SYNTHESIS OF THE 1,2-ANTI TYPE OF 3E-ALKENE-1,2,5-TRIOL DERIVATIVES†

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Abstract – We invented an efficient method to obtain 3E-alkene-1,2,5-triol derivatives with 1,2-anti stereochemistry from the 2Z,4E-alkadienyl alcohol derivatives, which were synthesized by using nickel-catalyzed coupling between lithium 1E-alkenyl borates and 1-halo-1Z-alken-3-ols. The method involves (1) asymmetric dihydroxylation at the E olefin moiety of the dienyl alcohol derivatives followed by formation of a cyclic carbonates; (2) palladium-catalyzed reaction with AcOH in the presence of Et₃N. The method was applied successfully to the synthesis of the C6–C20 part of trioxilin A₃.

Previously, we reported a nickel-catalyzed coupling reaction of alkenyl lithium borates 2 with less reactive 1-halo-1Z-alken-3-ols 3 and their silyl ethers (Scheme 1) to produce 2Z,4E-alkadien-1-ols 4 and their silyl ethers effectively. The high reactivity promoted by a nickel catalyst compensates for the low reactivity of alkenyl halides 3. Furthermore, the almost neutral character of the borates 2 is compatible with the hydroxyl group, while the halides 3 are available easily in enantiomerically enriched forms.

Later, the reaction was applied for the synthesis of 10,11-dihydroleukotriene B₄ and korormicin, both of which possess the structural unit of 4. Since then, we reported functionalization of 4 to 3E-alkene-1,2,5-triols 6 (Scheme 2), and the method was applied to the stereoselective synthesis of decaerstrictine D (Figure 1). The syn diol unit in it was stereoselectively introduced through epoxidation of alcohol 4 with m-CPBA. However, the method is hardly extended to the 1,2-anti isomers, which is seen in several biologically active compounds such as those delineated in Figure 1. To overcome this

† This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.
limitation, we envisioned a sequence consisting of asymmetric dihydroxylation\(^8\) (AD) with AD-mix-\(\beta\), cyclic carbonate formation, and palladium-catalyzed reaction of the resultant carbonates with AcOH. This transformation is illustrated in Scheme 3 with the MOM ethers 7 with the \(S\) chirality to produce diol derivatives 9. To realize the scheme, isomerization of the \(\pi\)-allylpalladium intermediate 11 to thermodynamically more stable 12 should precede the reaction with acetate anion, and the latter reaction from the B side should be stereoselective and regioselective. However, the electronic and steric effects on dictating the regiochemistry conflict each other, whereas extend of the effects was out of prediction.\(^9\) The same discussion would be applicable to the conversion of diastereomeric carbonates 13, giving \textit{anti} diol derivatives 14. Herein, we present the results of this investigation and a preliminarly study toward synthesis of trioxilin A\(_3\).

Scheme 1. Nickel-catalyzed coupling between lithium alkenyl borates and 1-bromo-1\(Z\)-alken-3-ols

Scheme 2. Transformation to the 1,2-\textit{syn}-3\(E\)-alkene-1,2,5-triols

Figure 1. Biologically active compounds with a 3\(E\)-alkene-1,2,5-triol structure
First, the MOM ether (S)-7a (R^1 = R^2 = C_5H_{11}) was prepared by the coupling reaction between borate 2 (R^2 = C_5H_{11}, R^3 = H) and the enantiomerically enriched alcohol 3 (R^1 = C_5H_{11}) of >99% ee followed by protection with MOMCl and i-Pr_2NEt in 72% yield based on the alcohol. AD reaction of (S)-7a with AD-mix-β run at 0 °C produced, after one day, diol 16a highly stereoselectively (Table 1, entry 1), whereas that with AD-mix-α took three days to afford 17a with somewhat low stereoselectivity (entry 3). The latter result indicates a mismatched pair of the substrate and the α reagent. To save reaction time, the reaction was examined at 6 °C (run in a refrigerator) to complete reaction after 1 day, giving 17a in good yield though the stereoselectivity dropped a little (entry 4). Similarly, AD reaction with the β reagent at 6 °C resulted in a little drop in stereoselectivity (entry 2), though the selectivity was still in high level.

To our surprise, R_f values of the diols 16a and 17a were sufficiently different each other (∆R_f = 0.2), suggesting easy separation by chromatography on silica gel. With the result in mind, racemic dienyl alcohol rac-7a was subjected to AD reaction with AD-mix-β and the resulting diastereomeric mixture of diols was separated, indeed easily, by chromatography to afford 16a and ent-17a in 45% and 42% yields, respectively (Scheme 4). Each diol was converted to carbonate 8a or ent-13a in good yields.

Scheme 3. Strategy to the 1,2-anti type of 3E-alkene-1,2,5-triol derivatives 9 and 14
Table 1. Asymmetric dihydroxylation of (S)-7a

<table>
<thead>
<tr>
<th>Entry</th>
<th>AD reagent</th>
<th>Temp., °C</th>
<th>Time, day</th>
<th>Isolated yield, %</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; of 16a : 17a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AD-mix-β</td>
<td>0</td>
<td>1</td>
<td>83</td>
<td>64 : 1</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix-β</td>
<td>6</td>
<td>1</td>
<td>99</td>
<td>53 : 1</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix-α</td>
<td>0</td>
<td>3</td>
<td>89</td>
<td>1 : 13</td>
</tr>
<tr>
<td>4</td>
<td>AD-mix-α</td>
<td>6</td>
<td>1</td>
<td>89</td>
<td>1 : 10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Of the major product. <sup>b</sup> Ratio was determined by <sup>1</sup>H NMR.

