ENANTIOSELECTIVE SYNTHESIS OF THE C(2)-C(11) CYCLOPROPYLEFURAN SEGMENT OF PINNATIN A

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Abstract – Synthesis of the C(2)-C(11) segment, cyclopropylfuran derivative, of pinnatin A was accomplished by Suzuki cross-coupling between chiral cyclopropylboronic acid and bromofuran as a key step. Addition of silver (I) oxide was found to promote the Suzuki cross-coupling reactions.

Pinnatin A 1 is a unique gersolane-type furanoditerpene isolated from a Caribbean gorgonian, Pseudopterogorgia bipinnata. The compound shows significant differential antitumor activity in the National Cancer Institute’s 60-cell-line tumor panel. Pinnatin A has a highly functionalized polycyclic \( \alpha,\gamma \)-disubstituted \( \alpha,\beta \)-unsaturated \( \gamma \)-lactone and consists of bicyclo[11.1.0]carbon skeleton joined in a trans fashion. With its unusual structural features and specific cytotoxic properties, pinnatin A is a challenging target. No total synthesis of pinnatin A has been reported to date. Recently, we have achieved a diastereoselective construction of syn- and anti-isopropenyl alcohol moieties at the C(1) and C(2) positions of 2,5-bridged furanocycles based on the [2,3] Wittig rearrangement of cyclic furfuryl ethers as a key step.2 Thus we intended to study the synthesis of pinnatin A using this strategy. We report here the stereoselective synthesis of the C(2)-C(11) segment 2, cyclopropylfuran part, of pinnatin A 1.

Scheme 1. Retrosynthesis of pinnatin A

Dedicated with respect to Dr. Albert Eschenmoser on the occasion of his 85th birthday.
We first investigated Suzuki cross-coupling between furanboronic ester 4 and cyclopropyl iodide 5 under Charette’s conditions (eq. 1). Pd(OAc)₂-catalyzed cross-coupling reaction with K₂CO₃ and Bu₄NBr gave the adduct 6 in only 6% yield. The addition of CsF instead of K₂CO₃ afforded trisubstituted cyclopropane 6 in 25% yield. Poor yields and lower reactivities in this Suzuki cross-coupling could be due to the steric effect of geminal substitution in 5, since the coupling reaction of 2-alkyl-1-iodocyclopropanes with arylboronic acids gave good yields.

We next carried out Suzuki cross-coupling reaction between bromofuran 7 and cyclopropylboronic acid derivatives 8-11 under Falck’s and Deng’s conditions (Table 1). Moderate to good yields of the cross-coupling products 6 and 12 were obtained using a combination of Ag₂O-K₂CO₃. Increasing amounts of K₂CO₃ (5.0 eq) gave better coupling yields with both 6 and 12 (entries 1, 3 vs 2, 4). Boronic acids 8 and 9 were preferable to boronates 10 and 11 (entries 3, 4 vs 5, 6).

Table 1. Suzuki cross-coupling of cyclopropylboronic acid derivatives 8-11 with bromofuran

<table>
<thead>
<tr>
<th>entry</th>
<th>boronic acid derivative</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>12</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>6</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>12</td>
<td>81&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>6</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>12</td>
<td>71&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>6</td>
<td>55&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> K₂CO₃ (3 eq) was used. <sup>b</sup> K₂CO₃ (5 eq) was used.

With the optimized condition in hand, we embarked on the synthesis of chiral cyclopropylfuran 2 as follows. Scheme 2 shows a preparation of cyclopropyl iodide 15 from the known alkyne 13. Alkyne 13
was subjected to Organ’s carbometalation conditions\(^\text{10}\) to provide vinyl iodide \(14\) in one-pot sequence. Cyclopropanation of vinyl iodide \(14\) under Shi’s conditions\(^\text{11}\) resulted in the formation of cyclopropane \(15\) in a single diastereomer. The absolute configuration of cyclopropyl iodide \(15\) was determined by the MTPA esters of the corresponding cyclopropanol \(16\).

\[
\begin{align*}
\text{(a)} & \quad \text{Bu}_3\text{SnCu(Bu)(CN)Li}_2, \text{THF}, -78 ^\circ\text{C}, \text{then Mel, HMPA, then I}_2, 74\%; \\
\text{(b)} & \quad \text{Et}_2\text{Zn, CH}_2\text{Cl}_2, \text{TFA, CH}_2\text{Cl}_2, \text{rt, 85\%; (c) t-BuLi, THF, -78 ^\circ\text{C, then B(Oi-Pr)}_3, -78 ^\circ\text{C to rt, then 3N NaOH, 30\% H}_2\text{O}_2, 70\%} \\
\end{align*}
\]

\textbf{Scheme 2.} Reagents and conditions: (a) \text{Bu}_3\text{SnCu(Bu)(CN)Li}_2, \text{THF}, -78 ^\circ\text{C}, then Mel, HMPA, then I\(_2\), 74\%; (b) \text{Et}_2\text{Zn, CH}_2\text{Cl}_2, \text{TFA, CH}_2\text{Cl}_2, \text{rt, 85\%; (c) t-BuLi, THF, -78 ^\circ\text{C, then B(Oi-Pr)}_3, -78 ^\circ\text{C to rt, then 3N NaOH, 30\% H}_2\text{O}_2, 70\%}

