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

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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 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 monorhizopodin and 16-epi-monorhizopodin were achieved by Nicolaou and co-workers in 20115e and, since then, two total syntheses of rhizopodin have been reported.5f,5i

So far, total syntheses of the macrocycle of rhizopodin have employed either intramolecular Suzuki coupling reaction or macrolactonization.5e–i An alternative approach to the macrolactizations was sought and we opted to close the macrocyclic core by ene-diene cross-metathesis8 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 acetal 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 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 \((E/Z = 10:1; \text{Scheme 2})\).  

The preparation of coupling partners 3 and 5 commenced from methyl ester 14, which was prepared according to conditions described by Paterson\(^1\) (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.\(^1\) provided a 10:1 mixture of \(\text{syn}\)- and \(\text{anti}\)-monomethylated diols, favoring the desired isomer, which was protected as its TBS ether \((55\% \text{ yield over two steps})\). Oxidative cleavage of the terminal olefin by using the Sharpless protocol,\(^1\) and esterification of the resultant acid with trimethylsilyldiazomethane 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\(^1\) 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-
form and chromous chloride in THF gave vinyl iodide in 63% overall yield with greater than 10:1 E/Z selectivity.

With the four requisite fragments 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 of vinyl boronate and vinyl iodide under various conditions. Initially the widely used protocol was employed using [Pd(Ph3P)4]-Ph3As and Cs2CO3 in THF. Unfortunately, the desired product was obtained in only 35% isolated yield (Table 2, entry 1). When the catalyst was switched to [Pd(dppf)2Cl2], diene 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 and vinyl iodide were exposed to [Pd(Ph3P)4] and TlOEt in THF–H2O (v/v 4:1) to furnish in 73% isolated yield (entry 3).

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 and diene 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. Fortunately, performing this reaction at 60 °C in toluene with Grubbs II catalyst or Hoveyda–Grubbs II catalyst, afforded 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 1H 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 (%)</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>CH₂Cl₂</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda–Grubbs II</td>
<td>CH₂Cl₂</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>

* Reaction conditions: See table and text for details.

* 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 one-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.

References and Notes


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(21) Procedures for the synthesis of diene I:

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 NH4Cl (10 mL) and filtered through a pad of Celite, eluted with CH2Cl2 (10 mL). The filtrate was concentrated to remove volatiles and the aqueous residue was extracted with CH2Cl2 (3 × 30 mL). The combined organic layers were dried over Na2SO4 and concentrated under vacuum. The residue was purified by flash column chromatography (EtOAc–hexane, 1:4; Rf = 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; Rf = 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: [α]D20 +8.4 (c 1.1, CHCl3). 1H NMR (500 MHz, CDCl3): 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). 13C NMR (125 MHz, CDCl3): δ = 172.19, 162.85, 140.52, 130.63, 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 C30H55NO7Si2Na+: 620.3410; found: 620.3406.

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