Scheme 4. AD reaction of racemic diene rac-7a

Palladium-catalyzed reaction of ent-13a with AcOH (5 equiv) was examined in THF at 40 °C for 2 h. However, the reaction was unsuccessful (Table 2, entry 1), while decomposition took place at higher temperatures, giving a mixture of unidentified products. In contrast, addition of Et<sub>3</sub>N (5.5 equiv) was found to accelerate the reaction especially at 40 °C to afford ent-14a in high yield (entry 3). Other isomers that were expected in advance (such as ent-15a) were not detected by <sup>1</sup>H NMR spectroscopy. Although the reaction afforded ent-14a, migration of the Ac group to the next oxygen atom took place during chromatography on silica gel to afford a mixture of ent-14a and 18 in a 1 : 1 ratio (entry 3). We think that this migration is not a synthetic problem because removal of the Ac group from the mixture...
affords the corresponding diol, which would be useful for further transformation. A successful resolution of this issue along this way is seen in the synthesis of C6–C20 part of trioxilin A3 (vide infra). In addition, attempted reactions with other amines such as i-Pr₂NEt and pyridine resulted in incomplete reaction giving a mixture of ent-14a and the substrate.

Table 2. Palladium-catalyzed reaction of ent-13a with AcOH

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp., °C</th>
<th>Amine</th>
<th>Calculated yield(^a) of ent-14a, %</th>
<th>Isolated yield and ratio of ent-14a and 18, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>–</td>
<td>1(^b)</td>
<td>nd(^c)</td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>NEt(_3)</td>
<td>22(^b)</td>
<td>nd(^c)</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>NEt(_3)</td>
<td>83</td>
<td>83 (1 : 1)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>i-Pr₂NEt</td>
<td>48(^b)</td>
<td>nd(^c)</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>pyridine</td>
<td>45(^b)</td>
<td>nd(^c)</td>
</tr>
</tbody>
</table>

\(^{a}\) Yields were determined by \(^1\)H NMR spectroscopy using pyridine as an internal standard. 

\(^{b}\) The substrate was recovered. \(^{c}\) Not determined.

The trans stereochemistry of the newly created olefin of ent-14a (and 18) was easily confirmed by the coupling constant of the olefinic protons of the derived diol (\(J = 16\) Hz) (structure not shown), while the anti stereochemistry of the diol portion was determined by \(\Delta \delta_H\) of 0.11 ppm for the acetonide methyl groups of 19, which is almost equal to the characteristic value for anti isomers (cf. \(\Delta \delta\) for syn isomers is ca. 0.03 ppm).\(^{10}\)

Next, the above reaction conditions, when applied to carbonate 8a, produced 9a regio- and stereoselectively in 69% yield (Scheme 5). The product was converted to acetonide 21, which showed 0.11 ppm for \(\Delta \delta_H\) of the acetonide methyl groups, indicating the anti stereochemistry as well\(^{10}\) (Scheme 6).
These results clearly indicate that the regiochemistry is controlled predominantly by the steric factor provided by the MOM-oxy group (see the introduction for difficulty of predicting the regioselectivity). The steric effect by the MOM-oxy group was supported by another reaction of carbonate 22 that lacks the group, producing a mixture of regioisomers 23 and 24 (Scheme 7).

With the above results in mind, we studied a synthesis of 39, which corresponds to the C6–C20 portion of trioxilin A3 (Figure 1), a lipoxigenase metabolite of arachidonic acid.\(^\text{11}\) The elements for nickel-catalyzed coupling were borate 29 and vinyl iodide 30. The iodide 30 was prepared by the method published,\(^\text{12}\) while the boronate ester 28, a precursor of borate 29, was synthesized as delineated in Scheme 8. Copper-assisted coupling of propargyl bromide 25 with C\(_5\)H\(_{11}\)C≡CMgBr afforded 26 in 82% yield. Lindlar reduction of 26 was followed by removal of the TMS group with KF to furnish acetylene in 52% yield. Hydroboration of 27 with (c-Hex)\(_2\)BH proceeded cleanly and the resulting borane was transformed to the boronate ester 28 by oxidation with Me\(_3\)NO followed by transesterification with Me\(_2\)C(CH\(_2\))\(_2\). For the nickel-catalyzed coupling reaction, the ester was converted to borate 29 with MeLi, and the resulting borate was subjected to coupling with vinyl iodide 30 at room temperature for 14 h to deliver dienyl alcohol 31 in 57% yield, which was converted to the MOM ether 32. AD reaction with AD-mix-\(\beta\) produced a mixture of diol 33 and regioisomer 34 in a 5:1 ratio by \(^1\)H NMR spectroscopy. Since the products were eluted without separation, the mixture was converted to the cyclic carbonates 35 and 36 quantitatively. The mixture was subjected to palladium-catalyzed reaction with AcOH under the same conditions established above to afford a mixture of 37 and the unreacted carbonate 36. The products
were separated easily by chromatography on silica gel. Finally, the monoacetate 37 was converted to the MOM ether 39 in 59% yield.

Scheme 8. Preliminary study of the synthesis of trioxilin A₃

In summary, the 2Z,4E-alkadienyl alcohol derivatives 7, synthesized by the nickel-catalyzed coupling between borates and alkenyl halides (Scheme 1), were converted to the 1,2-anti type of 3E-alkene-1,2,5-triol derivatives 9 and 14 (Scheme 3). The transformation was applied to the synthesis of the C6–C20 part of trioxilin A₃ successfully (Scheme 8).

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REFERENCES AND NOTES