Suzuki cross-coupling of cyclopropylboronic acid \(17\), prepared from \(15\) by lithium/halogen exchange followed by treatment with B(i-Pr\(_3\)), with bromofuran \(7\) under the optimized condition gave the desired product \(18\) in 77\% (2 steps). Acetal group of \(18\) was switched from cyclohexylidene to \(p\)-methoxybenzylidene by acid hydrolysis followed by acetalization of the corresponding diol with \(p\)-methoxybenzaldehyde to give \(19\). Reduction of furoate \(19\) with LiAlH\(_4\) followed by etherification of the furfuryl alcohol with TBDPSCl afforded silyl ether \(20\). Regioselective cleavage of \(p\)-methoxybenzylidene acetal \(20\) with DIBAL gave an inseparable mixture (ratio: 2.5 : 1) of alcohols, which were oxidized with Dess-Martin periodinane to afford the desired aldehyde \(21\)\(^\text{12}\) together with ketone \(22\).

\[
\begin{align*}
\text{(a)} & \quad \text{t-BuLi, THF, -78 ^\circ\text{C, then B(Oi-Pr)}_3, -78 ^\circ\text{C to rt, then 1N HCl; (b) Pd(dppf)Cl}_2, \\
\text{Ag}_2\text{O, K}_2\text{CO}_3, 7, \text{THF, 80 ^\circ\text{C, sealed tube, 77\% (2 steps); (c) Dowex 50WX-8, MeOH, rt, 98\%; (d) } \text{p-MeOPhCHO, PPTS, PhH, reflux, 85\%; (e) LiAlH}_4, \text{THF, rt, 92\%; (f) TBDPSCl, imidazole, CH}_2\text{Cl}_2, \text{rt, 100\%; (g) DIBAL, PhMe, -78 ^\circ\text{C, 68\%; (h) Dess-Martin periodinane, CH}_2\text{Cl}_2, \text{rt, 50\%}} \\
\end{align*}
\]

\textbf{Scheme 3.} Reagents and conditions: (a) t-BuLi, THF, -78 ^\circ\text{C, then B(Oi-Pr)}_3, -78 ^\circ\text{C to rt, then 1N HCl; (b) Pd(dppf)Cl}_2, \\
\text{Ag}_2\text{O, K}_2\text{CO}_3, 7, \text{THF, 80 ^\circ\text{C, sealed tube, 77\% (2 steps); (c) Dowex 50WX-8, MeOH, rt, 98\%; (d) } \text{p-MeOPhCHO, PPTS, PhH, reflux, 85\%; (e) LiAlH}_4, \text{THF, rt, 92\%; (f) TBDPSCl, imidazole, CH}_2\text{Cl}_2, \text{rt, 100\%; (g) DIBAL, PhMe, -78 ^\circ\text{C, 68\%; (h) Dess-Martin periodinane, CH}_2\text{Cl}_2, \text{rt, 50\%}}
In conclusion, we have succeeded in the enantioselective synthesis of cyclopropylfuran derivative 21, the C(2)-C(11) segment of pinnatin A employing the silver (I) oxide promoted Suzuki cross-coupling as a key step. Further studies on the synthesis of pinnatin A are in due course.

ACKNOWLEDGEMENTS
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REFERENCES AND NOTES
12. 21: a colorless oil. [α]D22° -24.1 (c 0.64, CHCl3); IR (thin film) cm⁻¹: 1110, 1740; ¹H-NMR (CDCl3 270 MHz) δ: 0.91 (1H, dd, J = 5.1 and 5.9 Hz, 3'-CHH), 0.96 (3H, s, 2'-CCH3), 1.02 (9H, s, SiC(CH3)3), 1.08 (1H, dd, J = 5.1 and 9.2 Hz, 3'-CHH), 1.75 (3H, s, ArCH3), 2.11 (1H, dd, J = 5.9 and 9.2 Hz, 1'-CH), 3.29 (1H, d, J = 2.1 Hz, 1''-CH), 3.80 (3H, s, OCH3), 4.54 (2H, s, ArCH2O), 4.59 (2H, s, CH2OSi), 5.82 (1H, s, ArH), 6.89 and 7.29 (each 2H, each d, J = 8.6 Hz, CH3OC6H4)
7.28-7.64 (6H, m, ArH), 7.62-7.72 (4H, m, ArH), 9.69 (1H, d, J = 2.1 Hz, CHO); $^{13}$C-NMR (CDCl$_3$ 67.8 MHz) $\delta$: 9.7, 14.1, 16.1, 17.3, 19.3, 23.1, 26.7, 55.2, 56.6, 71.5, 87.3, 110.5, 113.9, 117.9, 127.6, 129.3, 129.5, 129.5, 133.7, 135.6, 147.8, 151.5, 159.5, 202.0; MS (EI): 582 (M$^+$); HRMS (EI): calcd for C$_{36}$H$_{42}$O$_5$Si: 582.2801. Found: 582.2800.