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Graphical Abstract

Enantioselective Construction of Biaryl Part in the Synthesis of Stegane Related Compounds

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Abstract

Stegane is a complex natural product isolated from the sponge Pseudoplea decipiens. The structure of Stegane contains a biaryl part with a unique arrangement of functional groups. In this study, we report the enantioselective construction of the biaryl part of Stegane-related compounds using a palladium-catalyzed coupling reaction. The reaction conditions and optimization of the coupling reaction are described, along with the synthesis of the target compounds.
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Abstract - A Pd-mediated intramolecular aryl-aryl coupling reaction of phenyl benzoate derivatives were examined to form benzo[c]chromen-6-ones, and then enantioselective lactone-opening reaction with a borane-oxazaborolidine combination was carried out. The resulting biphenyl was transformed into a key intermediate for the stegane related compounds. The absolute configuration of the biphenyl is also discussed.

Stegane and related compounds are important because of their interesting biological activities such as antileukemic properties. One of the most outstanding features of their chemical structures is an unsymmetrical 2,2′-disubstituted biphenyl moiety with an axial chirality (Figure 1). For the formation of such a biphenyl part in the syntheses of the stegane families, several approaches have been attempted such as photocyclization, Suzuki coupling, oxidative biaryl coupling, the S<sub>N</sub>Ar reaction, Ullmann coupling,
and the $2+2+2$ three-component cyclization reaction.$^7$

Figure 1

Diastereoselective formation of the chiral 2,2’-disubstituted biaryl has been a general method for the synthesis of the stegane related compounds. On the other hand, the enantioselective synthesis of the biaryl moiety is an unknown route to these targets. Bringmann has proposed a “lactone strategy” for the enantioselective preparation of biaryl compounds, which is very effective for the syntheses of biaryl-type natural products in the optically active form.$^8$ In this report, we extend the Bringmann’s “lactone strategy” to the first enantioselective synthesis of the biphenyl moiety of stegane and related compounds.$^9,10$

Initially, we prepared phenyl benzoates $1a$, $1b$, and $1c$ through simple esterification between the phenols and the benzoic acid.$^{11}$ These compounds were investigated for the Pd-mediated biaryl coupling reaction under various conditions. The reaction of $1a$ and $1b$ with Pd(OAc)$_2$ proceeded to give lactones $2a$ and $2b$ in good yields when the reaction was carried out in the presence of both the phosphin ligand and base (Table 1). Contrary to the above results, the methyl ester $1c$ did not afford the desired lactone at all in spite of our intensive investigation.

Table 1

Next, we examined the asymmetric lactone-opening reaction of $2a$ and $2b$ with a chiral oxaborolidine-borane complex, based on dynamic optical resolution. As shown in Table
2, lactone 2a was reduced to give a lactone-opened product 3a in an enantioselective manner (run 1). When this reaction was carried out at 0°C, the ee of 3a was only 47% although the reaction rate was accelerated (run 2). In order to improve the reaction conditions, 50 mol% of the chiral ligand 5 was employed to the same reaction. However, only moderate yield of 3a was obtained with 68% ee (run 3). Unfortunately, in each case, generation of undesired 4a could not be avoided (run 1-3). On the other hand, a more efficient result was obtained in the reaction of 2b, in which a higher yield of 3b was obtained (run 4). In sharp contrast to the reaction of 2a, no by-product 4b was detected under this reaction condition. However, when the same reaction was carried out at higher temperature, undesired 4b was obtained in 51% yield (run 5). Further attempts to improve these reaction conditions are under investigation in our group.

Table 2

In order to determine the absolute configuration of the obtained alcohol 3b, a short-step transformation into 6, which is a known compound, was carried out (Chart 1). The methylation of the phenolic hydroxy group followed by the oxidation with PDC successfully afforded aldehyde 7 without racemization. The reaction with methyl lithium produced two diastereomers which could be easily separated by chromatography to isolate a major diastereoisomer. O-Allylation of the resulting secondary alcohol gave 6, whereas the configuration at the benzylic position was not determined. All spectral data of 6 including the optical rotation agreed with those of a known compound which was reported by Uemura et al.\textsuperscript{3c,12} Consequently, the absolute configuration of 3b could be determined as $R$. 
In summary, we succeeded in preparing a key intermediate of the optically active stegane families through the Pd-mediated bi aryl coupling reaction of phenyl benzoate followed by the enantioselective lactone-opening reaction.

The synthesis of (-)-steganone from 6 has already been reported. Thus, we accomplished the formal total synthesis of (-)-steganone.

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References


9. Although many examples of asymmetric syntheses of natural products utilizing “lactone strategy” have been documented, there has been only a few reports on phenyl benzoate type substrates.10


12. The e.e. of 4 was 80% by HPLC analysis.
Figure 1

R¹ = R² = H: (-)-steganone
R¹, R² = O: (-)-steganone
R¹ = OAc, R² = H: (-)-steganacin
Table 1

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (min)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a : R = MOM</td>
<td>30</td>
<td>2a</td>
<td>71</td>
</tr>
<tr>
<td>1b : R = TBS</td>
<td>10</td>
<td>2b</td>
<td>63</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>BH$_3$ (mol%)</th>
<th>5 (mol%)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>E.e. (%) of 3 $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>400</td>
<td>300</td>
<td>-78 to r.t.</td>
<td>8</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>400</td>
<td>300</td>
<td>0</td>
<td>1.5</td>
<td>67</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>200</td>
<td>50</td>
<td>-40</td>
<td>40</td>
<td>55</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>400</td>
<td>300</td>
<td>-78 to -40</td>
<td>17</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>400</td>
<td>300</td>
<td>-78 to 0</td>
<td>17</td>
<td>49</td>
<td>51</td>
</tr>
</tbody>
</table>

$^a$) Determined by HPLC analysis using CHIRALCEL OD.
Reagents and conditions: (a) MeI, 'BuOK, THF, 88%; (b) PDC, CH₂Cl₂, 77%;
(c) MeLi, THF, 55%; (d) allyl bromide, NaH, DMF, 66%.