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*a,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
Received: 18.08.2013; Accepted after revision: 22.09.2013

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. Its structure and absolute stereochernistry 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 products4 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 monorrhizopodin and 16-epi-monorrhizopodin were achieved by Nicolaou and co-workers in 20115e and, since then, two total syntheses of rhizopodin have been reported.5f,6

So far, total syntheses of the macrocycle of rhizopodin have employed either intramolecular Suzuki coupling reaction or macrolactonization.5f,5j 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).2,3 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 stereochernistry 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 products4 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 monorrhizopodin and 16-epi-monorrhizopodin were achieved by Nicolaou and co-workers in 20115e and, since then, two total syntheses of rhizopodin have been reported.5f,6

So far, total syntheses of the macrocycle of rhizopodin have employed either intramolecular Suzuki coupling reaction or macrolactonization.5f,5j An alternative approach to the macrocyclizations was sought and we opted to close the macrocyclic core by ene-diene cross-metathesis 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.3 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; however, in our hands, we were unable to reproduce the reaction on large scales. Swern oxidation10 of the primary alcohol of 9, followed by Keck allylation11 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 1H 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 (Δδ), the signs of which are used to assign the configuration of the stereocenter. The signs of the Δδ 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-
Grubbs II catalyst furnished vinyl boronate 4 in 65% yield (E/Z = 10:1; Scheme 2).\(^\text{13}\)

The preparation of coupling partners 3 and 5 commenced from methyl ester 14, which was prepared according to conditions described by Paterson\(^\text{14}\) (Scheme 3). Methyl ester 14 was reduced to aldehyde 15 in 94% yield by using DIBAL-H in dichloromethane. Subsequent treatment of 15 with \(\beta\)-(+)‐allyldiisopinocampheylborane according to Brown et al.\(^\text{15}\) provided a 10:1 mixture of \(\text{syn}\)- and \(\text{anti}\)-monomethylated diols, favoring the desired isomer, which was protected as its TBS ether \(\text{16}\) (55% yield over two steps). Oxidative cleavage of the terminal olefin by using the Sharpless protocol,\(^\text{16}\) and esterification of the resultant acid with trimethylsilyldiazomethane \(\text{17}\) provided methyl ester \(\text{17}\) 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 \(\text{18}\) in 88% yield. Oxidation of the primary alcohol in \(\text{18}\) by using the Dess–Martin periodinane reagent\(^\text{18}\) 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 \(\text{18}\) successfully led to the required diene \(\text{3}\) in 53% yield and good E/Z selectivity (15:1). In parallel, treatment of the aldehyde with iodo-
form and chromous chloride in THF\textsuperscript{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\textsuperscript{20} of vinyl boronate 4 and vinyl iodide 5 under various conditions.

Initially the widely used protocol was employed using \([\text{Pd}(\text{Ph}_3\text{P})_4]\)-Ph3As and Cs$_2$CO$_3$ in THF. Unfortunately, the desired product 1 was obtained in only 35% isolated yield (Table 2, entry 1). When the catalyst was switched to \([\text{Pd}(\text{dppf})_2\text{Cl}_2]\), 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 \([\text{Pd}(\text{Ph}_3\text{P})_4]\) and TIOEt in THF–H$_2$O (v/v 4:1) to furnish 1 in 73% isolated yield (entry 3).\textsuperscript{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 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).
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 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>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (10 mol%)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs I</td>
<td>toluene</td>
<td>80</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs II</td>
<td>CH(_2)Cl</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda–Grubbs II</td>
<td>CH(_2)Cl</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Grubbs II</td>
<td>toluene</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Hoveyda–Grubbs II</td>
<td>toluene</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Hoveyda–Grubbs II</td>
<td>toluene</td>
<td>80</td>
<td>51</td>
</tr>
</tbody>
</table>

a) Reaction conditions: See table and text for details.

b) Yield based on recovered material.

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.

Acknowledgment
We acknowledge financial support from the Hong Kong Research Grants Council (Projects: PolyU 5040/10P; PolyU 5037/11P, PolyU 5020/12P, PolyU5030/13P), the Fong Shu Fook Tong Foundation, the Joyce M. Kuok Foundation, the NSFC (21072007, 21272011), GDSCF (10151805704000006), and The Shenzhen Bureau of Science, Technology and Information (JC200903160367A, JC201005260220A, JC201005260102A, ZYC20101570351A).

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

References and Notes


(b) Tidwell, T. T. Synthesis 1990, 857; and references cited therein.


