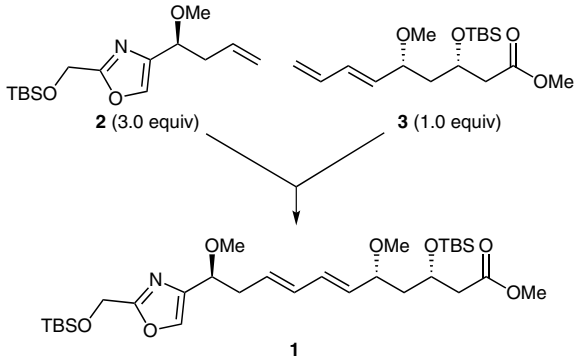
with 10 mol% of either Grubbs II catalyst or Hoveyda–Grubbs II catalyst in dichloromethane at reflux also failed to provide any detectable quantities of diene **1**. Fortunately, performing this reaction at 60 °C in toluene with Grubbs II catalyst or Hoveyda–Grubbs II catalyst, afforded **1** in 24% and 40% yield, respectively (entries 4 and 5).



Scheme 3 Preparation of intermediates **3** and **5**. *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, –78 °C; (ii) (+)-Ipc_2BOMe, allylmagnesium bromide, Et_2O, 0 to –78 °C; then **15**; (iii) TBSCl, Et_3N, DMAP, CH_2Cl_2; (iv) $RuCl_3$, $NaIO_4$, CCl_4–MeCN–H_2O; (v) $TMSCHN_2$, MeOH; (vi) (–)-CSA, CH_2Cl_2–MeOH; (vii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; (viii) diethyl allylphosphonate, *n*BuLi, HMPA, THF, –78 °C, then aldehyde; (ix) $CrCl_2$, CHI_3, THF.

Furthermore, by increasing the reaction temperature to 80 °C in toluene in the presence of Hoveyda–Grubbs II catalyst, the yield improved considerably, and diene **1** could be isolated in 51% yield[21] as the (*E*,*E*)-alkene, the conformation of which was determined by ^{1}H NMR spectroscopic analysis. Considering the thermal stability of both starting material and catalyst, attempts to further improve the yield by the use of elevated temperatures were not conducted.

Table 3 Cross-Metathesis of Alkene **2** and Diene **3**[a]



Entry	Catalyst (10 mol%)	Solvent	Temp (°C)	Yield (%)[b]
1	Grubbs I	toluene	80	–
2	Grubbs II	CH_2Cl_2	40	–
3	Hoveyda–Grubbs II	CH_2Cl_2	40	–
4	Grubbs II	toluene	60	24
5	Hoveyda–Grubbs II	toluene	60	40
6	Hoveyda–Grubbs II	toluene	80	51

[a] Reaction conditions: See table and text for details.
[b] Yield based on recovered **3**.

In summary, the C1–C15 fragment of rhizopodin was synthesized by either Suzuki coupling reaction of vinyl iodide and vinyl boronate or by cross-metathesis of a terminal olefin and a diene adduct in the presence of Hoveyda–Grubbs II catalyst. This study demonstrates the effectiveness of an ene-diene cross-metathesis approach to diene **1** and served as a model study for the total synthesis of rhizopodin based on ene-diene cross-metathesis strategy. Further efforts directed toward the asymmetric total synthesis of rhizopodin and its analogues are underway and will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) Procedures for the synthesis of diene **1**:
Suzuki Cross-Coupling; General Procedure: Vinyl iodide **5** (1.0 equiv), pinacol boronate **4** (1.2 equiv), base (2.0 equiv) and ligand (0.5 equiv) were dissolved in degassed THF (2.0 mL) and palladium catalyst (0.1 equiv) dissolved in degassed THF (1.0 mL) was added by using a cannula. The reaction mixture was stirred at ambient temperature and monitored by TLC. Upon completion of the reaction, it was quenched by addition of sat. aq NH_4Cl (10 mL) and filtered through a pad of Celite, eluted with CH_2Cl_2 (10 mL). The filtrate was concentrated to remove volatiles and the aqueous residue was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (EtOAc–hexane, 1:4; R_f = 0.4) to give diene **1** as a colorless oil.
Cross-Metathesis; General Procedure: To a solution of alkene **2** (3.0 equiv) and 1,3-diene **3** (1.0 equiv) in degassed solvent (1.5 mL), ruthenium catalyst (0.1 equiv; pre-dissolved in 1.0 mL degassed solvent) was added by using a cannula, and the reaction mixture was stirred at different temperatures and monitored by TLC. When the reaction reached completion, volatiles were removed under vacuum, and compound **1** was obtained after purification by flash column chromatography (EtOAc–hexane, 1:4; R_f = 0.4) as a colorless oil. The analytical data of the product were identical those of the main product of the Suzuki coupling reaction.
Analytical Data of 1: $[\alpha]_D^{25}$ +8.4 (*c* 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 6.24–5.97 (m, 2 H), 5.77–5.56 (m, 1 H), 5.50–5.31 (m, 1 H), 4.75 (s, 2 H), 4.33–4.14 (m, 2 H), 3.70–3.67 (m, 1 H), 3.66 (s, 3 H), 3.32 (s, 3 H), 3.21 (s, 3 H), 2.72–2.59 (m, 2 H), 2.58–2.45 (m, 2 H), 1.85 (ddd, *J* = 13.3, 7.9, 5.2 Hz, 1 H), 1.66–1.57 (m, 1 H), 0.91 (s, 9 H), 0.87 (d, *J* = 8.7 Hz, 9 H), 0.10 (s, 6 H), 0.05 (s, 3 H), 0.03 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.19, 162.85, 140.52, 136.03, 132.70, 131.98, 131.81, 129.99, 78.71, 76.08, 66.78, 58.42, 56.86, 55.96, 51.40, 43.40, 42.42, 37.79, 25.76, 18.37, 17.93, –4.49, –4.80, –5.39. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{55}NO_7Si_2Na^+$: 620.3410; found: 620.3406.

